Journal of the American Osteopathic College of Dermatology

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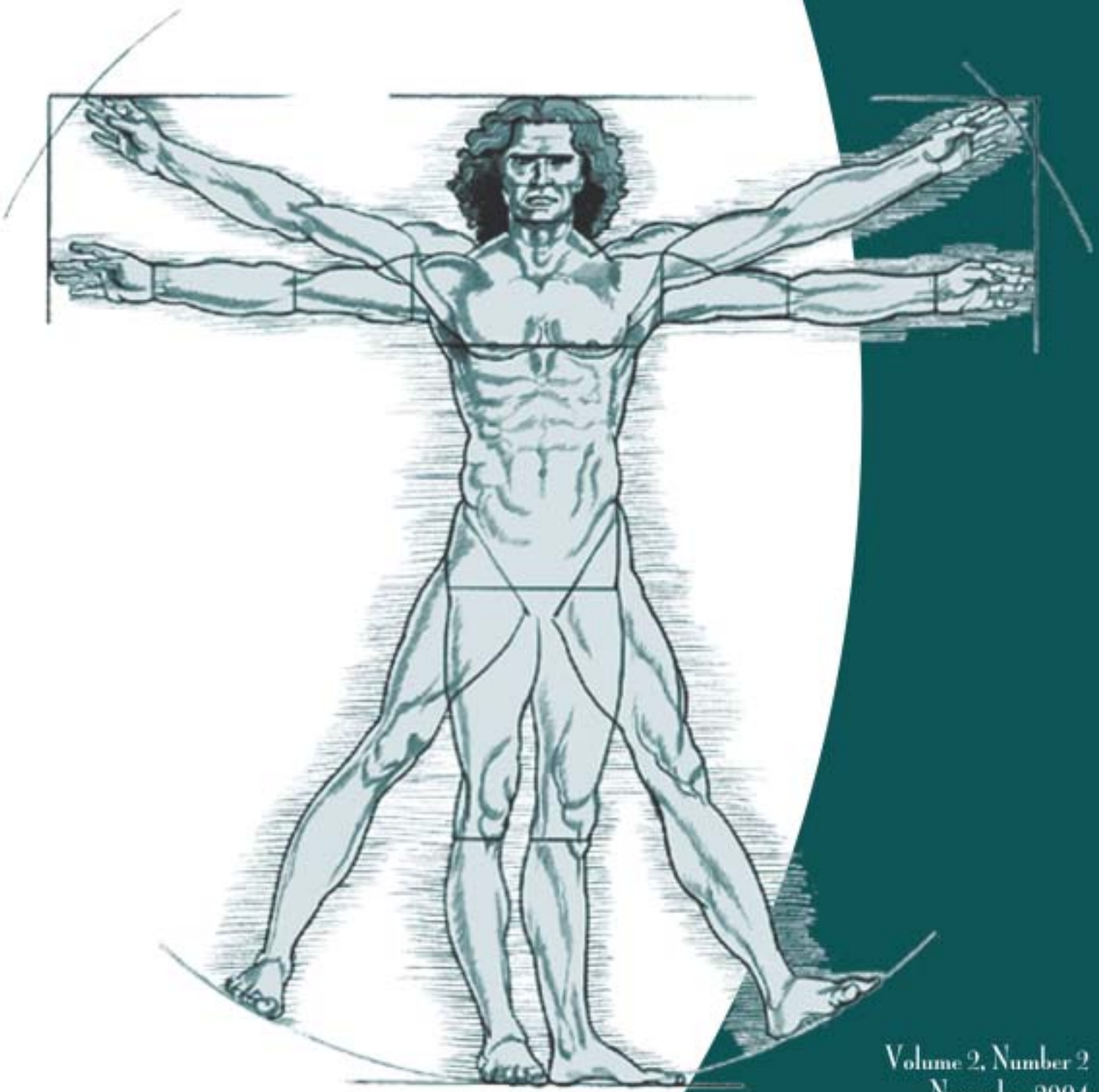

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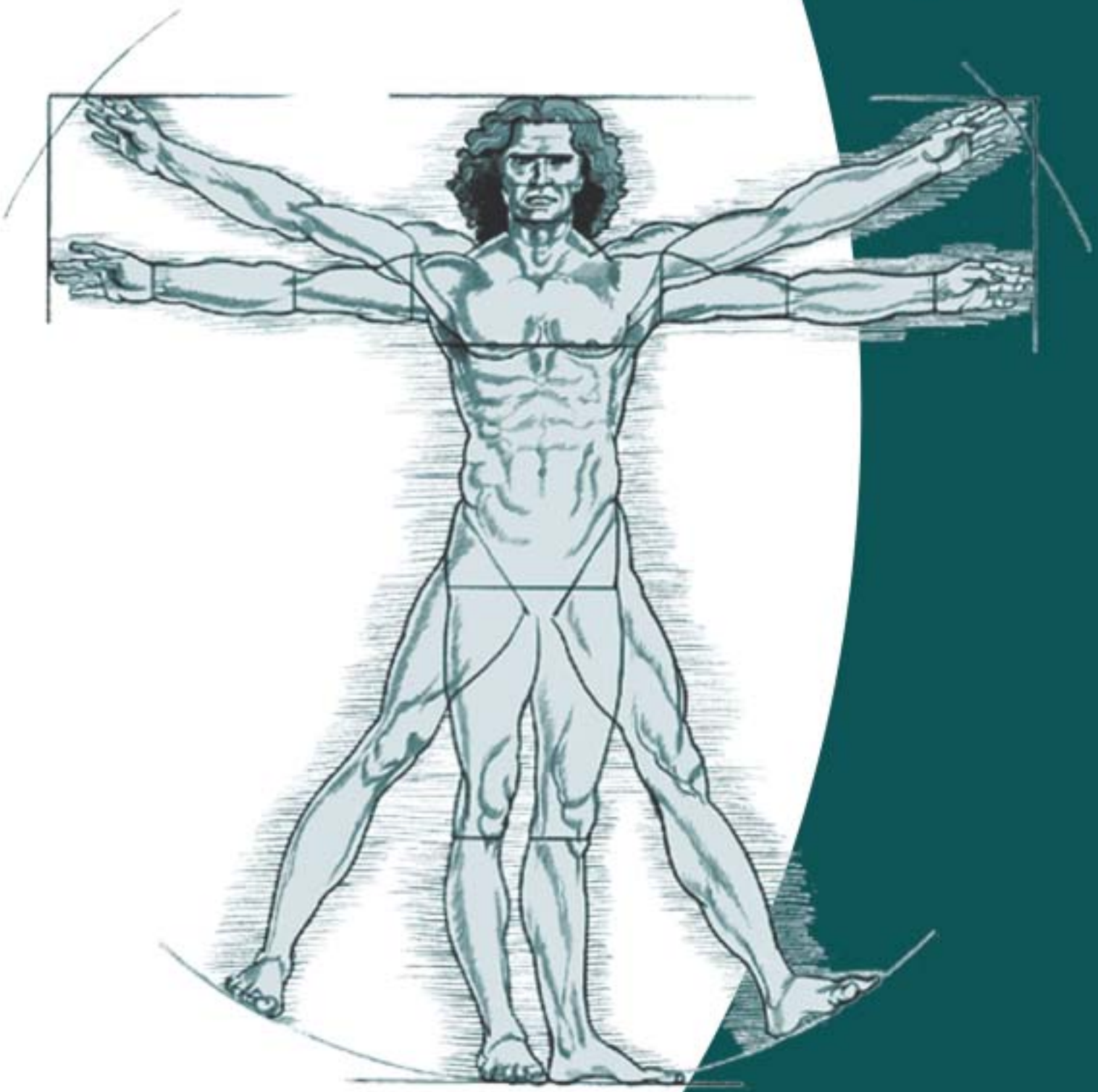

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Journal of the American Osteopathic College of Dermatology

CONTENTS

Letter From The JAOCD Editors

Jay S. Gottlieb, D.O.

Stanley E. Skopit, D.O.

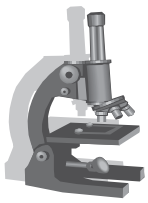
James Q. DelRosso, D.O.

We are extremely enthusiastic about this issue of the JAOCD. Even though this is only our third printing, we have made great strides. We now have an international presence and flare. We have gone from a black and white journal to a full color publication. The cover has been redesigned graphically and is even more aesthetically pleasing. We take great pride in all of these accomplishments that seem to have happened so quickly.

As your editors, we continue to strive for improvement and growth. What is the next step? Without question, the next milestone is to be able to publish the JAOCD four times a year. When this happens, we will be able to have our journal listed in the Library of Congress as well as have it listed in Index Medicus. We therefore turn to the general, resident and student membership of the AOCD to assist us in making this happen as soon as possible.

We solicit your contribution in the way of presenting an interesting case or even a pearl on office management. We require consistency. Become a consistent contributor, always looking out for what would be interesting to the readers of our journal. Also, our resident members are required to prepare and submit one paper each year to the AOCD that is suitable for publication. We have petitioned the education and evaluation committee to make it mandatory that each resident submit their yearly papers for consideration for publication. We need your support in these matters.

We will continue to cover topics that will be academically challenging. We will include such areas as dermatologic therapeutic modalities, original presentation of research, brief opinions, a review of dermatology affiliated clinical studies, brief individual case reports of unusual interest, basic science as it relates to dermatology, articles emphasizing cutaneous surgery, dermatopathology, cosmetic dermatology, pharmaceutical dermatology, editorials, letters to the editors, and finally Pearls and anecdotes in dermatology.



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We extend our sincere appreciation for continued support to our Founding Sponsors. Our deepest thank you goes to Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Novartis Pharmaceuticals Corporation, Medicis-The Dermatology Company and 3M Pharmaceuticals who have made the financial commitment to the JAOCD.

Jay S. Gottlieb, D.O., F.O.C.O.O. (Editor)
Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)
James Q. Del Rosso, D.O., F.A.O.C.D. (Associate Editor)

Letter from the President of the AOCD

Stanley Skopit, D.O., F.A.O.C.D., President

Greetings from the office of the president of the AOCD.

It appears that living in South Florida definitely comes with some risks. We have survived the onslaught of two hurricanes within a month of each other. Many of us here in the Miami area were spared the full ravages of both hurricanes although the middle of the state and portions of both coasts of Florida were not as lucky. We only hope that recovery is swift and life returns to some normalcy in the coming weeks for all those who were affected.

This has been a very busy spring and summer. I had the opportunity to attend the American Academy of Dermatology Unity Meeting held at the Ritz Carlton Hotel in San Francisco, which was attended by numerous members of the AAD and was hosted by Dr. Boni Elewski, the current president of the AAD. Dr. Elewski had invited several key individuals from the AAD as well as presidents of various specialty colleges within the American Academy of Dermatology. In addition to myself, our own College was represented by Dr. Ron Miller, President-elect, Dr. Ed Yob, Dr. Jim DelRosso and Becky Mansfield, Executive Director. Dr. Elewski's main purpose was to unite the various factions within the American Academy of Dermatology, the American Osteopathic College of Dermatology, and various other outside agencies. Her purpose was to evaluate the AAD's policy on promoting advocacy, education, and communication.

The AAD and its leaders were put on trial. They stood accused of not fostering unity in dermatology. The group that was present was divided into three distinct groups, involving a prosecution team, a defense team, and a judiciary team. There were three court room settings and each had a representative group from the judiciary, prosecution, and defense teams. The meeting was run by a facilitator, who was able to involve extensive interaction between the groups. It was the main purpose of the meeting to put the AAD on trial. The outcome of the trials found the AAD innocent of its charges; however, in all three trials, it showed that there were numerous deficiencies in education, advocacy, and communication within the AAD. Based on numerous recommendations, the American Academy of Dermatology proposed to make their Academy stronger and more unified. It was a very interesting and intense meeting.

Initially, as an osteopathic dermatologist, I was not sure what to expect. However, I was warmly received along with my other colleagues from our college that attended. In fact, I found that the attendees were extremely supportive of osteopathic dermatologists being admitted as full osteopathic fellows to their Academy. Of course, this meeting was very timely since we had just found out prior to attending this meeting that the osteopathic fellow amendment did not successfully pass, although it did receive 59% support from those that were voting and it needed 66% of those voting in favor of the amendment to carry. While, I was attending this meeting, I found that those individuals that were on the Board of the American Academy of Dermatology were very supportive and encouraged me as well as several of the other members of our college attending to make sure that we pursue this issue next year. The academy is sensitive to our needs and promised to put this back on the ballot in the very near future. So this was a very positive sign that I experienced.

I would like to take this opportunity to thank Dr. Ed Yob for his untiring effort along with his team; to push forward the Osteopathic Fellow Amendment on the AAD ballot This further put our College squarely on the map to success. Although it did not pass at this time, we were very close. We will not end here, but rather use the hard-fought work of Dr. Ed Yob and others to springboard our College to be recognized as full Fellows in the American Academy of Dermatology in the months ahead.

After the AAD unity meeting was over, I left to attend our mid year AOCD meeting in Tucson, Arizona. I want to thank Dr. Bill Way for an outstanding meeting. The location was superb. Despite some rain and cooler weather, there was still plenty to do in addition to attending the various lectures given by our guest faculty and residents.

On April 14, 2004, I attended the DO Day on Capitol Hill in Washington, DC representing our college. I was able to participate with numerous Congressmen and Senators, specifically from my state of Florida. We discussed such issues as tort reform and the malpractice crisis that several of the states were experiencing in addition to patient accessibility for physician care. Also on the agenda was needed legislation to reauthorize the Higher Education Act that supported loans for higher education from ending. It was important to stress to the congressional leaders, that these loans, made available to osteopathic medical students, not be curtailed.

At the conclusion of DO Day on the Hill, I was fortunate, along with my wife Sue, to be a guest at the White House. We toured the West Wing and the Eisenhower Executive Building on a private basis. This was certainly a highlight of my administration. I returned to sunny South Florida shortly after my visit to Washington where I am continuing to work diligently to improve and move our college further ahead over the remaining months of my presidency.

This past June, I had the opportunity to represent the AOCD as its President to attend the AOA Healthy Partnerships and Patient Advocacy Training Conference held in New York City. This conference dealt with how to successfully lobby state legislators and how to get and keep lawmaker's votes.

I would like to encourage our general membership and the residents, to submit articles or case vignettes for future JAOCD issues. It is our goal to become a quarterly publication and to continue to make this a quality journal as already evidenced in our two previous issues and now in this current full colored issue.

I trust all our members had a great summer with friends and family and enjoyed a wonderful Labor Day holiday. I want to take this opportunity to thank our membership for allowing me the privilege to serve as your President for this past year. I look forward to seeing all of you at the upcoming AOA meeting in San Francisco, November 7-11, 2004.

Stanley Skopit, DO, FAOCD
AOCD President 2003-2004

Surgical approach to Chondrodermatitis Nodularis Chronica Helicis (CNCH): A Case with a Review of Treatment Options.

by Jay Gottlieb, D.O., Assistant Clinical Professor-Nova Southeastern University & Sean Stephenson, D.O.

ABSTRACT

Chondrodermatitis Nodularis Chronica Helicis (CNCH) is a common nonmalignant nodule that presents with some degree of discomfort on the helix or the antihelix of the involved ear. Even though CNCH does not possess malignant potential, this lesion should be approached aggressively if intense pain occurs. This paper delineates a case with a review of treatment options. It is the authors' opinion that the best treatment is surgical and to perform an excision of the nodule and then repair the resulting defect via a posterior auricular, interiorly based advancement flap. This will obtain maximal results in both comfort and appearance, while markedly reducing the likelihood of recurrence.

Case

A 47 year old Hispanic male presented to the dermatology clinic complaining of an exquisitely painful right ear. The ear had been painful for 3 years. He described that initially the top of his right ear was painful and just red and then he develop a painful red bump. He was concerned that he had a skin cancer and was seen in another dermatology office. He underwent a biopsy and was told that he did not have cancer. He had an injection into the bump on his right ear on three separate occasions. His painful right ear interfered with sleeping. The injections did not help. He also applied a high potency steroid ointment for several months without any significant improvement.

Physical exam revealed a well nourished Hispanic male in no distress. There was a tender 8mm ulcerated papule on the superior aspect of his right helix. The histopathology slides from his previous biopsy were reviewed and were consistent with chondrodermatitis nodularis chronica helicis (CNCH).

The patient underwent excision of the painful mass with plastic reconstruction of the resultant defect via anterior and posterior advancement flaps (see fig.1 & fig.2). The sutures were removed on the 9th post operative day. He was given a foam rubber 'doughnut' pillow and instructed to avoid any pressure on the right ear. He has been asymptomatic for now for 3 years.

Discussion of Case

History

Chondrodermatitis Nodularis Chronica Helicis (CNCH) was originally described by Winkler in 1915[1]. Winkler described these nodules as cherry-seed sized growths with central crusts that were painful when pressed. Winkler hypothesized the underlying etiology was due to degenerative changes in the cartilage that caused an inflammatory reaction on the skin above. Foerster also independently reported this condition in 1918[2].

Epidemiology

CNCH is a common non-malignant painful inflammatory nodule of the helix or antihelix of the ear[3]. CNCH is a disorder that mainly affects adults, but occurrence in children has been reported[4]. CNCH chiefly affects middle-aged white men, but can occur in patient's age ranging from 20-90 years[5]. Depending on the study, 95% to 50% of patients with CNCH ranged between the ages of 50 and 80 years[6,7]. The incidence of this disease in women ranges from 10-35%, with one study showing only 19.6% incidence in women[8]. CNCH can affect all races, but is more common in fair-skinned individuals that have suffered sun damage[5].

Clinical Presentation

Clinically, CNCH appears as a dome shaped, firm reddish gray nodule with an erythematous rim ranging in size from 3 to 10mm, but can grow as large as 20mm[3,5]. It can also appear as a whitish-yellowish papule[9]. The surface of the nodule can be covered with scale or crust, be ulcerated or have a central depression[3]. The nodules are exquisitely painful, and spontaneous remission is rare[10]. The most common location of the nodule in men is the apex of the helix, while the most common location in women is the antihelix. Patients will commonly present with intense pain of the auricle, and will be unable to sleep on the affected ear.

Histology

Histologically, the lesions of CNCH demonstrate dermal inflammation and fibrosis associated with either a central hyperkeratotic plug or ulceration and crust. Ulcer margins often demonstrate hyperplasia[5]. Cartilage beneath the granulomatous and fibrotic dermis is disrupted, hemorrhagic and necrotic[5], although sometimes is appears undamaged[11]. The necrotic debris of CNCH are enveloped by pseudoepitheliomatous hyperplastic epidermis[9]. Because of this histopathology some authors now classify CNCH as a perforating dermatosis[9]. Figures 3-5 show acanthosis, hyperkeratosis, hypergranulosis, sub-epidermal fibrin deposition, fibrosis and cartilaginous degeneration. Figure 3 shows a high power view of the cartilage illustrating cartilaginous degeneration. Figure 4 shows a low power view of the dermis demonstrating sub-epidermal fibrin deposition and fibrosis. Figure 5 shows a low power view of the epidermis delineating acanthosis, hyperkeratosis and hypergranulosis.

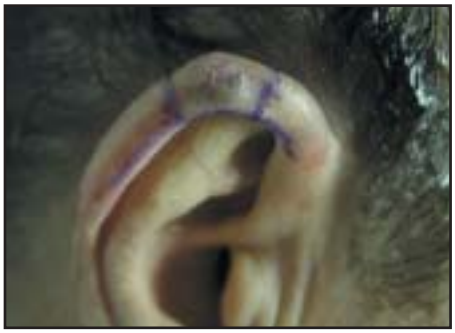

Figure 1

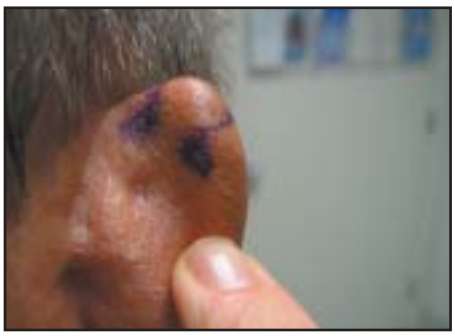

Figure 2

Pathogenesis

The pathogenesis of CNCH is unclear,

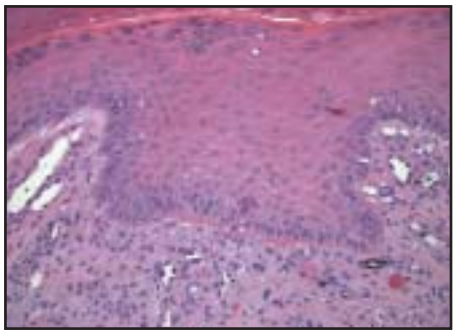

Figure 3
High power view of the cartilage illustrating cartilaginous degeneration.*

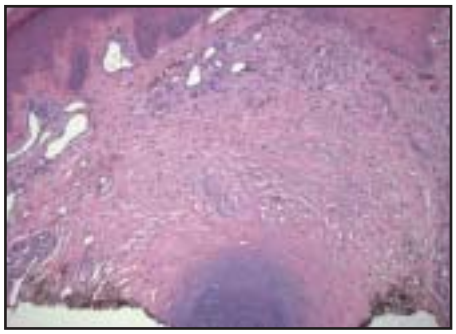

Figure 4
Low power view of the dermis demonstrating sub-epidermal fibrin deposition and fibrosis.

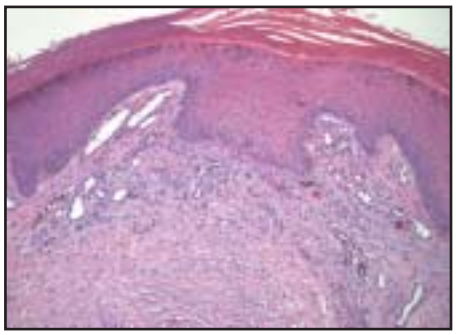

Figure 5
Low power view of the epidermis delineating acanthosis, hyperkeratosis and hypergranulosis.

but is now generally agreed upon that it is a disorder of transepidermal elimination in which damaged dermal connective tissue is engulfed and eliminated by a hyperplastic epidermis[9]. It has been suggested that anti-type II collagen antibody may play a role in CNCH but this has not yet been proven[9].

Etiology

The etiology of CNCH is unknown, but numerous causes have been suggested. Winkler suggested the cause had to do with something causing underlying degereration of the auricular cartilage[1]. While Carol and Van Haren thought the epidermis was the cause of the initial lesion and gave the name "clavus helices"[12]. Others suggest CNCH is caused by trauma which leads to chronic inflammation of the cutis and perichondrium[13]. This theory suggests irritation and ischemia play an important role possibly because the skin of the ear has little subcutaneous tissue to protect it from injury[4]. The evidence supporting this theory are that studies have shown 77-99% of CNCH patients sleep on the affected ear[7,14]. This theory also seems suggestive with patients that also have systemic sclerosis and Raynaud's phenomenon exhibiting CNCH[15]. Injury to the skin and cartilage seems to be the most import causative factor. It has also been hypothesized that the infundibular portion of the hair follicle is probably the primary cutaneous structure involved in this condition, with the lesion evolving from an acute, suppurative, granulomatous dermatitis into a later fibrosing dermatitis with the feature of perforating folliculitis and prurigo nodularis[11]. Another possible cause is low temperature affecting local circulation that limits blood supply and causes necrosis of the dermis and epidermis[4]. Actinic damage has also been implicated in CNCH and is a common finding, but the causal effect has not been well documented[4]. The suggested cause for the pain associated with CNCH is the glomoid proliferation of small capillaries[4].

Differential Diagnosis

The clinical differential diagnosis for CNCH includes basal cell carcinoma, squamous cell carcinoma, actinic keratoses, cutaneous horns, keratoacanthomas, warts, elastotic nodules, calcinosis cutis, gout tophi, and amyloid[4,5]. Normally the history and clinical presentation of pain out of proportion to the lesion will lead to the diagnosis, but a biopsy can be performed to rule out malignant lesions.

Treatment

The treatment of CNCH has a variety of options including surgical and non surgical. CNCH is still often difficult to treat because of its high rate of recurrence. The recurrence rate is estimated, depending on the author, between 30 and 88%[16]. The non surgical options are many, including the simplest, pain relief from a special pillow that relieves pressure or other devices patients have used to relieve pressure on their auricle. Beck reported no recurrences with topical corticosteroids with 0.1% betamethasone valerate and 3% clioquinol proprietary cream applied twice daily[17]. Lawrence used intralesional corticosteroid injection with only a 27% cure rate[14]. The usual dosing for intralesional corticosteroids is 0.1 to 0.2 ml of triamcinolone acetonide (10-40 mg/mL)[3]. Nelson used topical Bacitracin ointment with successful treatment in 8 of 9 patients[18]. Greenbaum used collagen injections successfully with Zyplast and Zyderm II of 5 patients without recurrence[19]. Many of these options are chosen when a patient either refuses surgery, or is a non surgical candidate.

Surgical treatments are often accepted as having a better outcome over non surgical techniques[3]. Taylor successfully used carbon dioxide laser ablation therapy using a Pfizer Model 10-C, 10 watt portable laser with 8 to 10 watts of power with 5 to 10 microseconds pulsed continuous wave energy with zero recurrences[20]. Kromann et al reported a 31% recurrence rate using electrodesiccation and curettage[21]. Shave excision with curettage and desiccation has been reported to have 21% recurrence rate[22,23]. Wide excision of the skin and cartilage was shown a 31% recurrence rate by Newcomer et al[6]. Metzger et al showed wedge removal of skin and cartilage had a 10% recurrence rate[24].

In the senior author's experience, the surgical technique that offers the best probability for cure and optimum cosmetic results is the one that utilizes a complete excision of the nodule with plastic reconstruction via a posterior helical-conchal flap. The area is prepped and draped. A skin marker is utilized to outline a rectangular excision from the superior helix. The marker is then used to design a posterior helical-conchal flap by extending two lines vertically down the posterior aspect of the ear. Two burrows triangles are then drawn at the base of the flap. This flap has a random blood supply and therefore is designed with a 3 to 1 length to width ratio. 1% lidocaine with 1:200,000 epinephrine is then used for anesthesia. A #15 scalpel is then used to perform the excision. This excision then includes the nodule, skin, underlying perichondrium and the helical cartilage. The posterior helical-conchal flap is then incised and elevated. The two burrows triangles are excised. Bleeding is controlled with the electrocautery. The helical-conchal flap is then advanced into position and sutured in place with simple 5-0 nylon. Tissue adhesive and steri-strips are then used. The sutures are removed in 7-10 days.

Conclusion

In conclusion CNCH is a common non-malignant nodule that presents with some degree of discomfort on the helix or the antihelix of the involved ear. Even though CNCH does not possess malignant potential, this lesion should be approached aggressively if intense pain occurs. If surgical intervention is required, it is the senior authors recommendation to first perform a surgical excision of the nodule and then repair the resulting defect via a posterior auricular, interiorly based advancement flap. The bunching that occurs at the lateral aspect of the base of the flap is easily corrected with bilaterally burrow's triangles. This will obtain maximal results in both comfort and appearance, while markedly reducing the likelihood of recurrence.

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AOCD Mid Year Meeting

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Jay Gottlieb, D.O. • Program Chairman

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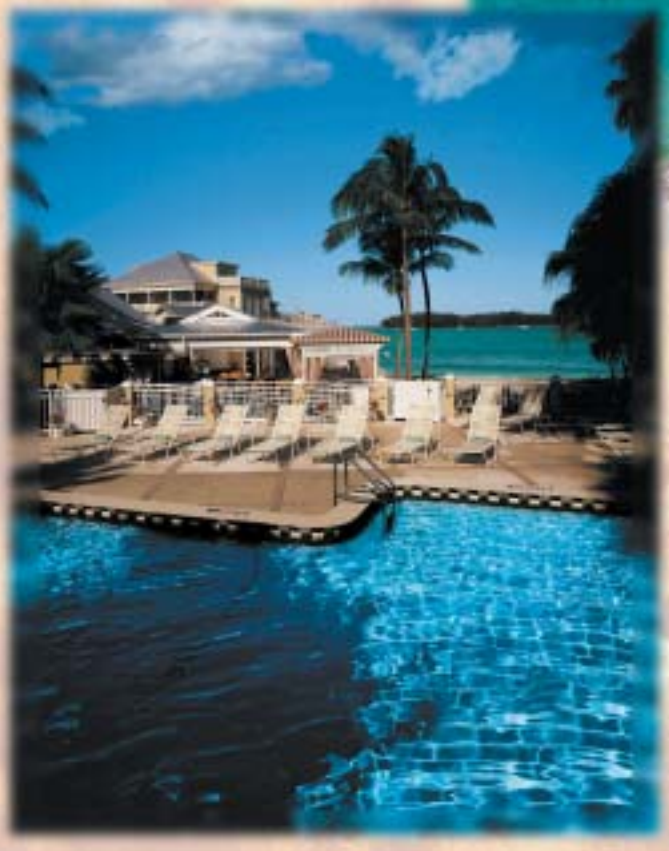

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This project has been funded in whole or in part with Federal funds from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health, Department of Health and Human Services and with Funds from The Carl J. Herzog Foundation, Inc. under Contract No. NO1-AR-1-2255.

Eruptive Psoriasis in a Patient with Human Immunodeficiency Virus: A Case Report and Literature Review

Nilam Amin, D.O., Igor Chaplik, D.O., Charles Gropper, M.D., Cindy Hoffman, D.O., Damian DiCostanzo, M.D., Richard Hwang, M.D.

ABSTRACT

A case of eruptive psoriasis in a patient with acquired immunodeficiency syndrome is described. A review of the literature on psoriasis as it relates to infection with the human immunodeficiency virus was undertaken. The unique epidemiology, pathogenesis, clinical features, histopathology, and treatment in this patient population are discussed.

Case Report

The dermatology service was asked to evaluate a 60 year-old Hispanic male from the nursing home for nodular lesions on his hands and feet of 3 days duration with associated painful joints. The patient's past medical history was significant for acquired immunodeficiency syndrome (AIDS), type 2 diabetes mellitus, anemia, osteoarthritis, and onychomycosis. His medications included terbinafine (Lamisil), cephalexin (Keflex), clotrimazole (Lotrimin), oxycodone/acetaminophen (Percocet), acetaminophen (Tylenol), amlodipine (Norvasc), erythropoietin (Epogen), pantoprazole (Protonix), senna (Senokot), iron, clonidine, and lactulose. He had no known drug allergies.

Physical examination revealed multiple, verrucous, hyperkeratotic papules, nodules, and plaques on bilateral dorsal hands, palms, dorsal feet, soles, and right knee. Dystrophic, thickened nails were also noted (Figures 1-2). Laboratory evaluation was significant for the following: white blood cell count 3800/_l, hemoglobin 7.4 g/dL, hematocrit 24.1%, glucose 131 mg/dL, alkaline phosphatase 253 U/L, absolute CD3 count 824/mm3, and absolute CD4 count 101/mm3. Polymerase chain reaction analysis of human immunodeficiency virus (HIV) ribonucleic acid was 252,791 (reference <400).

Our differential at the time of evaluation included a deep fungal infection, eruptive keratoacanthomas, eruptive psoriasis, eruptive xanthomas, and granuloma annulare. A 3-millimeter punch biopsy was performed from a lesion on his right thumb. Microscopic evaluation revealed eruptive hyperplasia with upper epidermal pallor, numerous intraepidermal neutrophils and spongiform pustules, a small amount of parakeratosis, and papillary dermal edema consistent with eruptive psoriasis (Figures 3-4). All special stains were negative for microorganisms. Bacterial culture of tissue revealed few coagulase-negative staphylococcus. Cultures for fungus and acid-fast bacilli were both negative.

The patient was started on clobetasol propionate (Temovate) ointment twice daily and Keflex 500 milligrams 3 times daily. Acitretin (Soriatane) was another therapeutic consideration due to the severity of lesions; however the patient refused to take any systemic medications for this problem.

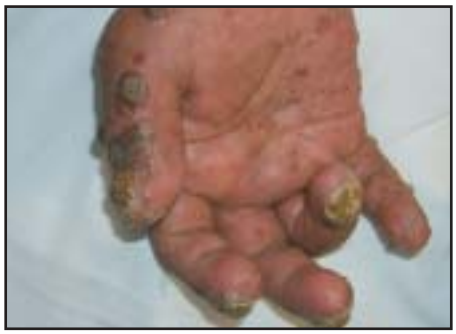

Figure 1

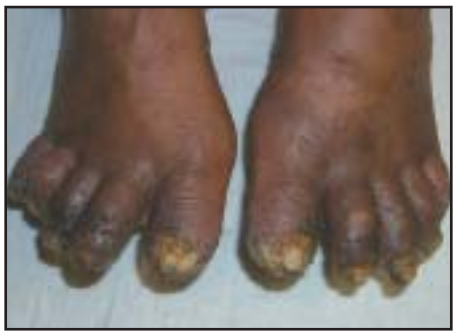

Figure 2

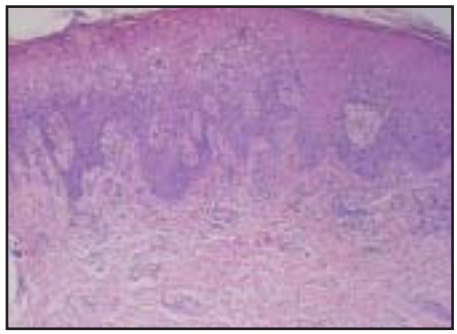

Figure 3

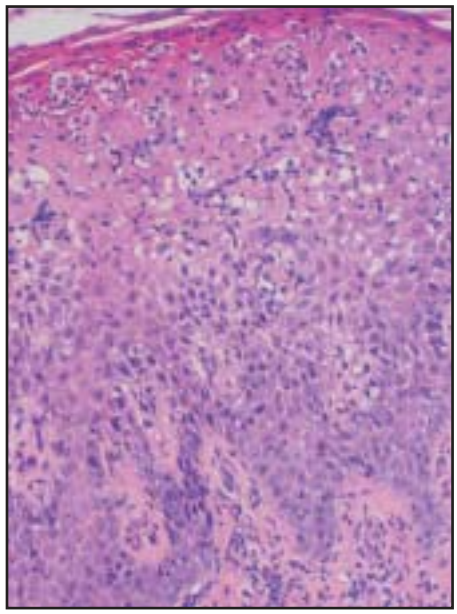

Figure 4

Discussion- HIV and Psoriasis

Introduction

Cutaneous disorders occur frequently in HIV-infected patients; the frequency and severity of these disorders increases with progression of the disease and immune function deterioration.[1] The incidence of psoriasis in patients with HIV is similar to the general population, but tends to be more severe and refractory to treatment, with a higher prevalence of psoriatic arthritis. A severe, explosive episode of psoriasis is often seen in this patient population, whether or not the patient was previously diagnosed with psoriasis.[2] Patients with full-blown AIDS may especially present with severe, extensive forms of the disease.[3]

Epidemiology

The prevalence of psoriasis in the HIV population is estimated to be 1-3%.[4] Psoriatic arthropathy has a prevalence of 23-50% in those with HIV and psoriasis.[5] Twenty percent of patients with HIV-associated psoriasis have their presentation with a CD4 count greater than 400 and psoria-

sis may actually be the initial clinical manifestation of HIV infection.[6]

Pathogenesis

Psoriasis is characterized by an accelerated epidermal turnover and increased deoxyribonucleic acid synthesis (DNA) by keratinocytes.[3] The exact pathogenesis of psoriasis remains unclear, although human leukocyte antigen (HLA) status, genetic factors, and environmental factors including infection, trauma, and drugs have been known to predispose to expression of the disease. HLA-B27, HLA–B17, and HLA-Cw6 are the most commonly described associations.[5, 6] An association with the Cw0602 allele in particular is seen in 79% of HIV-associated psoriasis cases.[7]

There is strong evidence that T-lymphocyte activation plays an important role in triggering or maintaining psoriatic lesions. In light of this involvement, the occurrence of psoriasis in the setting of HIV is intriguing due to the depletion of T lymphocytes associated with the disease process.[4]

Multiple factors have been proposed in the pathogenesis of HIV-associated psoriasis. Psoriasis is considered an autoimmune disease; the dysregulation caused by HIV infection could therefore act as a trigger of psoriasis. HIV destroys CD4 T cells; it is therefore unlikely that these cells are the direct mediators in the formation of psoriasis in this population. CD8 T cells, on the other hand, are relatively spared by HIV, and are more likely the pathogenic mediators due to their recognition of major histocompatibility complex class I antigens.[8] Second, the decreased cellular immunity associated with HIV may allow the emergence of opportunistic infections, which could also act as a trigger for psoriasis. Third, HIV may have a direct role in the development of psoriasis.[9] In patients with AIDS, interferon-_, a known trigger of psoriasis is increased. It is also postulated that the HIV tat protein may have a proliferative effect on epithelial cells; other viral proteins may also act as superantigens triggering development of psoriatic lesions.[3]

Clinical Features

The clinical manifestations of HIV-associated psoriasis are similar to those without infection.[5, 6] The presentation of psoriasis in HIV-infected patients includes plaque psoriasis, guttate psoriasis, palmoplantar psoriasis, pustular psoriasis, and erythrodermic psoriasis. Sebopsoriasis and acral psoriasis are other common presentations in the setting of HIV disease.[4] Several patterns may coexist within the same patient.[8]

Some have categorized HIV-associated psoriasis into two groups. The first group includes those with expression of psoriasis before HIV seroconversion in which classical psoriatic patterns such as plaque psoriasis, guttate psoriasis, and erythrodermic psoriasis are seen.[6] These patients usually present in the second decade of life and often have a positive family history of psoriasis.[3] The second group expresses psoriasis after HIV seroconversion where less common forms of psoriasis including inverse psoriasis, acral psoriasis, and pustular psoriasis are seen.[6] These patients tend to be older at the time of presentation, usually lack a family history of psoriasis, and have an increased incidence of associated arthritis. The onset of psoriasis in one study occurred approximately 5 years after HIV infection in this group.[10] As mentioned earlier, the severity of psoriasis in this population tends to reflect the stage of HIV disease and worsens as HIV disease progresses.[1, 6]

Psoriatic arthropathy in HIV disease shows a polyarticular and asymmetric involvement.[3] It primarily affects the lower extremities with sausaging of digits, inflammation of ligamentous attachments in the heel and foot, and distal interphalangeal joint involvement. The arthritis tends to be more severe than that seen in the general population and is often refractory to anti-inflammatory treatment.[11]

Psoriasis of the nail may occur along with cutaneous lesions, or it can occur alone. Superficial pitting, subungal hyperkeratosis, and onycholysis may be seen. A destructive onychopathy associated with pustular psoriasis may also occur as well as a proliferative, granulomatous process which can permanently damage the nail.[3]

Histopathology

The histopathology of all subtypes is similar. Psoriasis shows epidermal hyperplasia, acanthosis, hyperkeratosis, parakeratosis, collections of neutrophils in the stratum corneum, and a dermal inflammatory infiltrate. The dermal infiltrate is composed of activated T lymphocytes, Langerhans cells, and occasional neutrophils.[4] There is a relative decrease in the number of T lymphocytes in the infiltrates of psoriatic lesions from HIV-positive patients with an increase in the number of plasma cells.[12] Special testing has revealed an infiltrate composed predominantly of CD8+ cells; CD4+ and Langerhans cells are depleted due to infection with HIV.[13, 14]

Treatment

A stepwise approach from topical to systemic therapy is the usual course of treatment.[4] Topical preparations including corticosteroids and calcipotriol are first line treatments.[8, 15] In more severe cases, psoralen plus ultraviolet A therapy (PUVA), ultraviolet B therapy (UVB), methotrexate, cyclosporine, or oral retinoids may be required. Some of these drugs can accelerate immunosuppression, although beneficial use in HIV-psoriatics has been demonstrated.[5, 6] PUVA and UVB phototherapy are commonly used to treat HIV-associated psoriasis. Both forms of treatment are safe and effective, and although there is a strong preference for use of UVB, PUVA therapy has been shown to be more effective. Adverse reactions to phototherapy include nausea, erythema, photoaging of the skin, and nonmelanoma skin cancer.[16] Methotrexate and cyclosporine have also been used and shown to be effective in the treatment of both cutaneous and arthropathic forms of HIV-associated psoriasis, although some argue that their use should be reserved until other treatments have failed.[17, 18] Acitretin, in a pilot study, has shown to be effective in treating skin and joint manifestations of HIV-associated psoriasis while lacking immunosuppressive effects, making it well-suited for treatment in this patient population.[19] A recent case reported the effectiveness of etanercept, a tumor necrosis factor receptor:Fc fusion protein, in treating both psoriasis and a crippling psoriatic arthritis in a patient with HIV. Etanercept was discontinued, though, due to recurrent polymicrobial infections, suggesting that caution and careful follow-up be excercised when prescribing this drug in the setting of HIV disease.[20]

Effective antiretroviral therapy has also shown improvement of cutaneous lesions in this patient population, supporting the role of HIV in the pathogenesis of psoriasis.[21] Zidovudine (AZT) was the first antiretroviral shown to be useful for the treatment of HIV-associated psoriasis in a dose-dependent fashion.[22] AZT is a thymidine analogue that inhibits retroviral reverse transcriptase, terminating DNA chain synthesis and inhibiting viral replication. It has been shown to be safe and effective at clearing psoriasis, but not the associated arthritis. Long-term relapses, possibly due to lowered CD4 levels or retroviral resistance, have been reported.[23] Other antiretrovirals from case reports that have shown improvement of psoriasis in HIV patients include the following: lamivudine, ritonavir, saquinavir, and nevirapine.[21, 24]

Other novel approaches to the treatment of psoriasis in the HIV population as documented in various reports include ranitidine, 25 carbamazepine, 26 monoclonal anti-CD25 antibody, 27 and interleukin 10.[28] Often, flares of HIV-associated psoriasis can be accompanied by skin infection. It is therefore important to identify and treat all known infections.[6, 8]

Conclusion

Atypical and severe forms of psoriasis may occur in HIV-positive patients with exacerbation of preexisting lesions or an explosive new onset seen clinically. The occurrence of psoriasis in the setting of HIV infection is interesting in terms of both pathogenesis and therapy, because of the

background of profound immune dysfunction. Further research needs to be undertaken to better evaluate the unique role of HIV in the formation of psoriasis within this population.

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Multiple Eruptive Dermatofibromas: A Case Report and Review

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ABSTRACT

Dermatofibroma (DF) is a common, benign fibrohistiocytic tumor, commonly occurring on the legs of women. Occasional few dermatofibromas are common, but multiple eruptive dermatofibromas (MEDF) are rare. Dermatofibromas may represent a neoplastic process or persistent inflammatory proliferation of fibroblasts. MEDF may be associated with underlying diseases, such as diabetes mellitus, obesity, hyperlipidemia, hypertension, systemic lupus erythematosus, HIV, myasthenia gravis, pemphigus vulgaris, ulcerative colitis, and immunosuppressive therapy. We present a case of a 16 year-old female with obesity who developed MEDF over the course of 2 months.

Case Report

In 2003, a 16 year-old Indian female with a history of obesity presented to our clinic for the evaluation of several pruritic, nontender lesions of 2 months duration. There was no history of preceding trauma or insect bites. On physical examination, approximately sixty flesh-toned and hyperpigmented papules and nodules were noted on her upper back, chest and upper arms (see photographs). The sizes of the dermatofibromas ranged from 1mm to 8mm. A biopsy was taken on her right upper back, with diagnosis consistent with dermatofibroma. On laboratory findings, patient's HDL cholesterol was decreased at 28, and cholesterol/HDL risk ratio was elevated at 5.1. CBC, chemistry panel, ANA, lupus panel, Sjogren's antibodies and thyroid peroxidase antibodies were within normal limits. Serum pregnancy test was negative, and glycohemoglobin was borderline at 5.9. Her dermatofibromas were treated with Kenalog® (triamcinolone acetonide) 10 mg/cc intralesional injections with improvement in appearance (see photograph).

Definition

A dermatofibroma (DF) is a common, benign fibrohistiocytic tumor that usually occurs on the legs.[1] These tumors occur in the skin as firm, single or multiple well-circumscribed palpable nodules.[2] The surface may be shiny or keratotic. Color may vary from pink, red, brown, purple, yellow[3] or rarely blue-black color secondary to hemosiderin within the tumor.[2] Lateral compression produces a dimple-like depression in overlying skin. They are usually asymptomatic, although they can be pruritic and may ulcer after trauma. Although they are usually a few millimeters in diameter, they can occasionally measure 2-3 centimeters.[2] Dermatofibromas persist indefinitely, although spontaneous resolution has occurred.[2] Solitary or occasional few dermatofibromas are common, but multiple eruptive dermatofibromas (MEDF) are rare.[1]

MEDF were first reported by Baraf and Shapiro in 1970. They defined "multiple" dermatofibromas as presence of at least 15 lesions. This criteria was arbitrarily chosen and may not be valid for all cases. For example, in patients with less than 15 dermatofibromas, new dermatofibromas could be in the process of proliferation or DF may spontaneously disappear. Therefore, the definition of MEDF based on purely the number of DFs may not be valid. A more accurate definition may include the eruption of several multiple eruptive DF reported within a short period of time.[1]

MEDF have a slight female predominance. They usually occur on the legs, but also occur in other parts of the body; trunk and arms being the other preferred locations.[4] Lesions on the face, palms and soles are rare. In general, MEDF occurring in a limited area may not be associated with any underlying disease.[1]

Patients with MEDF may have underlying diseases. The incidence of MEDF is higher among patients with underlying disease than among healthy persons. MEDF are most likely associated with systemic lupus erythematosus and HIV, or immune mediated diseases such as myasthenia gravis and pemphigus vulgaris. MEDF may occur in patients with diabetes mellitus, obesity, hyperlipidemia, hypertension, Sjogren's syndrome, ulcerative colitis, atopic dermatitis, neoplastic disease, history of immunosuppressive therapy, hydronephrosis, or following organ transplant.[5]

Etiology

The etiology of dermatofibroma is unclear. It may represent a neoplastic process or persistent inflammatory proliferation of fibroblasts secondary to trauma.[6] An alternative hypothesis attributes the growth of DF to an abortive immunoreactive process mediated by dermal dendritic cells which are strong antigen presenting cells (APCs).[4] On the basis that APCs are present in dermatofibroma, it has been suggested that stimulation of an unknown antigen is a primary event.[7] Such an antigen could originate from insect saliva or tissue fragments induced by trauma. Therefore, dermatofibroma could be regarded as an abortive immunoreactive process mediated by APCs (dermal dendritic cells).[7]

The development of MDEF can be triggered by inhibition of down regulatory T cells in immunodeficiency states. The increased incidence of MEDF in patients with immunosuppressive treatment strongly suggest that immune mechanism may play a role in the pathogenesis of dermatofibromas.[4]

Mast cells are increased in the solitary dermatofibroma lesion and are increased in MEDF. Yamamoto et al quantified mast cell numbers of multiple dermatofibromas and found an increased number of mast cells in the upper portion of the early lesions. Mast cells contain chemical mediators, such as histamine, proteases and TNF-like factor, whose enzymes can cause destruction of connective tissue, and fibroblast proliferation may be promoted. Therefore, mast cells may play an important role in the induction and exacerbation of fibrotic processes.[8]

Differential Diagnosis

Because of the various clinical presentations of dermatofibromas, the differential diagnosis should include dermatofibrosarcoma protuberans, which are less defined and are multilobulated.[9] Dermatofibroma may be confused with keratoacanthoma, nodular fasciitis, neurofibroma, Kaposi's sarcoma, keloid[7] and melanocytic nevi.[9]

Histology

Dermatofibroma is also known as benign fibrous histiocytoma, histiocytoma, or sclerosing hemangioma.[2] Gross examination reveal a basophilic nodule in the dermis.[3] The epidermis consists of hyperplasia, hyperpigmentation of the basal layer with elongation of the rete ridges. It is separated by a clear Grenz zone from the spindle cell tumor in the dermis, which is composed of fibroblastlike spindle cells, histiocyte and

blood vessels.[2]

The dermal tumor is poorly demarcated on both sides, where spindle cells infiltrate between collagen.[3] There are whorling fascicles of spindle cells with a small amount of pale blue cytoplasm and elongate nucleus. Mitosis may be present. Some extend to involve the superficial panniculus in a radial pattern.[3] There is proliferation of fibroblasts and histiocytes in the reticular dermis, arranged as short intersecting fascicles.[9] Dermatofibromas are positive for Factor XIIIA, vimentin, and muscle-specific actin. In contrast to dermatofibrosarcoma protuberans, dermatofibromas are negative for S-100 and CD34.[3]

Underlying Diseases

Multiple dermatofibromas have been associated with altered humoral and/or cellular immune system,[10] including systemic lupus erythematosus, Sjogren's syndrome, HIV, leukemia, myasthenia gravis, pemphigus vulgaris, ulcerative colitis and iatrogenic immunosuppression. Immunosuppressive therapy with systemic glucocorticosteroids, azathioprine, cyclophosphamide or alpha-interferon can induce the formation of MEDF.

Several reports have described the development of MEDF in patients with systemic lupus erythematosus on immunosuppressive therapy. Massone et al reported a 46 year-old female with SLE who developed 16 dermatofibromas while on prednisone 5 mg/day.[11] Niyama et al reported MEDF in a 48 year-old female with SLE.[5] She was treated with prednisolone 40 mg daily and azathioprine 150 mg daily for many years. Lin et al reported 2 African-American patients who developed MEDF before being either diagnosed with or treated for SLE.[12] One patient who developed MEDF had both SLE and Sjogren's syndrome. Newman and Walter reported MEDF in 3 female patients with SLE who were treated with prednisone, azathioprine, or both.[13] Sharata et al reported an unusual case where a 38 year-old African-American female with SLE who was taking prednisone, azathioprine and hydroxychloroquine. She developed an extraordinary number of dermatofibromas, and continued to develop new lesions many years after the discontinuation of immunosuppressive therapy.[14]

Several have reported MEDF in patients with HIV infection. Ammirati et al reported 3 men in the setting of HIV infection alone who developed MEDF.[15] These patients did not have any pharmacologic immune modulators or other immunosuppression besides the HIV virus. Murphy et al reported MEDF in a patient with the HIV infection and chronic hepatitis B, after receiving alpha-interferon for 3 months.[16] Alpha-interferon exerts a wide range of effects on the production of many cytokines including interleukin 1, interleukin 2 and tumor necrosis factor.[16] It can be speculated that alterations in the normal balance of these factors could lead to abnormal collagen synthesis by fibroblasts, fibrohistiocytic and capillary proliferation resulting in the formation of a dermatofibroma. Armstrong et al described MEDF in a 26 year-old patient with hemophilia B, psoriasis, psoriatic arthritis and HIV infection who received prednisone and UVB phototherapy.[17] Kanitakis et al reported MEDF on the legs and forearms in a 45 year-old male patient with HIV infection and large-cell carcinoma of the lung.[18] Lu et al reported a case of a 33 year-old African-American female with HIV infection and systemic lupus erythematosus in whom 15 dermatofibromas developed while she was receiving systemic corticosteroid therapy.[19]

The only case strongly associated with diabetes mellitus and necrobiosis lipoidica occurred in a 36 year-old Caucasian female.[7] Omulecki et al reported nine giant dermatofibromas in a patient with diabetes mellitus type II and necrobiosis lipoidica, occurring on the back, right hip, palm and both legs. These MEDF were giant because the lesions were large, measuring

Figure 1
Left upper back.

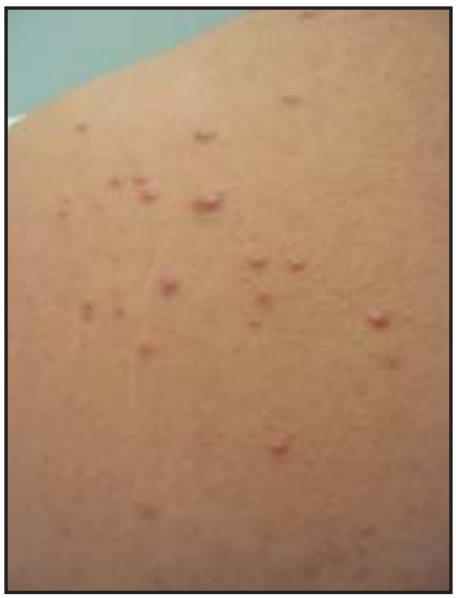


Figure 2
Right upper back.

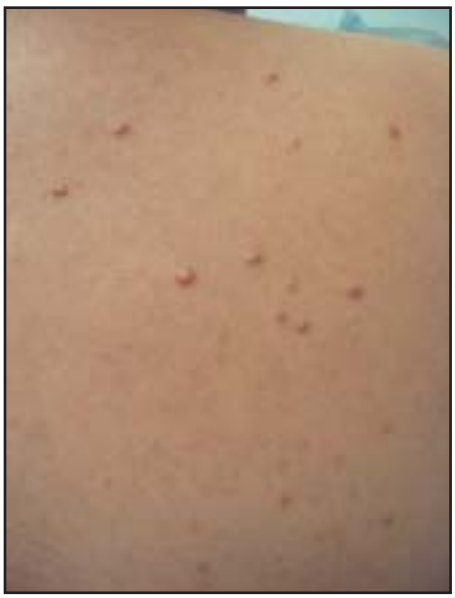


Figure 3
Chest.

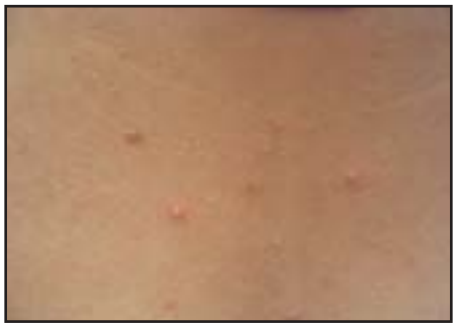


Figure 4
Right upper arm.

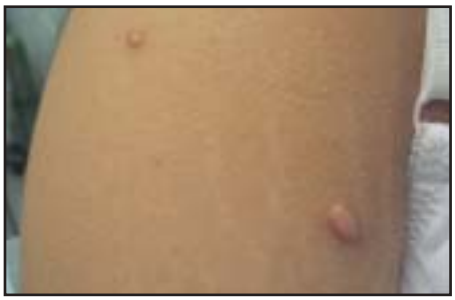


Figure 5
Upper back, before Kenalogin injection.

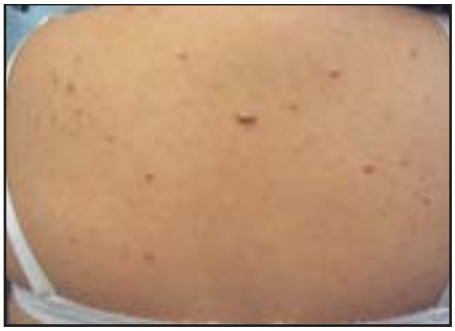
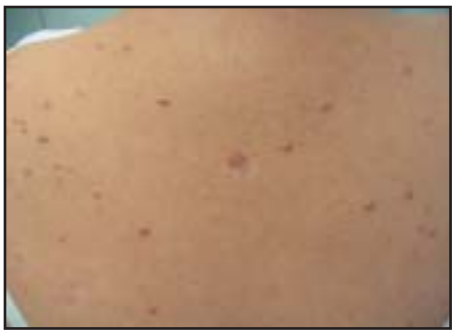


Figure 6
Upper back, after Kenalogin injection.



1.3-5.6 centimeters.[7]

Gelfarb and Hyman reported over 30 cutaneous nodules in a 71 year-old female with hydronephrosis and diabetes, in which a nephrectomy was performed.[20] The lesions were on her legs and thighs.

Marks reported four patients with MEDF who were otherwise well apart from a possible tendency to obesity.[21]

MEDF can occur during pregnancy. Pregnancy modifies the maternal immune system. The exact mechanism is undetermined. It may be through blocking antibodies or via nonspecific local immunosuppression. Stainforth and Goodfield reported that MEDF occurred in a healthy 25 year-old female during her first pregnancy, a state of altered immunity.[22] She presented 4 months postpartum with a history of dermatofibromas during the last few weeks of her pregnancy. One was pruritic and eight were nonpruritic. The MEDF were treated with cryotherapy, which was helpful.

Ashworth et al described a 29 year-old man with severe atopic dermatitis since childhood who routinely used topical corticosteroids.[23] He developed widespread dermatofibromas during a 7-year period. Most patients with atopic dermatitis have altered cell-mediated immunity, with a decreased number of circulating total T cells and suppressor T cells, and therefore an increase ratio of helper to suppressor T cells.[23]

Bargman and Fefferman reported a male patient with myasthenia gravis and thymoma who rapidly developed sixty MEDF on the trunk and arms.[24] They started approximately 4 months after the patient began a regimen of prednisone and cyclophoshamide for myasthenia gravis. What is interesting about this case is that the MEDF began shortly after cyclophosphamide was added to the treatment schedule.

Chang et al reported a 60 year-old male with acute myeloid leukemia who developed MEDF on his neck, trunk, legs, and arms.[25] His chemotherapy consisted of cyclophoshamide and prednisolone.

Cohen reported a 45 year-old male with pemphigus vulgaris and ulcerative colitis, who developed 23 dermatofibromas on his legs.[10] The MEDF occurred 24 years after prednisone therapy was initiated.

Treatment

The treatment of solitary dermatofibroma includes cryotherapy, excision, or no treatment. For multiple dermatofibromas, treatment includes cryotherapy, corticosteroid intralesional injections, and excisions which result in scars.[3] Undisturbed dermatofibromas usually persist, but with time may undergo regression. Our patient was treated with Kenalog® 10 mg/cc intralesional injections, which flattened the dermatofibromas and therefore improved their appearance. Lesions should initially be biopsied or excised to exclude neoplasm, cyst, or melanocytic proliferation.[9]

Conclusion

For the diagnosis of MEDF, it is important to remember that the lesions occur over a short period of time, and not necessarily associated with being greater than 15 lesions. The etiology remains debatable. It may represent a reactive versus a neoplastic process. MEDF may occur in patients with immune-mediated diseases, immunodeficiences, or following immunosuppressive therapy.

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MEDICIS
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LOPROX® SHAMPOO
(ciclopirox) 1%

PEOPLE PAY LOTS OF ATTENTION TO THEIR HEADS.

FORTUNATELY, OUR RESEARCHERS HAVE, TOO.

LOPROX Shampoo (ciclopirox) 1% is the FIRST and ONLY antifungal shampoo indicated specifically for seborrheic dermatitis of the scalp in adults.[1] The most common adverse reactions reported are pruritus, burning, erythema, seborrhea, and rash. See following page for full prescribing information.

Loprox Shampoo. Because all skin has the potential to be beautiful and healthy. Even the skin you can't see.

1. *Physicians' Desk Reference 2003.*

LOPROX
SHAMPOO
(ciclopirox) 1%

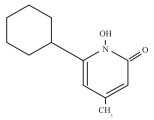
Rx Only
FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE
KEEP OUT OF REACH OF CHILDREN

DESCRIPTION

LOPROX® (ciclopirox) Shampoo 1% contains the synthetic antifungal agent, ciclopirox.

Each gram (equivalent to 0.96 mL) of LOPROX Shampoo contains 10 mg ciclopirox in a shampoo base consisting of Purified Water USP, Sodium Laureth Sulfate, Disodium Laureth Sulfosuccinate, Sodium Chloride USP, and Laureth-2.

LOPROX Shampoo is a colorless, translucent solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, with the empirical formula $C_{12}H_{17}NO_2$ and a molecular weight of 207.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:



CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property for the indication of seborrheic dermatitis is not known. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics and Pharmacodynamics

In a study in patients with seborrheic dermatitis of the scalp, application of 5 mL ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3 ng/mL to 13.2 ng/mL. Total urinary excretion of ciclopirox was less than 0.5% of the administered dose.

CLINICAL STUDIES

In two randomized, double-blind clinical trials, patients 16 years and older with seborrheic dermatitis of the scalp applied LOPROX Shampoo or its vehicle two times per week for 4 weeks. Patients who were immunocompromised, those with psoriasis or atopic dermatitis, women of childbearing potential not using adequate contraception, and pregnant or lactating women were excluded from the clinical studies. An evaluation of the overall status of the seborrheic dermatitis, and the presence and severity of erythema or inflammation, and scaling, was made at week 4, using a scale of 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = pronounced, and 5 = severe. Effective treatment was defined as achieving a score of 0 (or a score of 1 if the baseline score was ≥ 3) simultaneously for status of the seborrheic dermatitis, erythema or inflammation, and scaling at Week 4. Ciclopirox shampoo was shown to be statistically significantly more effective than vehicle in both studies. Efficacy results for the two studies are presented in the following table.

Effective Treatment Rates at Week 4 in Studies 1 and 2

	Ciclopirox Shampoo	Vehicle
Study 1	220/380 (58%)	60/192 (31%)
Study 2	65/250 (26%)	32/249 (13%)

Efficacy for black patients was not demonstrated, although only 53 black patients were enrolled in the two pivotal studies.

Microbiology

Ciclopirox is fungicidal *in vitro* against *Malassezia furfur (Pityrosporum spp.), P. ovale*, and *P. orbiculare*. Ciclopirox acts by chelation of polyvalent cations (Fe^{3+} or Al^{3+}), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

INDICATIONS AND USAGE

LOPROX Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults.

CONTRAINDICATIONS

LOPROX Shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

LOPROX Shampoo is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

PRECAUTIONS

General

If a reaction suggesting sensitivity or irritation should occur with the use of LOPROX Shampoo, treatment should be discontinued and appropriate therapy instituted.
Contact of LOPROX Shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

There is no relevant clinical experience with patients who have a history of immunosuppression (e.g., extensive, persistent, or unusual distribution of dermatomycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (e.g., HIV-infected patients and transplant patients), or who have a diabetic neuropathy.

Information for Patients

The patient should be instructed to:

1. Use LOPROX Shampoo as directed by the physician. Avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water. LOPROX Shampoo is for external use on the scalp only. Do not swallow.
2. Use the medication for seborrheic dermatitis for the full treatment time even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks.
3. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, or oozing) indicative of possible allergic reaction.
4. Not use the medication for any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Long-term animal studies have not been performed to evaluate the carcinogenic potential of LOPROX Shampoo or ciclopirox.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe3+, with and without metabolic activation (negative); gene mutation assays in the HGPRT-test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An in vitro cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

A combined oral fertility and embryofetal developmental study was conducted in rats with ciclopirox olamine. No effect on fertility or reproductive performance was noted at the highest dose tested of 3.85 mg/kg/day ciclopirox (approximately 1.3 times the maximum recommended human dose based on body surface area comparisons).

Pregnancy:

Teratogenic effects: Pregnancy Category B

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits and monkeys, respectively (approximately 13, 42, 54 and 26 times the maximum recommended human dose based on body surface area comparisons, respectively).

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day ciclopirox in rats and rabbits, respectively (approximately 31 and 54 times the maximum recommended human dose based on body surface area comparisons, respectively).

There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. Because animal reproduction studies are not always predictive of human response, LOPROX Shampoo should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LOPROX Shampoo is administered to a nursing woman.

Pediatric Use:

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

Geriatric Use:

In clinical studies, the safety and tolerability of LOPROX Shampoo in the population 65 years and older was comparable to that of younger subjects. Results of the efficacy analysis in those patients 65 years and older showed effectiveness in 25 of 85 (29%) patients treated with LOPROX Shampoo, and in 15 of 61 (25%) patients treated with the vehicle; due to the small sample size, a statistically significant difference was not demonstrated. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity to adverse effects in some older individuals cannot be ruled out.

ADVERSE REACTIONS

In 626 patients treated with LOPROX Shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were increased itching in 1% of patients, and application site reactions, such as burning, erythema, and itching, also in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (26/1738) of patients treated with Loprox Shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse events leading to termination of study medication in either group was seborrhea. In the LOPROX Shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

DOSAGE AND ADMINISTRATION

Wet hair and apply approximately 1 teaspoon (5 mL) of LOPROX Shampoo to the scalp. Up to 2 teaspoons (10 mL) may be used for long hair. Lather and leave on hair and scalp for 3 minutes. A timer may be used. Avoid contact with eyes. Rinse off. Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications.

If a patient with seborrheic dermatitis shows no clinical improvement after 4 weeks of treatment with LOPROX Shampoo, the diagnosis should be reviewed.

HOW SUPPLIED

LOPROX,® (ciclopirox) Shampoo 1% is supplied in 120 mL plastic bottles (NDC 99207-010-10). Discard unused product after initial treatment duration. Store between 15ºC and 30ºC (59ºF and 86ºF).

Manufactured for:
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CANADA

PRESCRIBING INFORMATION AS OF FEBRUARY 2003

Lichen Striatus Following Botulinum Toxin Type A (BOTOX) Injection

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ABSTRACT

Lichen striatus is a self-limited dermatosis seen most commonly on an extremity in a linear distribution. A case is presented of a forty-five year old Caucasian female who developed lichen striatus of the left lower extremity two weeks after receiving a botulinum toxin type A (BOTOX) injection for muscle pain in the left calf.

The typical clinical and histopathological features of lichen striatus are discussed and the proposed etiologies of lichen striatus are explored. The occurrence of lichen striatus in an adult woman after BOTOX injection is examined in the context of current thinking about the etiology of lichen striatus.

Introduction

Lichen striatus is a papulosquamous, self-limited dermatosis. It is seen most often in children but rarely can be seen in adults and is characterized by a distinctive linear eruption following the lines of Blaschko, usually on an extremity.

The histopathology is non-specific although it is frequently characterized by a superficial and deep perivascular, periadnexal and perieccrine lymphocytic infiltrate. Lichen striatus is considered benign and transitory in nature and treatment is usually not necessary.

The pathogenesis of lichen striatus is not completely understood. Proposed mechanisms for the induction of lichen striatus include: an acquired stimulus inducing loss of immunotolerance to abnormal epithelial clones leading to an inflammatory reaction, a post-zygotic somatic mutation of keratinocyte clones causing an autoimmune response, altered T-cell immunity and viral infection. We present the case of an adult female whose lichen striatus may have been induced by *BOTOX* injection.

Case Report

A forty-five year old Caucasian woman presented to our office with a two year history of a painful and pruritic linear eruption over her posterior left lower extremity. The eruption began approximately two weeks after she received a botulinum toxin type A *(BOTOX)* injection (ten units) in the lower left leg for treatment of a painful left gastrocnemius muscle secondary to a motor vehicle accident years prior. Of interest, our patient was also treated with botulinum toxin type A *(BOTOX)* injections (>ninety units) in her neck and shoulders for similar muscular pain. These injections were given concomitantly with the lower extremity injection and again after the eruption began without cutaneous side effects.

The patient's medical history included asthma, seasonal allergies and a motor-vehicle accident in 1998 leading to cervical, lumbar and left lower extremity pain, specifically in the left gastrocnemius muscle. There was no history of atopic dermatitis. Medications taken included ibuprofen, a multivitamin and salmeterol inhaled *(Serevent)*. Review of systems was negative and there were no known drug allergies.

On physical exam there were pink to violaceous flat-topped papules scattered and coalescing in a linear distribution over the posterior left lower leg extending from the popliteal fossa to the medial malleolus (Figure 1 and 2). No nail changes were noted and mucous membranes were normal.

Histopathologic Findings

Two biopsy specimens were obtained from the posterior inferior left leg and histopathology of both showed focal parakeratosis, dyskeratosis, vacuolar alteration and a lymphocytic lichenoid infiltrate at the dermal-epidermal junction. In the dermis, a moderately intense perivascular and perieccrine lymphocytic infiltrate was seen. A PAS stain for fungus was negative and showed no thickening of the basement membrane (Figure 3, 4 and 5).

Topical fluocinonide cream *(Lidex)* was applied twice a day for four weeks with improvement of her pruritus and mild fading of the dermatitis.

Discussion

Lichen striatus is an uncommon, papulosquamous, self-limited dermatosis. It is seen most often in children aged five to fifteen years old, but rarely can be seen in adults. The onset of lesions is usually sudden and progression of the eruption develops over days to weeks.[4] It is characterized by a distinctive linear distribution of discrete to coalescing pink papules following the lines of Blaschko usually on an extremity. It may be seen in one or more continuous or interrupted parallel linear bands and is usually seen unilaterally,

Figure 1
Pink to violaceous flat-topped papules scattered and coalescing in a linear distribution over the posterior left lower leg extending from the popliteal fossa to the medial malleolus.

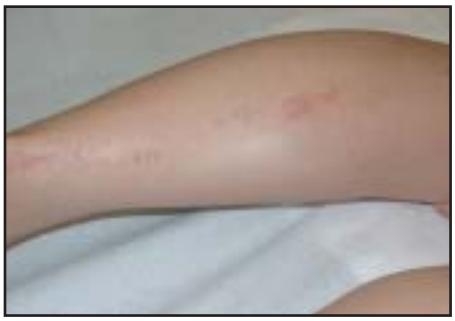

Figure 2
Closer view of flat-topped papules scattered and coalescing in a linear distribution.

however, bilateral distribution has been reported[1,4,6]. Occasionally the eruption may be seen on the neck, face or trunk[2,9]. Distribution in certain areas may show a bizarre pattern of a "V" on the spine, "S" on the abdomen or of an inverted "U" from the breast area to the upper arm[1,12].

When lichen striatus affects an extremity it may extend the entire length of the limb to involve the digits and uncommonly the nails. Nail changes include longitudinal ridging, splitting and nailbed thinning due to inflammation in the nail matrix resulting in a localized defect in the nail plate. Such involvement may occur before, after or

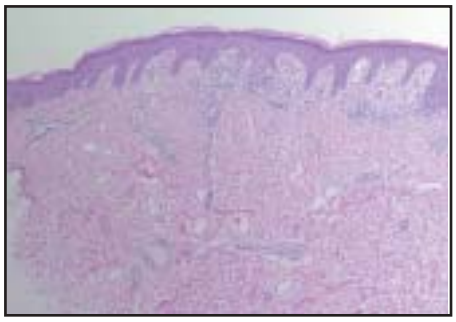

Figure 3
Focal parakeratosis, dyskeratosis, vacuolar alteration and a lymphocytic lichenoid infiltrate at the dermal-epidermal junction.

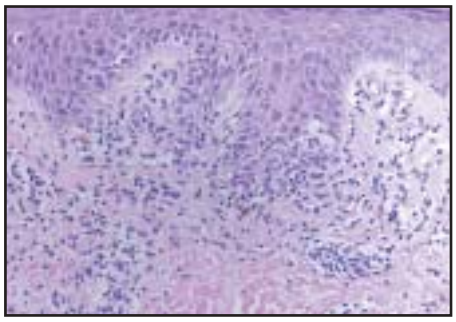

Figure 4
A moderately intense perivascular and perieccrine lymphocytic infiltrate is seen.

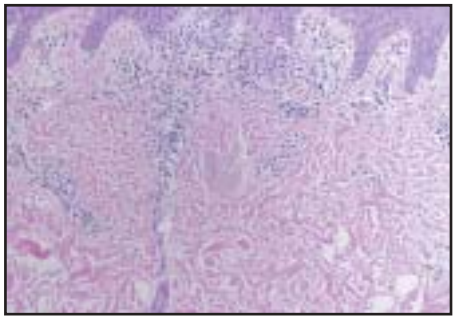

Figure 5
Closer view of the moderately intense perivascular and perieccrine lymphocytic infiltrate.

simultaneously with the cutaneous eruption and nail involvement alone may be the only manifestation of LS.[8] When lichen striatus is limited to the nail, a nail biopsy will show histologic changes similar to those of cutaneous lichen striatus. The presence of such nail involvement may signal a longer course but the nail changes will usually resolve without deformity in six months to more than five years without treatment[8,10].

Lichen striatus is more commonly seen in females than males with a 2:1 ratio and has been reported to involve the left side of the body more than the right[4,6,17]. Generally, lichen striatus is asymptomatic but may be pruritic. Active lesions may last for months with spontaneous resolution usually within one year without scarring. Residual post inflammatory hyperpigmentation may result; however, hypopigmentation may be more common and persist for months to years especially in darker skinned individuals[4,9].

In adults, the clinical presentation of lichen striatus is often much different than in children. The dermatosis is usually more extensive and commonly pruritic. The area appears more inflammatory and vesicles may or may not be present.[16] The terms 'adult blaschkitis', 'acquired relapsing self-healing Blaschko dermatitis', 'acquired Blaschko dermatitis' and 'Blaschko linear acquired inflammatory skin eruption' (BLAISE) have been used to describe an adult form of lichen striatus[6,9,12]. However, in a literature review by Hofer it was concluded that clinical or morphological differences between lichen striatus and adult blaschkitis do not exist[6].

The pathogenesis of lichen striatus is not completely understood. Genetic, infectious and environmental factors have each been considered to play a role. Initially the linearity of the lesions led to a suspicion of nerve, blood vessel or lymphatic involvement. Later the eruption was shown to correspond to the pattern of Blaschko's lines which do not follow any known vascular or neural anatomy but correlate to the pattern of cell migration during embryogenesis.[17] It has been postulated that an acquired stimulus induces a loss of immunotolerance to embryonically abnormal epithelial clones leading to a T-cell mediated inflammatory reaction[16]. More specifically, it is thought that during fetal development, a subpopulation of mutated epithelial cells migrate to areas of the integument along the lines of Blaschko and are believed to acquire distinct qualities allowing certain dermatoses to occur exclusively along these lines[5]. It is via cytotoxic lymphocytes that these mutated keratinocytes are eliminated. This hypothesis has been corroborated by some authors using immunohistochemisty showing scattered CD8+ intraepidermal T lymphocytes around necrotic keratinocytes in the epidermis[17]. Another hypothesis includes a post-zygotic somatic mutation of a keratinocyte clone leading to an autoimmune host response[6].

Several other acquired conditions such as graft-versus-host disease, vitiligo, lupus erythematosus, and fixed drug eruption occur in the distribution of Blaschko lines and may have similar underlying mechanisms of cutaneous lesion development. Immunologic tolerance to an abnormal clone of cells along the lines of Blaschko may have developed early in fetal life and donor lymphocytes, autoimmune disease or external agents respectively may cause recognition of these cells and induce a cytotoxic reaction to eliminate the mutated cells.[9]

One case in the literature reports the occurrence of lichen striatus on the shoulder and forearm in a seventy day old female two weeks after receiving BCG (Bacille Calmette-Guérin) vaccination in the ipsilateral shoulder. A linear eruption developed at the site of injection, posterior and distal to it. The vaccine was cited as a possible precipitating factor via an immune potentiating effect and activation of macrophages which attack clonal melanoblasts.[7] Lichen striatus has also been reported in an adult male with an eight year history of psoriasis after his third treatment with ultraviolet-B phototherapy. This may have been coincidental since the patient's psoriasis had progressed just prior to the onset of lichen striatus. However, the authors raise the possibility of an abnormal immune status associated with psoriasis and facilitation of the eruption through an immunological mechanism[3].

An increased incidence of lichen striatus has been reported in patients with atopic dermatitis. The mechanism is thought to involve altered T-cell immunity predisposing to its induction[10,17]. Viral infection has also been proposed as a possible trigger in genetically predisposed individuals due to the fact that lichen striatus is more common in the spring and summer in addition to simultaneous occurrences in siblings[9,11,15]. One source reported concurrent lichen striatus in two siblings after an episode of flu-like fever while another source reported simultaneous lichen striatus in two unrelated adopted children living in the same household with eight other unaffected children[11,15]. These examples further validate the hypothesis of viral infection as a candidate and emphasize the possible need for genetic predisposition in certain individuals. Some authors believe the rarity of lichen striatus may be due to the infrequent simultaneous occurrence of sporadic events such as viral infection, atopy, and genetic predisposition.[11]

Since lichen striatus is considered a variant of lichen planus, induction via Koebner phenomenon could be considered where physical trauma or injury induces lesions characteristic of the disease. However, an extensive review by Rubin and Stiller report no Koebner phenomena associated with lichen striatus.[13]

The histopathology of lichen striatus has been described as nonspecific. General features include hyperkeratosis and parakeratosis with or without necrotic keratinocytes in the epidermis and vacuolar degeneration of keratinocytes. Mild spongiosis and exocytosis may be seen. A focal or lichenoid infiltrate at the dermal-epidermal junction consisting of lymphocytes and macrophages and a superficial and deep perivascular, periadnexal and

perieccrine lymphocytic infiltrate are considered more specific for lichen striatus. Colloid bodies are present in approximately fifty percent of cases.

It may be difficult to differentiate lichen striatus from other acquired inflammatory dermatoses occurring along the lines of Blaschko. These conditions include linear lichen planus, linear lupus erythematosus, linear psoriasis, linear lichen nitidus, linear lichen simplex chronicus, linear fixed drug eruption, linear porokeratosis, linear vitiligo, and linear scleroderma. Lichen striatus can usually be identified by a combination of clinical history and histopathology of typical lesions. Although difficult, the most important entities to differentiate are linear lichen planus and linear lupus erythematosus. Indeed, there is ongoing debate whether lichen striatus lies in the same spectrum as linear lichen planus.[6]

Clinically, linear lichen planus presents with pruritic violaceous flat-topped papules commonly lasting more than one year with or without mucous membrane involvement. Histologically, linear lichen planus shows acanthosis, focal hypergranulosis, spongiosis, exocytosis, colloid bodies in upper dermis and lower epidermis, vacuolar degeneration, and a band-like inflammatory dermal infiltrate. In lichen striatus the presence of appendageal involvement and a deep perivascular infiltrate help to differentiate it from linear lichen planus although according to one source there may be an overlap between the two entities based on the clinical history and histopathology[14]. Histopathologically similar to lichen striatus, linear lupus erythematosus may also show a superficial band-like infiltrate with a superficial and deep perivascular and periadnexal infiltrate. The findings of a PAS-positive basement membrane and dermal mucin deposition will help to distinguish linear lupus erythematosus from lichen striatus.[17]

Due to the benign and transitory nature of lichen striatus, treatment is usually not necessary and the prognosis is excellent. Patients with lichen striatus can expect a spontaneous resolution usually within one year. Topical corticosteroids have been reported successful for treating symptoms of pruritus, cosmetic concerns or attempting to accelerate the resolution of the eruption; however, they have no influence on the duration of post-inflammatory hypopigmentation[4,9]. Our patient applied a topical corticosteroid, fluocinonide cream *(Lidex)* two times per day with improvement in pruritus and fading of the lesions. One case report in the literature of lichen striatus affecting the face, present for more than one year in a twenty-two year old woman, was successfully treated with topical 0.1% tacrolimus ointment *(Protopic)* once or twice a day. Resolution was noted within six weeks without adverse effects.[2]

Conclusion

To our knowledge, there have been no reports in the literature of lichen striatus associated with *BOTOX* injections. Our case is unique in that lichen striatus of the lower extremity presented two weeks after botulinum toxin type A *(BOTOX)* injection of the gastrocnemius muscle in an adult female. Although a temporal correlation was present between the injection and the onset of lichen striatus, it is not clear if there was a causal relationship. Both coincidence and causal effect must be considered. Similar to the case report of lichen striatus after BCG vaccination, it is unclear if the actual botulinum toxin played a major role in the induction of lichen striatus or if the injection itself was a precipitating factor. We propose that a combination of underlying congenital factors predisposed our patient to the development of a certain dermatosis along the lines of Blaschko and the provoking factor the injection or toxin itself may have led to the development of lichen striatus in this patient.

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Macular Amyloidosis: A Case Report

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ABSTRACT

A 53 year-old female presented to the office with a chronic hyperpigmented pruritic patch previously diagnosed as notalgia paresthetica. Dermatopathological evaluation resulted in the diagnosis of macular amyloidosis. This disease is a form of primary localized cutaneous amyloidosis characteristic of amyloid deposition in the skin without organ involvement. This case study reviews the clinical presentation, histopathology, differential diagnosis, and treatment of the disease.

History

A 53 year-old female presented to the office complaining of an extremely itchy pigmented area covering a large portion of her lower back. She had presented with a similar rash in the same general area five years earlier with the diagnosis of notalgia paresthetica. The history revealed a type II skin phototype. She denied any known trauma to the area. She had been treated with Halobetasol 0.05% cream, Clobetasol 0.05% ointment, Cetirizine 10mg, Triamcinolone 40mg/ml/Betamethasone 6mg/ml IM, and Lac-Hydrin lotion in the past with little improvement. Her past medical history is positive for hypertension and gastroesophageal reflux disease which are controlled by Amlodipine/Benazepril 5mg/10mg and Lansoprazole 30mg, respectively.

Physical Exam

The patient appeared to be well-nourished and in good general health. There is a 16 cm x 11 cm well-demarcated hyperpigmented reticulated patch in the center of her lower back (Figure 1). The surrounding skin appeared normal without erythema. The rest of the physical exam was within normal limits.

Differential Diagnosis

Notalgia paresthetica, post inflammatory hyperpigmentation, erythema ab igna, prurigo pigmentosa, drug induced hyperpigmentation, pityriasis versicolor, phototoxic contact dermatitis, atrophic lichen planus, erythema dyschromicum perstans (ashy dermatosis).[1]

Biopsy Results

A 2 mm punch biopsy was performed to the rash. The biopsy report described the following histology: sections revealed superficial dermal melanophages, scattered necrotic epidermal keratinocytes and intradermal deposition of a pink extracellular material. Crystal violet stain confirmed the presence of amyloid (Figures 2 and 3).

Diagnosis

Macular amyloidosis

Clinical Discussion

Macular amyloidosis is a subtype of primary localized cutaneous amyloidosis (PLCA). This disease is associated with the deposition of amyloid in normal skin without organ deposition or systemic effects.[1] PLCA is classically grouped into macular and lichen amyloidosis. The two forms are identical histologically and can only be differentiated clinically.[3]

Macular amyloidosis is characterized as being a chronic pruritic hyperpigmented macular rash that coalesces into a larger reticulated or rippled patch. The rash usually presents in young adulthood on the extremities or back, with the intrascapular area being the most commonly affected.[1] It is thought that the disease may originate from chronic damage to the epidermis through rubbing and irritation of areas of notalgia paresthetica.[2] Macular amyloidosis has also been called "friction amyloidosis" secondary to its development with the repeated use of nylon towels and backscratchers.[3] The disease affects males and females equally and is most common in patients of Asian, Hispanic and Middle Eastern ancestry.[2] PLCA has been reported to occur along side diseases such as systemic lupus erythematosus, scleroderma, dermatomyositis, and primary biliary cirrhosis.[1] PLCA has been reported as rare familial form in conjunction with Sipple's syndrome, also known as multiple endocrine neoplasia type II.[4]

Lichen amyloidosis is the most common form of PLCA and consists of pruritic normal to hyperpigmented papules that coalesce into rippled appearing plaques usually on the shins or other extensor surfaces of extremities.[1] Lichen amyloidosis can occur with macular amyloidosis in a biphasic form. This combined form is characterized by fine papules that are superimposed on a hyperpigmented back-

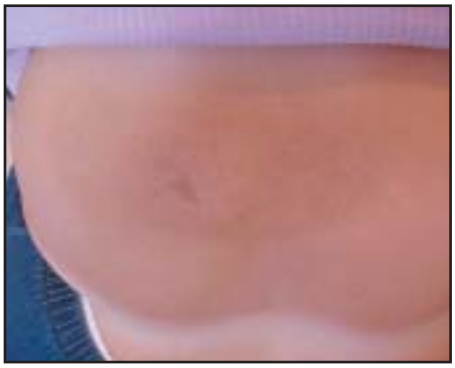

Figure 1
Patient's lower back

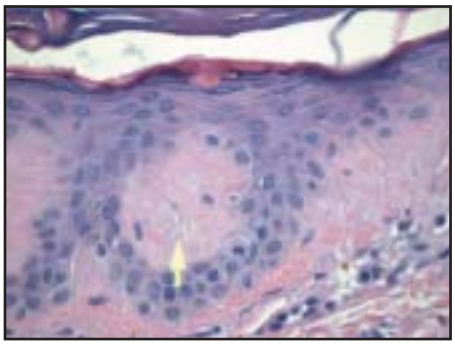

Figure 2
Amyloid deposits in the dermis

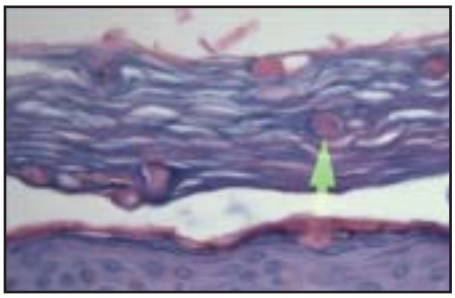

Figure 3
Degenerating keratinocytes within the superficial epidermis

ground.[1] PLCA has also been described in hyperpigmented lichenified ano-sacral variant that often occurs in association with bisphasic amyloidosis of the trunk and extremities.[1]

Histological Appearance

Macular amyloidosis is characterized histologically based on amyloid deposits limited to the papillary dermis (Figure 2). Dermal papillae are expanded by the deposition of amyloid and are seen directly adjacent to the above hyperkeratotic and acantholytic epidermis[1,2] (Figure 3). Additionally, classic findings include melanin deposits within the amyloid, and a perivascular lymphohistiocytic infiltrate.[2, 1]

There are many different stains that can be used to identify amyloid. The classic for amyloidosis is congo red, which has a reddish-orange appearance under light microscopy and an apple green birefringence under polarized light.[1] Additionally, stains such as crystal violet, periodic acid-Schiff (PAS), thioflavin T, anti-keratin antibodies, and various other immunohistochemical stains can be used to detect amyloid deposition.[2]

Histopathology

The exact pathology of PLCA is not known. The cause is likely multifactorial, consisiting of environmental factors and genetic predisposition.[1] As noted previously, it is postulated that chronic local injury to the epidermis causes damage to epidermal keratinocytes[2] (Figure 3). These damaged keratinocytes begin to slowly degenerate and are ejected into the underlying dermis.[3] The tonofilaments within these dermal degenerating keratinocytes are recognized as foreign by the cells own lysosomes.[3] The end result is digestion and conversion of tonofilaments to amyloid with subsequent deposition in the dermis.[1,3] A second theory suggests that the damaged keratinocytes in the dermis are converted by histiocytes and fibroblasts into amyloid material.[1] A third theory proposes that amyloid protein precursors are produced by basal keratincoytes and are deposited at the epidermo-dermal interface.[1] This hypothesis is supported by the findings of type IV collagen and laminin within the amyloid deposits. [1]

Treatment

There are no known effective treatments of macular or lichen amyloidosis. Current treatment is aimed at alleviating the pruritic symptoms of PLCA. The discontinuation of aggravating factors such as chronic rubbing and itching of the area can provide symptomatic relief. Medications such as potent topical corticosteroids, immunomodulators, UVB phototherapy, systemic retinoids, dermabrasion, CO2 laser therapy, topical dimethyl sulfoxide, and cyclosporine have shown only mild efficacy in treatment of the disease.[4]

Acknowledgements

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A Clinical Survey Of Pediatric Skin Diseases In Nicaragua With A Focus On Pediculosis Capitus

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ABSTRACT

BACKGROUND

Information on the prevalence of notable dermatological conditions, with a focus on pediculosis capitis, will be presented.

METHODS

One hundred sixty-three children (several months to 13 years old) were examined in their underclothes from head to toe for any skin conditions. The study was conducted in a primary school in Managua, Nicaragua.

RESULTS

Dermatological examination of these children showed that Pediculus capitis (25.76%), miliaria rubra (6.13%) and cafe au lait spots (5.5%) were the most common. Eleven-year-old children had the highest percentage of head lice (62.5%), followed by nine-year olds (33.3%). Head lice infestation was more common in girls (78.6%) than boys (21.4%).

CONCLUSIONS

There is a high prevalence of pediculosis capitis in this primary school in Nicaragua, affecting girls more than boys. There's a need for an effective prevention and treatment strategy for these skin conditions that has to be balanced with the limited health resources available.

Little is known about the prevalence and morbidity of pediatric skin diseases throughout Latin America. There are few detailed studies that record clinical field surveys of skin problems in this area. The availability of information on specific skin diseases in Nicaragua is even more limited. We intend to present information gleaned from our own study of school children in Nicaragua on two distinct observations: the witnessed high prevalence of head lice, and the presence of other notable dermatological issues.

Background

Etiologic Agent

The etiologic agent responsible for head lice is an arthropod of the insect class, *Pediculus humanus capitis*.[1-10] Figure 1 depicts a typical head louse. This insect belongs to the Pteriogotes group of the Anoplura order.[9] Head lice can be differentiated from *Pediculus corporis* or body lice. Although both belong to the same species and are morphologically similar, genetic studies show significant differences. Comparison of gene sequences from cytochrome oxidase I (COI) mitochondrial DNA reveals that head and body lice do not represent reciprocally monophyletic lineages and are conspecific.[11]

Head lice are exquisitely adapted to survive on their human host, specifically on the scalp and neck hairs. This successful adaptation becomes apparent in the fact that head lice infestation has been documented for centuries. Even prehistoric mummies buried in Egypt 5000 years ago were found to harbor preserved head lice.[12]

The life cycle of a head louse begins as an egg, a tiny whitish to semi-translucent object that adheres strongly to human hair.[13-15] Figure 2 shows an unhatched egg case or nit adhering to a hair shaft. The nymph hatches from its egg within 6-7 days and become sexually mature 9-12 days later. During its 30-day lifespan, an inseminated female louse lays about 6 eggs daily. If no treatment is given, the cycle repeats itself every three weeks.

The head louse derives its nutrients by sucking blood and simultaneously releasing its saliva into its host. This can cause scalp itching, secondary bacterial skin infections and general malaise.[16]

Transmission

Head lice are transmitted by direct head to head contact and possibly by fomite transmission. Canyon, Speare and Muller investigated the spatial and kinetic factors influencing the dynamics of this hair-to-hair transfer by positioning freshly caught lice on a stationary or mobile hair in multiple angles: dorsally, laterally and ventrally.[12] The highest transfer proportion was 85% when the presented hair was slowly moving laterally (4 m/min) in a parallel tail-to-head orientation.[12] There are other proposed indirect mechanisms of head lice transmission such as sharing items such as hairbrushes, caps or pillows but evidence-based studies on these mechanisms are lacking. An adult louse cannot survive for more than 55 hours away from its food source but the survival rate of viable nits still attached to the hair shaft but dislodged from the scalp is unclear.[16]

Figure 1
The Head Louse: Pediculus humanus capitis

Figure 2
An unhatched Nit (Egg Case) adhering on a hair shaft

Figure 3 - Gender and Age Distribution

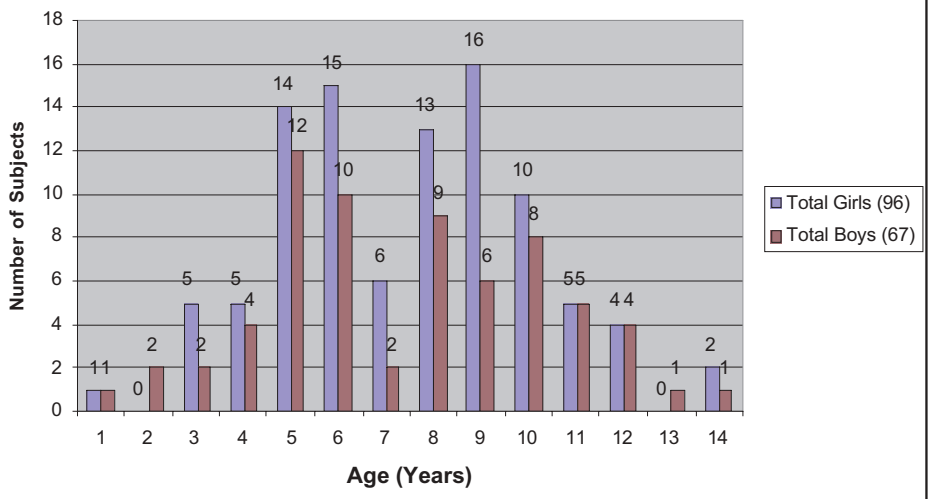
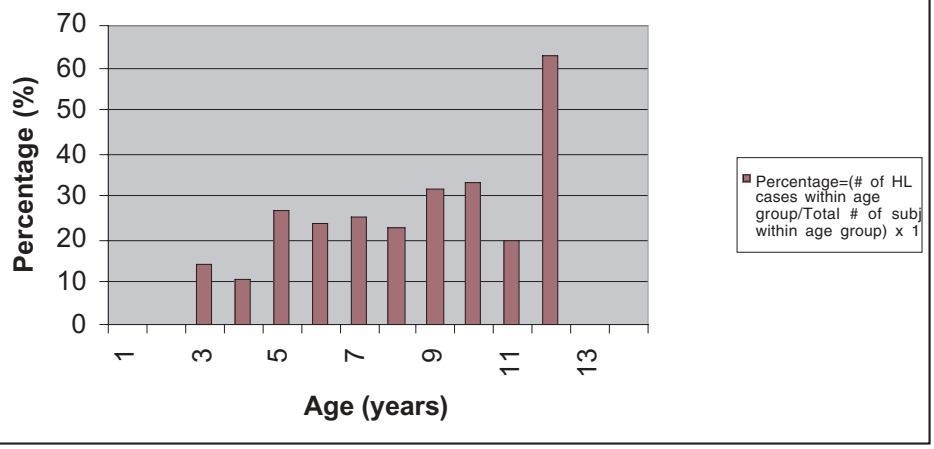


Figure 4 - Distribution of Head Lice within Different Age Groups



Prevalence

Head lice infestation is a worldwide problem, although the infestation rates may be variable.[1-9] Although finding nits is evidence of past infestation, it is not a stand-alone diagnostic measure of current infection. The gold standard for diagnosing head lice is finding a live louse on the person's head. Active infestation is defined as the presence of lice or viable eggs on the hair shaft. In the United States, approximately 6 to 12 million children between 3 and 12 years of age are infested with head lice each year.

Head lice infestation was found in many other parts of the world as well, independent of socioeconomic status. In rural Ethiopia, the prevalence of skin diseases was 49.2% in children, 58% of whom had head lice.[1] In other studies, head lice prevalence figures in children were similar: Istanbul, 20.16% (1-6 year olds) and 26.98% (7-14 year olds);[2] Wales, 4.1%;[4] Turkey 9.42%;[5] northern Jordan 13.4%.[6] In Australia, 21% of the 456 pupils who participated in the survey had active infestation.[7] Similarly, in a study in Israel, 11.2% of the children were infested with living lice and eggs while 23.4% had nits only.[3] Interestingly and inexplicably, a dermatological study of children and adolescents in a student health service center in Hong Kong reported no incidence of head lice infestation at all.[17]

A cross-sectional survey of three primary schools in Guerrero, Mexico reported a prevalence of head lice infestation ranging from 18 to 33%.[8] An even higher infestation rate was found in Argentina. In a primary school in Buenos Aires, the endemic parasitosis had a prevalence of 81.5%.[9]

Only one study reported the prevalence of head lice in Nicaragua. A clinical survey of skin diseases conducted from 1972-73 reported a pediculosis infestation of 1.7% (out of 230 subjects) in the urban regions and 0.4% (out of 458 subjects) in the rural areas.[10] There are no known current studies being conducted.

In the light of not having current studies to draw upon, we elected to undertake our own study. We will provide data on the epidemiology of head lice in a small school in Nicaragua and comment on possible treatment and control strategies. We will also present other less prevalent dermatological findings acquired during the clinical survey.

Methods

Background

Nicaragua is a small country in Latin America with 2 primary seasons: hot/dry and rainy/wet. The country has a total population of over 5 million people, mostly "mestizo", a combination of Spanish and Indian ethnicities. This country has an annual population growth rate of 2.9% (1991-2001) with a gross domestic product (GDP) per capita of USD $2,479.18. The total health expenditure in 2000 as a percentage of the GDP was 4.4%. The government subsidized 51.7% of the total health care expenditure while the private sector accounted for 48.3%, of which 45.4% were out-of-pocket payment sources.[18]

Subjects

One hundred sixty-three children with an age range of several months to 13 years old participated in this study. In March 2003, 23 medical students from the University of Miami School of Medicine, together with three volunteer physicians (an internist, pediatrician and dermatologist), provided free health services on a medical mission trip to Nicaragua. The study was conducted at La Escuela Evangelica Canaan, a small school in cuidad Santiago, Managua. The school provides Christian and health education for preschool children and primary education (1st to 6th grade) to children between 5 and 14 years old. Prior to our arrival, the school principal disseminated information to parents on these available health screenings/services. Nearly the whole school showed, giving us enough subjects to conduct the survey.

Physical Examination

Children were screened in natural lighting in one of the classrooms. They were examined in their underclothes from

Table 1 – Clinical Survey of Skin Diseases

DISEASE	# OF CASES	PT PREVALENCE (%)
INFECTIOUS DISEASES		
Pediculosis capitis	42	25.76
Tinea pedis	4	2.50
Pitted keratolysis	3	1.84
Onychomycosis	2	1.23
Molluscum contagiosum	1	0.61
Pityriasis versicolor	1	0.61
DERMATITIS, ECZEMA & RELATED		
Atopic dermatitis	2	1.23
Seborrheic dermatitis	2	1.23
PAPULOSQUAMOUS & GRANULOMATOUS DISORDERS OF THE SKIN		
Lichen nitidis	2	1.23
Juvenille xanthogranuloma	1	0.61
DISORDERS OF THE DERMIS & SUBCUTANEOUS TISSUE		
Striae	2	1.23
NEVI		
Nevus, congenital pigmented	2	1.23
Epidermal nevus	1	0.61
Telangiectatic nevus	1	0.61
OTHERS		
Millaria rubra	10	6.13
Caf au lait	9	5.60
Friction keratosis	1	0.61
Acanthosis nigricans	1	0.61
Any skin condition	**68**	**41.72**
Only one skin condition	**60**	**36.81**
Two or more skin conditions	**8**	**4.91**

** Classification modified from the British Association of Dermatologists Index*

Table 2 – Distribution of Head Lice by Gender

	BOYS	GIRLS
Total Subjects (163)	**67**	**96**
Total # of HL Cases (42)	**9**	**33**
Total # of HL cases/Total Subjects (42/163=25.76%)	**13.4% (9/67)**	**34.4% (33/96)**
Total # HL Cases per gender/Total # of HL Cases	**21.4% (9/42)**	**78.6% (33/42)**

head to toe for any skin conditions. Genitalia were not examined. One dermatologist, assisted by two medical students, performed the examinations. Work was done in the school where sophisticated laboratory equipment was unavailable. Diagnoses were made based upon clinical judgment and the aid of a magnifying eyepiece and a light microscope. Each child's name, age, sex, extent of education and diagnoses were recorded in a notebook. Typical mosquito bites were not recorded except when the child complained of them and/or requested treatment. Also noncongenital melanocytic nevi were not noted since almost all children had a few. Focus was made on the detection of head lice. Careful attention was paid to differentiate nits from hair casts (muffs), debris, dandruff, and hair shaft abnormalities.

Results

Table 1 is an overview of skin diseases observed during our survey in descending prevalence by category. Dermatological examination of these children showed that *Pediculosis capitis* (25.76%) was the most common, followed by miliaria rubra (6.13%) and cafe au lait spots (5.5%). The point prevalence of any skin condition in this survey is high (41.7%). Only a single skin condition was present in 36.8% (60/163) of the children while 4.9% (8/163) had 2 or more skin conditions.

There were 163 children examined, of which 67 (41%) were boys and 96 (59%) were girls. Figure 3 presents the gender and age distribution of the children who participated in the study. The mean age was 6.46 years old with a standard deviation of 2.72.

Figure 4 presents the distribution of children with active infestation (referring to the presence of lice and viable eggs) sorted by age group. Results show the variability in the number of cases of head lice within different age groups.

Figure 4 also takes into account the distribution of children with head lice to the number of total subjects in the study within that age group. Eleven-year-old children had the highest percentage of head lice at 62.5% (5 out of 8 children),

Drug List

Generic Names	Brand Names
Malathion	Ovide lotion 0.5% (0.5% malathion) [Medicis, Phoenix, AZ]
Pyrethrin product with piperonyl butoxide	A-200 shampoo [Hogill Pharmaceutical Corp, Purchase, NY] RID [Bayer, Morristown, NJ]
Permethrin (1%)	Nix, Pfizer Consumer Health Care Group, New York, NY]
Lindane (1%)	Kwell [Reed & Carnick, Jersey City, NJ]
Carbaryl (1-naphthyl N-methylcarbamate)	Sevin®, Chipco®
Cotrimoxazole	Septra [GlaxoSmithKline, Middlesex, United Kingdom] Bactrim [Roche Laboratories, Nutley, NJ]
Ivermectin	Stromectal [Merck & Co., West Point, PA]

followed by nine-year olds at 33.3% (6 out of 18 children). No evidence of head lice was found in children under 2 years of age and those 12 years or older.

Table 2 presents the distribution of head lice infestation by gender. Head lice infestation was more common in girls than boys. Evidence of active infestation was 78.6% and 21.4% respectively. However, since there were unequal number of girls and boys in the study, this was also taken into consideration. Of the 96 girls in the study, 34.4% had evidence of active infestation whereas only 13.4% of the boys (67 in total) did.

Discussion

Head lice infestation is a prevalent problem in this primary school in Nicaragua and an effective strategy for its management and control is necessary. In keeping with other developing countries where limited family income needs to be allocated toward health services, an additional challenge lies between provision of and demand for treatment.[19]

Treatment Strategies

There are three basic treatment methods described in the literature: use of pediculicidal agents, oral pharmacological therapy and wet combing.[16] Combination of all three has also been considered.

Pediculicides

The choice of a pediculicide can be challenged by widespread insecticide resistance.[20-22] In a comparative in vitro pediculicidal efficacy study conducted in a resistant head lice population in Panama, Meinking, Entzel, and Villar ranked the order of effectiveness of various products by observing the percentage of dead lice at regular intervals.[21] Two prescription products, 0.5% malathion (Ovide [Medicis, Phoenix, AZ]) and 1% lindane (Kwell [Reed & Carnick, Jersey City, NJ]), as well as three over the counter (OTC) preparations were used. The OTC products tested consisted of two pyrethrin preparations synergized with piperonyl butoxide: A-200 shampoo [Hogill Pharmaceutical Corp, Purchase, NY] and RID [Bayer, Morristown, NJ] and permethrin 1% (Nix [Pfizer Consumer Health Care Group, New York, NY]). Continuous exposure time ranged from 5 minutes to 3 hours. Ovide was the fastest, killing 88% of the lice at 10 minutes, 100% at 20 minutes.[21] Ovide consists of 0.5% malathion, an organophosphate, with high ovicidal activity. This product is highly flammable due to its high alcohol content and presents with a high risk of respiratory complications if ingested by accident. In decreasing order of effectiveness following ovide were A-200 shampoo, undiluted Nix, diluted Nix, RID and 1% lindane shampoo.[21] Pyrethrins are derived from natural plant extracts and have a low toxicity in humans but may cause allergic reactions. Permethrin is a synthetic pyrethroid and has an even lower mammalian toxicity and do not cause plant allergies. Lindane is an organochloride with reported harmful side effects such as seizures and central nervous system toxicity.

Oral Agents

Oral pharmacological agents include cotrimoxazole and ivermectin.[23-24] Cotrimoxazole is an antibiotic containing sulfamethoxazole and trimethoprim. This antibiotic is theorized to be directly toxic to the louse. Rare potential side effects include severe allergic reactions (Stevens-Johnson syndrome).[24] Ivermectin, an antihelmintic agent, has been shown to have some activity against head lice. However, younger children may be at a higher risk for blockade of essential neural transmission if this drug passes through the blood-brain barrier.[24]

Potential toxicities and side effects need to be always considered in choosing the appropriate pediculicide or oral pharmacologic agent. Another important point to consider is whether these studies on pediculicide efficacy and resistance conducted in industrialized nations are equally applicable to developing countries such as Nicaragua.

Manual removal and use of occlusive agents

Mechanical removal of head lice by wet combing is a treatment option, which removes the complication of drug resistance and potential toxicities that may accompany pediculicide use. Also referred to as “bug-busting”, this method requires the systematic fine-tooth combing of hair that’s been made wet by the use of a lubricant such as olive oil or hair conditioner.[4,16,25-26] Other lubricating agents include petrolatum, mayonnaise and other essential oils such as those from the leaves of *Lippia multiflora*.[27] Use of these agents were found more effective when used in an enclosed system to suffocate the lice.[23,27] Further data are needed to fully assess the safety and efficacy of these alternative therapies.

Eradication of infestation by wet combing is explained by correlation with the lice’s life cycle. Because newly hatched lice remain on its host within 7 days and do not become sexually mature until 9-12 days later, one can theoretically eradicate the infestation by removing all the lice as they hatch and ensuring that none reach maturity to lay a new generation of eggs.[4,16] Wet combing treatment is repeated every 3-4 days for several

weeks, extending the course of treatment if an adult louse is found. In a study conducted in UK, this method cured 38% of the children, half the cure rate for malathion (78%).[4] Both approaches were carried out by the children's parents after being trained by investigators.

Control Strategies

Lice and school policy

Variable opinions exist as to whether imposition of a "no-nit policy" in schools is justified or unnecessary. The no-nit policy was developed to decrease lice transmission to other students but concerns arose due to increased costs brought about by student absenteeism, loss of work hours for the parents and treatment interventions. There is a lack of general agreement on the infestation criteria and an added uncertainty on the likelihood of viable nits developing into lice. However, in a prospective cohort study, Williams, et al found that those having more than 5 nits within one-fourth inch from the scalp were at least four times more likely to convert from having nits alone to active infestation with living lice than those with a lesser number of nits. Only 18% of children with nits alone developed lice over the next two weeks.[28]

Intervention Program

Evaluation and treatment of head lice should include an intervention program that provides education to family members, teachers and other school personnel, enhancing dissemination of information regarding head lice, improve parent adherence to proper treatment instructions and help implement possible prevention strategies[8,28-30]

Nicaragua does not have a "no-nit" policy and no current educational program exists in this nation. A national educational campaign is necessary. The school administrator was provided with the results of the screen and the children's respective parents were subsequently notified. Further studies are needed to determine the response to treatment and to investigate the recurrence rate of head lice infestation in this population. Because fomite transmission may occur via sharing of items such as hairbrushes and clothing or increased by crowding and co-dwelling with close head contact, future studies that contain information on the children's family demographics, including the number of siblings with concurrent head lice infestation and the classroom assignments versus lice infestation pattern would be useful. This information could not be obtained during the clinical survey.

Conclusions

There is a high prevalence of pediculosis capitis in this primary school in Nicaragua, affecting girls more than boys. The factors that contribute to this skewed gender distribution will need to be further investigated.

There is a need for an effective prevention and treatment strategy for pediculosis capitis and other skin conditions in Nicaragua that has to be balanced with the limited health resources available in this community.

Acknowledgement

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YEARS OF TREATING SEVERE PSORIASIS PROVES

SORIATANE IS FOUNDATION THERAPY

Connetics® presents

SORIATANE® 10 mg 25 mg capsules

acitretin

Flexible

- For initial clearing and long-term maintenance[1,2]
- Compatible with phototherapy[3,4]

Effective

- 52% of patients achieve PASI 75 at 12 weeks (n=104)[1]
- Non-immunosuppressive, non-cytotoxic

Established Safety

- Can reduce phototherapy dosages[3]
- Over 1 million patients treated[1]
- 10-year safety data[5]

Convenient

- Available in 10 and 25 mg capsules
- Cost effective[6]

SORIATANE is indicated for the treatment of severe psoriasis in adults. In females of reproductive potential, SORIATANE should be reserved for nonpregnant patients with severe psoriasis who are unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS: SORIATANE® (acitretin) must not be used by females who are pregnant or who may become pregnant during therapy or at any time for at least 3 years after discontinuation of treatment. SORIATANE also must not be used by females of reproductive potential who may not use 2 effective forms of contraception (birth control) simultaneously for at least 1 month before, during and for at least 3 years after treatment. Two effective forms of contraception (birth control) are to be used simultaneously, even when 1 form is a hormonal contraceptive. Patients should not self-medicate with St. John's Wort because of a possible interaction with hormonal contraceptives. Prescribers must obtain negative results for 2 pregnancy tests before initiating treatment with SORIATANE. The first test is a screening test; the second is a confirmation test done during the first 5 days of the menstrual period immediately preceding SORIATANE therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse. Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment. Females must sign a Patient Information/Consent about the risks of birth defects. Acitretin is a metabolite of etretinate and major fetal abnormalities have been reported with both drugs. Acitretin can interact with ethanol to form etretinate. Therefore, females of reproductive potential must not ingest ethanol during treatment and for 2 months after cessation of treatment. Before prescribing, please see complete pregnancy warning in the accompanying complete product information. Females who have undergone treatment with Tegison® (etretinate) must continue to follow the contraception requirements for Tegison.

Less frequent, but potentially serious, adverse events include hepatotoxicity, pancreatitis, and pseudotumor cerebri (please see Warnings in complete product information), as well as hyperostosis, alteration in lipids and possible cardiovascular effects, and ophthalmologic effects.

Please see brief summary of full prescribing information, including CONTRAINDICATIONS AND WARNINGS, on the adjacent pages.

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Photographs do not represent actual patients.

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SORIATANE® (acitretin)

CAPSULES

Before prescribing, please see complete product information, a summary of which follows:

CONTRAINDICATIONS AND WARNINGS: Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment and for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected. Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification. Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m^2 comparison. Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low-set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae. Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity. *Important Information for Women of Childbearing Potential:* Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments. Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- **Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously). Timing of pregnancy testing throughout the treatment course should be monthly or individualized based on the prescriber's clinical judgment.**
- **Must have selected and have committed to use 2 effective forms of contraception (birth control) simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.**
- **Patients must use 2 effective forms of contraception (birth control) simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a regular basis by the prescriber. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed. Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include diaphragms, latex condoms, and cervical caps; each secondary form must be used with a spermicide. Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[1] Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.* Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).**
- **Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, and about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.**

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows: Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- **In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.**
- **In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,**
  - **greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean elimination half-life of 120 days.**
  - **greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days.**

  However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin therapy.[2]
- **Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.**
  - **There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred *after* the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.**
  - **There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).**
  - **Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer marketed in the U.S.; for information, call Roche at 1-800-526-6367.**
  - **Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.**

Important Information For Males Taking Soriatane:

- **Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.**
- **Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is 1/200,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows: There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome)[3]:**

Timing of paternal acitretin treatment relative to conception	Delivery of healthy neonate	Spontaneous abortion	Induced abortion	Total
At time of conception	5*	5	1	11
Discontinued ~ 4 weeks prior	0	0	1**	1
Discontinued ~ 6-8 months prior	0	1	0	1

***Four of 5 cases were prospective**

****With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus)**

For All Patients: A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.

CONTRAINDICATIONS: Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS). Soriatane is contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values. An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with Soriatane is also contraindicated. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated. Soriatane is contraindicated in cases of hypersensitivity to the preparation (acitretin or excipients) or to other retinoids.

WARNINGS (see also boxed CONTRAINDICATIONS AND WARNINGS)

Hepatotoxicity: Of the 525 patients treated in US clinical trials, 2 had clinical jaundice with elevated serum bilirubin and transaminases considered related to Soriatane treatment. Liver function test results in these patients returned to normal after Soriatane was discontinued. Two of the 1289 patients treated in European clinical trials developed biopsy-confirmed toxic hepatitis. A second biopsy in one of these patients revealed nodule formation suggestive of cirrhosis. One patient in a Canadian clinical trial of 63 patients developed a three-fold increase of transaminases. A liver biopsy of this patient showed mild lobular disarray, multifocal hepatocyte loss and mild triaditis of the portal tracts compatible with acute reversible hepatic injury. The patient's transaminase levels returned to normal 2 months after Soriatane was discontinued. The potential of Soriatane therapy to induce hepatotoxicity was prospectively evaluated using liver biopsies in an open-label study of 128 patients. Pretreatment and posttreatment biopsies were available for 87 patients. A comparison of liver biopsy findings before and after therapy revealed 49 (58%) patients showed no change, 21 (25%) improved and 14 (17%) patients had a worsening of their liver biopsy status. For 6 patients, the classification changed from class 0 (no pathology) to class I (normal fatty infiltration; nuclear variability and portal inflammation; both mild); for 7 patients, the change was from class I to class II (fatty infiltration, nuclear variability, portal inflammation and focal necrosis; all moderate to severe); and for 1 patient, the change was from class II to class IIIb (fibrosis, moderate to severe). No correlation could be found between liver function test result abnormalities and the change in liver biopsy status, and no cumulative dose relationship was found. Elevations of AST (SGOT), ALT (SGPT), GGT (GGTP) or LDH have occurred in approximately 1 in 3 patients treated with Soriatane. Of the 525 patients treated in clinical trials in the US, treatment was discontinued in 20 (3.8%) due to elevated liver function test results. If hepatotoxicity is suspected during treatment with Soriatane, the drug should be discontinued and the etiology further investigated. Ten of 652 patients treated in US clinical trials of etretinate, of which acitretin is the active metabolite, had clinical or histologic hepatitis considered to be possibly or probably related to etretinate treatment. There have been reports of hepatitis-related deaths worldwide; a few of these patients had received etretinate for a month or less before presenting with hepatic symptoms or signs.

Hyperostosis: In adults receiving long-term treatment with Soriatane, appropriate examinations should be periodically performed in view of possible ossification abnormalities (see ADVERSE REACTIONS). In clinical trials with Soriatane, patients were prospectively evaluated for evidence of development or change in bony abnormalities of the vertebral column, knees and ankles. *Vertebral Results:* Of 380 patients treated with Soriatane, 15% had preexisting abnormalities of the spine which showed new changes or progression of preexisting findings. Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification and narrowing and destruction of a cervical disc space. De novo changes (formation of small spurs) were seen in 3 patients after 1½ to 2½ years. *Skeletal Appendicular Results:* Six of 128 patients treated with Soriatane showed abnormalities in the knees and ankles before treatment that progressed during treatment. In 5, these changes involved the formation of additional spurs or enlargement of existing spurs. The sixth patient had degenerative joint disease which worsened. No patients developed spurs de novo. Clinical complaints did not predict radiographic changes. ***Lipids and Possible Cardiovascular Effects:*** Blood lipid determinations should be performed before Soriatane is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% of patients. These effects of Soriatane were generally reversible upon cessation of therapy. Patients with an increased tendency to develop hypertriglyceridemia included those with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions. Because of the risk of hypertriglyceridemia, serum lipids must be more closely monitored in high-risk patients and during long-term treatment. Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status. Although no causal relationship has been established, there have been postmarketing reports of acute myocardial infarction or thromboembolic events in patients on Soriatane therapy. In addition, elevation of serum triglycerides to greater than 800 mg/dL has been associated with fatal fulminant pancreatitis. Therefore, dietary modifications, reduction in Soriatane dose, or drug therapy should be employed to control significant elevations of triglycerides. If, despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of Soriatane should be considered. ***Ophthalmologic Effects:*** The eyes and vision of 329 patients treated with Soriatane were examined by ophthalmologists. The findings included dry eyes (23%), irritation of eyes (9%) and brow and lash loss (5%). The following were reported in less than 5% of patients: Bell's Palsy, blepharitis and/or crusting of lids, blurred vision,

conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties and subepithelial corneal lesions. Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation. ***Pancreatitis:*** Lipid elevations occur in 25% to 50% of patients treated with Soriatane. Triglyceride increases sufficient to be associated with pancreatitis are much less common, although fatal fulminant pancreatitis has been reported. There have been rare reports of pancreatitis during Soriatane therapy in the absence of hypertriglyceridemia. ***Pseudotumor Cerebri:*** Soriatane and other retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Some of these events involved concomitant use of isotretinoin and tetracyclines. However, the event seen in a single Soriatane patient was not associated with tetracyline use. Early signs and symptoms include papilledema, headache, nausea and vomiting and visual disturbances. Patients with these signs and symptoms should be examined for papilledema and, if present, should discontinue Soriatane immediately and be referred for neurological evaluation and care. Since both Soriatane and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS). **PRECAUTIONS:** ***Information for Patients:*** Patients should be instructed to read the Medication Guide supplied as required by law when Soriatane is dispensed. ***Females of reproductive potential:*** **Soriatane can cause severe birth defects.** Female patients must not be pregnant when Soriatane therapy is initiated, they must not become pregnant while taking Soriatane, and for at least 3 years after stopping Soriatane (see boxed CONTRAINDICATIONS AND WARNINGS). **Females of reproductive potential should also be advised that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued.** This allows for elimination of the acitretin which can be converted to etretinate in the presence of alcohol. Female patients should be advised that any method of birth control can fail, including tubal ligation, and that microdosed progestin "minipill" preparations are *not* recommended for use with Soriatane. Female patients should sign a consent form prior to beginning Soriatane therapy (see boxed CONTRAINDICATIONS AND WARNINGS). ***Nursing Mothers:*** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. ***All Patients:*** **Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm have been reported.** These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane. Patients should be counseled to stop taking Soriatane and notify their prescriber immediately if they experience psychiatric symptoms. Patients should be advised that a transient worsening of psoriasis is sometimes seen during the initial treatment period. Patients should be advised that they may have to wait 2 to 3 months before they get the full benefit of Soriatane. Decreased night vision has been reported with Soriatane therapy. Patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night. Visual problems should be carefully monitored (see ADVERSE REACTIONS). Patients should be advised that they may experience decreased tolerance to contact lenses during the treatment period and sometimes after treatment has stopped. Patients should not donate blood during and for at least 3 years following therapy because Soriatane can cause birth defects and women of childbearing potential must not receive blood from patients being treated with Soriatane. Because of the relationship of Soriatane to vitamin A, patients should be advised against taking vitamin A supplements in excess of minimum recommended daily allowances to avoid possible additive toxic effects. Patients should avoid the use of sun lamps and excessive exposure to sunlight (non-medical UV exposure) because the effects of UV light are enhanced by retinoids. Patients should be advised that they must not give their Soriatane capsules to any other person. ***For Prescribers: Phototherapy:*** Significantly lower doses of phototherapy are required when Soriatane is used because Soriatane-induced effects on the stratum corneum can increase the risk of erythema (burning). ***Laboratory Tests:*** If significant abnormal laboratory results are obtained, either dosage reduction with careful monitoring or treatment discontinuation is recommended, depending on clinical judgment. *Blood Sugar:* Some patients receiving retinoids have experienced problems with blood sugar control. In addition, new cases of diabetes have been diagnosed during retinoid therapy, including diabetic ketoacidosis. In diabetics, blood-sugar levels should be monitored very carefully. *Lipids:* In clinical studies, the incidence of hypertriglyceridemia was 66%, hypercholesterolemia was 33% and that of decreased HDL was 40%. Pretreatment and follow-up measurements should be obtained under fasting conditions. It is recommended that these tests be performed weekly or every other week until the lipid response to Soriatane has stabilized (see WARNINGS). *Liver Function Tests:* Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. It is recommended that these tests be performed prior to initiation of Soriatane therapy, at 1- to 2-week intervals until stable and thereafter at intervals as clinically indicated (see CONTRAINDICATIONS AND boxed WARNINGS). ***Drug Interactions:*** *Ethanol:* Clinical evidence has shown that etretinate can be formed with concurrent ingestion of acitretin and ethanol (see boxed CONTRAINDICATIONS AND WARNINGS). *Glibenclamide:* In a study of 7 healthy male volunteers, acitretin treatment potentiated the blood glucose lowering effect of glibenclamide (a sulfonylurea similar to chlorpropamide) in 3 of the 7 subjects. Repeating the study with 6 healthy male volunteers in the absence of glibenclamide did not detect an effect of acitretin on glucose tolerance. Careful supervision of diabetic patients under treatment with Soriatane is recommended. *Hormonal Contraceptives:* It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it *has been* established that acitretin interferes with the contraceptive effect of microdosed progestin "minipill" preparations. Microdosed "minipill" progestin preparations are *not* recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy. Methotrexate:* An increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Consequently, the combination of methotrexate with acitretin is also contraindicated (see CONTRAINDICATIONS). *Phenytoin:* If acitretin is given concurrently with phenytoin, the protein binding of phenytoin may be reduced. *Tetracyclines:* Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated (see CONTRAINDICATIONS AND WARNINGS: *Pseudotumor Cerebri*). *Vitamin A and oral retinoids:* Concomitant administration of vitamin A and/or other oral retinoids with acitretin must be avoided because of the risk of hypervitaminosis A. There appears to be no pharmacokinetic interaction between acitretin and cimetidine, digoxin, or glyburide. Investigations into the effect of acitretin on the protein binding of anticoagulants of the coumarin type (warfarin) revealed no interaction. ***Carcinogenesis, Mutagenesis and Impairment of Fertility:*** *Carcinogenesis:* A carcinogenesis study of acitretin in Wistar rats, at doses up to 2 mg/kg/day administered 7 days/week for 104 weeks, has been completed. There were no neoplastic lesions observed that were considered to have been related to treatment with acitretin. An 80-week carcinogenesis study in mice has been completed with etretinate, the ethyl ester of acitretin. Blood level data obtained during this study demonstrated that etretinate was metabolized to acitretin and that blood levels of acitretin exceeded those of etretinate at all times studied. In the etretinate study, an increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas at several different sites) was noted in male, but not female, mice at doses approximately one-half the maximum recommended human therapeutic dose based on a mg/m^2 comparison. *Mutagenesis:* Acitretin was evaluated for mutagenic potential in the Ames test, in the Chinese hamster (V79/HGPRT) assay, in unscheduled DNA synthesis assays using rat hepatocytes and human fibroblasts and in an in vivo mouse micronucleus assay. No evidence of mutagenicity of acitretin was demonstrated in any of these assays. *Impairment of Fertility:* In a fertility study in rats, the fertility of treated animals was not impaired at the highest dosage of acitretin tested, 3 mg/kg/day (approximately one-half the maximum recommended therapeutic dose based on a mg/m^2 comparison). Chronic toxicity studies in dogs revealed testicular changes (reversible mild to moderate spermatogenic arrest and appearance of multinucleated giant cells) in the highest dosage group (50 then 30 mg/kg/day). No decreases in sperm count or concentration and no changes in sperm motility or morphology were noted in 31 men (17 psoriatic patients, 8 patients with disorders of keratinization and 6 healthy volunteers) given 30 to 50 mg/day of acitretin for at least 12 weeks. In these studies, no deleterious effects were seen on either testosterone production, LH or FSH in any of the 31 men.[4-6] No deleterious effects were seen on the hypothalamic-pituitary axis in any of the 18 men where it was measured.[4,5] ***Pregnancy:*** *Teratogenic Effects:* **Pregnancy Category X (see boxed CONTRAINDICATIONS AND WARNINGS).** ***Nursing Mothers:*** Studies on lactating rats have shown that etretinate is excreted in the milk. There is one prospective case report where acitretin is reported to be excreted in human milk. Therefore, nursing mothers should not receive Soriatane prior to or during nursing because of the potential for serious adverse reactions in nursing infants. ***Pediatric Use:*** Safety and effectiveness in pediatric patients have not been established. No clinical studies have been conducted in pediatric patients. Ossification of interosseous ligaments and tendons of the extremities, skeletal hyperostoses, decreases in bone mineral density, and premature epiphyseal closure have been reported in children taking other systemic retinoids, including etretinate, a metabolite of Soriatane. A causal relationship between these effects and Soriatane has not been established. While it is not known that these occurrences are more severe or more frequent in children, there is special concern in pediatric patients because of the implications for growth potential (see WARNINGS: *Hyperostosis*). ***Geriatric Use:*** Clinical studies of Soriatane did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. A two-fold increase in acitretin plasma concentrations was seen in healthy elderly subjects compared with young subjects, although the elimination half-life did not change. **ADVERSE REACTIONS:** During clinical trials with Soriatane, 513/525 (98%) of patients reported a total of 3545 adverse events. One-hundred sixteen patients (22%) left studies prematurely, primarily because of adverse experiences involving the mucous membranes and skin. Three patients died. Two of the deaths were not drug related (pancreatic adenocarcinoma and lung cancer); the other patient died of an acute myocardial infarction, considered remotely related to drug therapy. In clinical trials, Soriatane was associated with elevations in liver function test results or triglyceride levels and hepatitis. ***Postmarketing Reports:*** *Cardiovascular:* Acute myocardial infarction, thromboembolism (see WARNINGS), stroke. *Nervous System:* Myopathy with peripheral neuropathy has been reported during Soriatane therapy. Both conditions improved with discontinuation of the drug. *Psychiatric:* Aggressive feelings, and/or suicidal thoughts have been reported. These events, including self-injurious behavior, have been reported in patients taking other systemically administered retinoids, as well as in patients taking Soriatane. Since other factors may have contributed to these events, it is not known if they are related to Soriatane (see PRECAUTIONS). *Reproductive:* Vulvo-vaginitis due to *Candida albicans. Skin and Appendages:* Thinning of the skin, skin fragility and scaling may occur all over the body, particularly on the palms and soles; nail fragility is frequently observed. Hypervitaminosis A produces a wide spectrum of signs and symptoms primarily of the mucocutaneous, musculoskeletal, hepatic, neuropsychiatric, and central nervous systems. Many of the clinical adverse reactions reported to date with Soriatane administration resemble those of the hypervitaminosis A syndrome. The following information lists by body system and frequency the adverse events reported during clinical trials of 525 patients with psoriasis. **Adverse Events Frequently Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: *CNS:* 10% to 25%: Rigors. *Eye Disorders:* 10% to 25%: Xerophthalmia. *Mucous Membranes:* >75%: Cheilitis; 25% to 50%: Rhinitis; 10% to 25%: Dry mouth, Epistaxis. *Musculoskeletal:* 10% to 25%: Arthralgia, Spinal hyperostosis (progression of existing lesions). *Skin and Appendages:* 50% to 75%: Alopecia, Skin peeling; 25% to 50%: Dry skin, Nail disorder, Pruritus; 10% to 25%: Erythematous rash, Hyperesthesia, Paresthesia, Paronychia, Skin atrophy, Sticky skin. **Adverse Events Less Frequently Reported During Clinical Trials (Some of Which May Bear No Relationship to Therapy) (Percent of Patients Reporting):** BODY SYSTEM: *Body as a Whole:* 1% to 10%: Anorexia, Edema, Fatigue, Hot flashes, Increased appetite; <1%: Alcohol intolerance, Dizziness, Fever, Influenza-like symptoms, Malaise, Moniliasis, Muscle weakness, Weight increase. *Cardiovascular:* 1% to 10%: Flushing; <1%: Chest pain, Cyanosis, Increased bleeding time, Intermittent claudication, Peripheral ischemia. *CNS:* 1% to 10%: Headache, Pain; <1%: Abnormal gait, Migraine, Neuritis, Pseudotumor cerebri (intracranial hypertension). *Eye Disorders:* 1% to 10%: Abnormal/blurred vision, Blepharitis, Conjunctivitis/irritation, Corneal epithelial abnormality, Decreased night vision/night blindness, Eye abnormality, Eye pain, Photophobia; <1%: Abnormal lacrimation, Chalazion, Conjunctival hemorrhage, Corneal ulceration, Diplopia, Ectropion, Itchy eyes and lids, Papilledema, Recurrent sties, Subepithelial corneal lesions. *Gastrointestinal:* 1% to 10%: Abdominal pain, Diarrhea, Nausea, Tongue disorder; <1%: Constipation, Dyspepsia, Esophagitis, Gastritis, Gastroenteritis, Glossitis, Hemorrhoids, Melena, Tenesmus, Tongue ulceration. *Liver and Biliary:* <1%: Hepatic function abnormal, Hepatitis, Jaundice. *Mucous Membranes:* 1% to 10%: Gingival bleeding, Gingivitis, Increased saliva, Stomatitis, Thirst, Ulcerative Stomatitis; <1%: Altered saliva, Anal disorder, Gum hyperplasia, Hemorrhage, Pharyngitis. *Musculoskeletal:* 1% to 10%: Arthritis, Arthrosis, Back pain, Hypertonia, Myalgia, Osteodynia, Peripheral joint Hyperostosis (progression of existing lesions); <1%: Bone disorder, Olecranon bursitis, Spinal hyperostosis (new lesions), Tendonitis. *Psychiatric:* 1% to 10%: Depression, Insomnia, Somnolence; <1%: Anxiety, Dysphonia, Libido decreased, Nervousness. *Reproductive:* <1%: Atrophic vaginitis, Leukorrhea. *Respiratory:* 1% to 10%: Sinusitis; <1%: Coughing, Increased sputum, Laryngitis. *Skin and Appendages:* 1% to 10%: Abnormal skin odor, Abnormal hair texture, Bullous eruption, Cold/clammy skin, Dermatitis, Increased sweating, Infection, Psoriasiform rash, Purpura, Pyogenic granuloma, Rash, Seborrhea, Skin fissures, Skin ulceration, Sunburn; <1%: Acne, Breast pain, Cyst, Eczema, Fungal infection, Furunculosis, Hair discoloration, Herpes simplex, Hyperkeratosis, Hypertrichosis, Hypoesthesia, Impaired healing, Otitis media, Otitis externa, Photosensitivity reaction, Psoriasis aggravated, Scleroderma, Skin nodule, Skin hypertrophy, Skin disorder, Skin irritation, Sweat gland disorder, Urticaria, Verrucae. *Special Senses/Other:* 1% to 10%: Earache, Taste perversion, Tinnitus; <1%: Ceruminosis, Deafness, Taste loss. *Urinary:* <1%: Abnormal urine, Dysuria, Penis disorder. ***Laboratory:*** Soriatane therapy induces changes in liver function tests in a significant number of patients. Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by approximately 1 in 3 patients treated with Soriatane. In most patients, elevations were slight to moderate and returned to normal either during continuation of therapy or after cessation of treatment. In patients receiving Soriatane during clinical trials, 66% and 33% experienced elevation in triglycerides and cholesterol, respectively. Decreased high density lipoproteins (HDL) occurred in 40% (see WARNINGS). Transient, usually reversible elevations of alkaline phosphatase have been observed. The following information lists the laboratory abnormalities reported during clinical trials. **Abnormal Laboratory Test Results Reported During Clinical Trials (Percent of Patients Reporting):** BODY SYSTEM: *Electrolytes:* 10% to 25%: Increased: Phosphorus, Potassium, Sodium; Increased and decreased: Magnesium; 1% to 10%: Decreased: Phosphorus, Potassium, Sodium; Increased and decreased: Calcium, Chloride. *Hematologic:* 25% to 50%: Increased: Reticulocytes; 10% to 25%: Decreased: Hematocrit, Hemoglobin, WBC; Increased: Haptoglobin, Neutrophils, WBC; 1% to 10%: Increased: Bands, Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes; Decreased: Haptoglobin, Lymphocytes, Neutrophils, Reticulocytes; Increased or decreased: Platelets, RBC. *Hepatic:* 25% to 50%: Increased: Cholesterol, LDH, SGOT, SGPT; Decreased: HDL cholesterol; 10% to 25%: Increased: Alkaline phosphatase, Direct bilirubin, GGTP; 1% to 10%: Increased: Globulin, Total bilirubin, Total protein; Increased and decreased: Serum albumin. *Miscellaneous:* 50% to 75%: Increased: Triglycerides; 25% to 50%: Increased: CPK, Fasting blood sugar; 10% to 25%: Decreased: Fasting blood sugar, High occult blood; 1% to 10%: Increased and decreased: Iron. Renal: 10% to 25%: Increased: Uric acid; 1% to 10%: Increased: BUN, Creatinine. *Urinary:* 25% to 50%: WBC in urine; 10% to 25%: Acetonuria, Hematuria, RBC in urine; 1% to 10%: Glycosuria, Proteinuria. **OVERDOSAGE:** In the event of acute overdosage, Soriatane must be withdrawn at once. Symptoms of overdose are identical to acute hypervitaminosis A, ie, headache and vertigo. The acute oral toxicity (LD_{50}) of acitretin in both mice and rats was greater than 4000 mg/kg. In one reported case of overdose, a 32-year-old male with Darier's disease took 21 x 25 mg capsules (525 mg single dose). He vomited several hours later but experienced no other ill effects. All female patients of childbearing potential who have taken an overdose of Soriatane must: 1) Have a pregnancy test at the time of overdose. 2) Be counseled as per the boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS sections regarding birth defects and contraceptive use for at least 3 years duration after the overdose.

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SCURVY:
The Past and the Present
A Case Report and Review

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The history of scurvy is replete with colorful and rich anecdotes and experiments. Scurvy results from vitamin C deficiency due to poor nutrition, systemic disease, malignancy, alcoholism and psychiatric disease. Scurvy, because of its rarity, is often misdiagnosed. Fatigue is the earliest symptom of scurvy. Since cutaneous manifestations are the most overt signs of scurvy, dermatologists often are the first to diagnose the disease. A distinguishing feature of scurvy is follicular hyperkeratosis with corkscrew hair. Perifollicular hemorrhage, petechiae and ecchymoses are also common and may, therefore, mimic vasculitis. Oral findings consist of gingival hemorrhage in a dentate patient and less often loss of teeth. The ocular muscosa, although rarely affected, may present with orbital and subconjunctival hemorrhage. Scurvy, a systemic disease virtually affecting all organ systems, may present with myalgia, arthralgia, anemia, cardiac tamponade gastrointestinal bleed, syncope and even sudden death. Acknowledgement of these signs results in proper diagnosis and rapid treatment. We present a scorbutic alcoholic patient with poor diet who was treated with vitamin C resulting in dramatic improvement.

Learning objective: To discuss the history, pathogenesis, clinical manifestations, differential diagnosis and treatment of adult scurvy.

Case Report

A 32 year old African American male presented to the emergency room only at the assistance of his sister for a two-week history of fatigue, pruritic “rash”, easy bruising, painful swollen knees and difficulty walking. The “rash” started on his upper extremities and progressed to his chest, abdomen and lower extremities. He bruised easily especially in areas of pressure and trauma. In addition, he had a 35 pound weight loss during the last three months. He denied fever, chills, blurred vision, epistaxis, chest pain, dyspnea, hematemesis, hematochezia, melena, headache or suicidal ideation. He was admitted for generalized weakness.

His past medical history was consistent with seizure disorder of unknown etiology treated with phenytoin (Dilantin) for one year. He had no known drug allergies. His family history was unremarkable.

He had a history of alcohol abuse but had been abstinent during the last five months. He admitted to tobacco use but denied any illicit drug use. During the past year, he was anorexic and ate only one meal a day largely as a result of depression. His diet consisted solely of hamburgers without any lettuce or tomatoes, steamed chicken and sometimes bread. He had no vegetable or fruit intake during the past year.

Examination revealed a cachectic, malnourished appearing 32 – year old African American male weighing 134 lbs. at 6’ 3’’ tall. Located on his upper arms, abdomen, anterior thighs and posterior lower legs were perifollicular hyperkeratosis (Fig. 1) with numerous corkscrew hairs, most of which appear broken (Fig. 2). Sandpaper-like texture was evident.

Perifollicular hemorrhage was also apparent, especially on his lower posterior legs (Fig. 3).

Ecchymoses of varying sizes, 0.5 cm to 3 cm, and 2+ pre-tibial pitting edema were also evident on his anterior lower legs (Fig. 4). His knees were edematous and tender to palpation (Fig. 5). He had no palmar or plantar lesions. His ocular and genital findings were unremarkable. His nails did not exhibit onycholysis or splinter hemorrhage. His scars appear intact.

Examination of the oral mucosa revealed poor oral hygiene, fetor oris and marked gingivitis surrounding his remaining teeth. His buccal, palatal and lingual mucosa showed hyperemia and edema (Fig. 6). Loss of tooth was evident. No angular stomatitis was noted.

Because of the high index of suspicion for scurvy, serum vitamin C was obtained and revealed to be <0.1mg/dL (normal 0.4- 2.0). Other laboratory studies showed hemoglobin 9.2 g/dl and hematocrit 27% with hyperchromic, macrocytic indices. Other laboratory tests were as follows: WBC 6.2 th/cmm (normal 4.8-10.8), platelets102 th/cmm (normal 130-400), prothrombin time 13.2 seconds (normal 10-13, INR 1.16 (normal 2.0-3.0). His folate, vitamin B12, vitamin A and essential fatty acids, HIV test and buffy coat for sezary cells were unremarkable.

Figure 1
Perifollicular hyperkeratosis on right abdomen.

Figure 2
Perifollicular hyperkeratosis with corkscrew and broken hair.

Figure 3
Perifollicular hemorrhage on right posterior leg.

Figure 4
Ecchymoses of varying sizes.

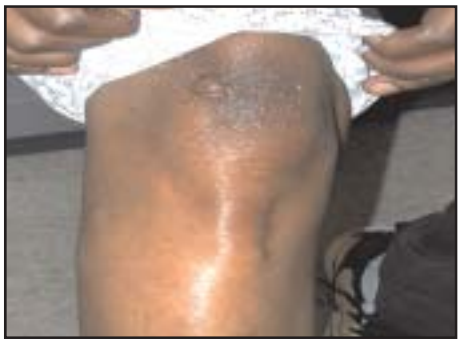


Figure 5
Tender, edematous knees.

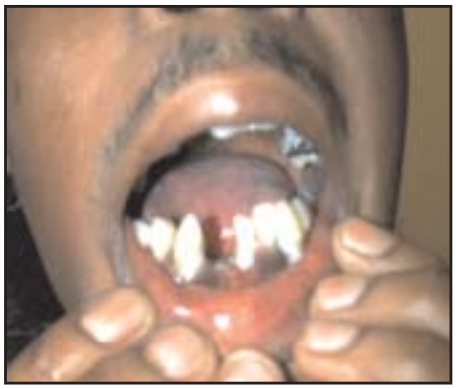


Figure 6
Gingival hypertrophy. Loss of tooth.

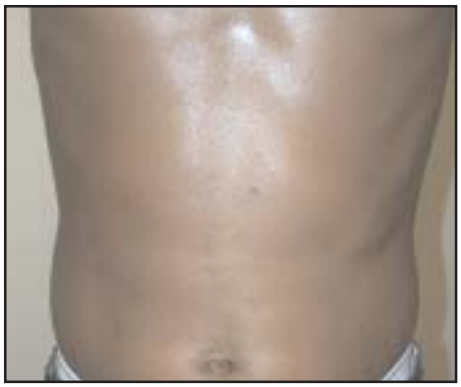


Figure 7
Four weeks after Vitamin C therapy.

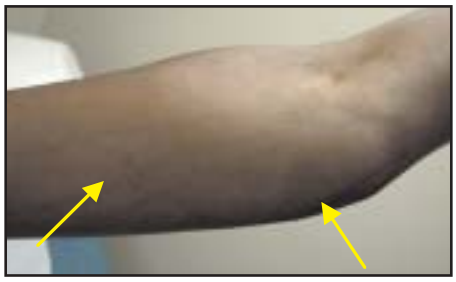


Figure 8
Right forearm. Post-inflammatory Hyperpigmentation on previous sites of ecchymoses.

His chest radiograph revealed no pulmonary infiltrates. There was no evidence of hemopericardium on echocardiogram. A 4-mm punch biopsy revealed hyperkeratosis and perivascular chronic inflammatory infiltrates without any evidence of vasculitis.

He was treated with vitamin C 1 gram for five days followed by 500mg for one week. Maintenance therapy consisted of 100mg/day. Additional treatment included folic acid 1mg and multivitamin daily. He was instructed to eat fruit and vegetables that are high in vitamin C. Within two days, his pruritus resolved and within four weeks, follicular papules and perifollicular hemorrhages improved (Fig. 7).

His lower extremity edema and knee pain eventually improved. The easy bruisability on his legs and upper extremities and subsequent ecchymoses resolved with post-inflammatory pigmentation within eight weeks (Fig. 8).

Within 6 months after diagnosis, he gained 50 pounds due to increased appetite and adequate nutrition. More over, he remained abstinent from alcohol.

Discussion

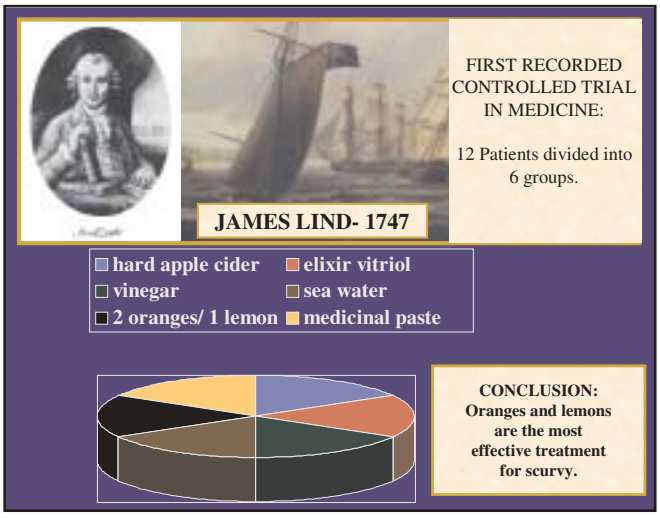
History

Scurvy is replete with rich anecdotes and history. Scurvy has been known since the time of Hippocrates but it has not been a significant problem until the advent of long ocean voyages. After ten weeks at sea around the tip of Africa in 1498, Portuguese sailor, Vasco da Gama, described his crew as having edematous hands, feet and gums that resolved with eating oranges. The problem recurred during their voyage resulting in numerous deaths. While circumnavigating the world in 1740-1744, one thousand and three hundred of George Anson's crew had scurvy. Only 145 returned to England.

Captain James Lind, a Scottish physician, recorded what has been considered the first clinical trial in the history of medicine. In response to a scurvy outbreak aboard HMS Salisbury in 1747, he conducted a study in 12 scorbutic men and divided them into groups of two. His study was done under identical conditions using common therapies used for the treatment of scurvy during that time (Fig. 9.)

Lind assigned each group to six different therapies:

Hard apple-cider –	1 quart/day
Elixir vitriol –	25 gutts, 3x /day
(Cinnamon, ginger, alcohol diluted sulfuric acid)	
Vinegar -	2 spoonfuls, 3x/day, empty stomach
Sea water -	_pint/day
Oranges:lemon	2:1, empty stom
Medicinal paste -	bigness of a nutmeg, 3x/day
(drinking barley,tamarind)	



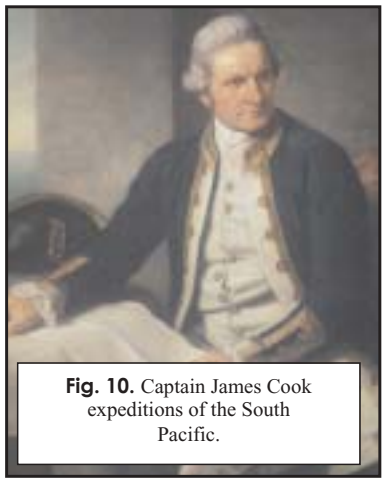


Fig. 10. Captain James Cook expeditions of the South Pacific.

Figure 9
James Lind's clinical controlled trial under identical conditions (same living arrangements and diet), using common therapy used for the treatment of scurvy during that time.

Fig. 9. Scurvy and its target population.

GENERAL:
Adults living alone:
- Bachelor's scurvy
- Widower's scurvy

Poor dentition
Food faddist
Barlow's disease
- Infantile scurvy

SYSTEMIC DISEASE:
Peptic ulcer disese
Iatrogenic scurvy
Whipple's disease
Crohn's disease
Malignancy

PSYCHIATRIC DISORDERS:
Alcoholism
Anorexia nervosa
Schizophrenia
Depression

Table 1. Scurvy & alcoholism.

Lee RV et al.[5]
Reuler JB et al.[6]
Leung FWet al. [7]
Allen Jl et al.[2]
Fain O et al.[3]
George GCW et al.[8]
Adelman HM et al.[9]
Onorato J et al.[10]
Gabay C et al.[11]
Charbeneau TD et al.[12]

Table 2. Factors involved in alcoholism and scurvy.

1. Live alone
2. poor dietary intake
3. alcohol is devoid of vitamin C
4. alcohol decreased vitamin C absorption[14,15]

Table 3. Scurvy and anorexia nervosa.

Scobie BA et al. [14]
Mehta CL et al. [15]

The group who received the two oranges and one lemon daily for 6 days had the most remarkable improvement. In 1753, the now famous *Treatise of Scurvy* was published. He concluded that oranges and lemons were the most effective treatment for scurvy but he did not say that scurvy was due to vitamin C deficiency. With this information, Captain James Cook (Fig. 10), during one of the expeditions of the South Pacific, encouraged his crew to eat vegetables and fruits wherever they stopped. He was able to circumnavigate the world without a single case of scurvy in his crew.

In 1844, the British parliament mandated that each sailor had lime juice as a part of their daily diet. Hence, they were called "limeys".

Epidemiology

Although considered rare, many cases of scurvy go unrecognized. Scurvy is considered rare in industrialized countries because accessibility to fresh produce and vitamin supplements is easy and reliable. Still, certain groups are at risk for developing scurvy largely as a result of eating inadequate amounts of fresh fruits and vegetables (Fig. 9). Adults living alone, mostly men but sometimes women, may have deficient nutrition due to poverty, reclusiveness, nutritional ignorance or poor access to groceries. Thus vitamin C defiency is also called *Bachelor's scurvy* or *Widower's scurvy*. Poor dentition may prohibit patients to eat fruits and vegetables. Some may claim vitamin C "allergy" and thus avoid "acidic" foods due to dyspepsia, diarrhea or heartburn. Furthermore, patients with unusual dietary habits may avoid these foods due to taste or some fad beliefs. During the late 19th and early 20th century, infants who were fed evaporated or condensed milk which lacked vitamin C were at risk for scurvy. Pseudoparalysis of the lower extremities, a common finding, due to subperiosteal hemorrhage was first described by Thomas Barlow in 1884; therefore, *Infantile scurvy* is also known as *Barlow's disease*.

Patients with malabsorption such as Crohn's and Whipple's disease and peptic ulcer disease are also at risk. There also reports of *"Iatrogenic scurvy"* due to physician's recommendation to avoid fruits and vegetables to prevent abdominal symptoms. Patients with malignancy are also at risk due to various factors such as:

1. gastrointestinal symptoms caused by underlying malignancy
2. anorexia
3. depression
4. chemotherapy
5. radiation treatment
6. parenteral nutrition.

Certain behavioral disorders are associated with scurvy. There are several case

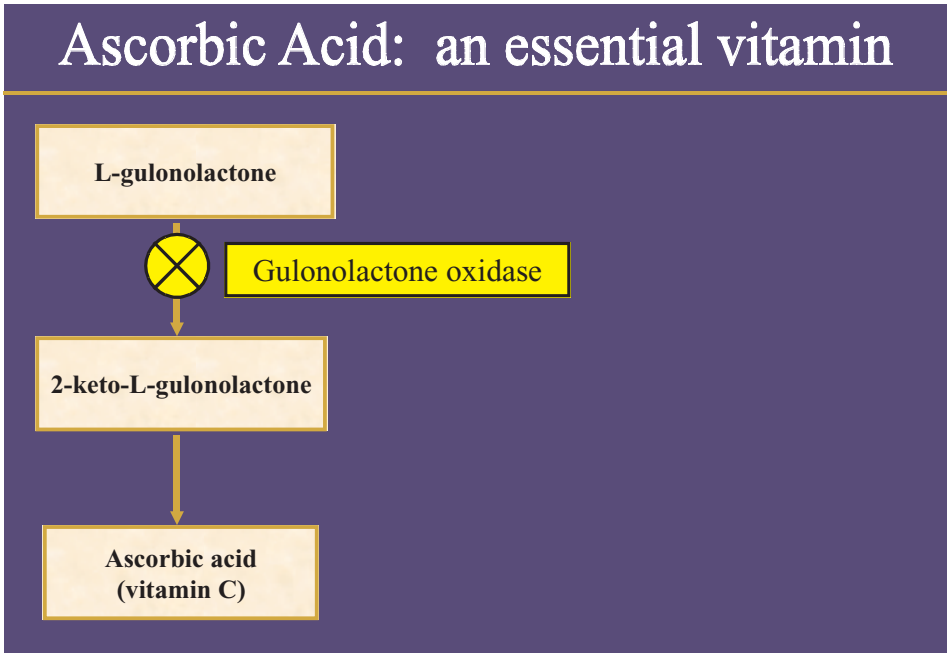


Figure 9
Humans lack gulonolactone oxidase unabling them to synthesize vitamin C from glucose.

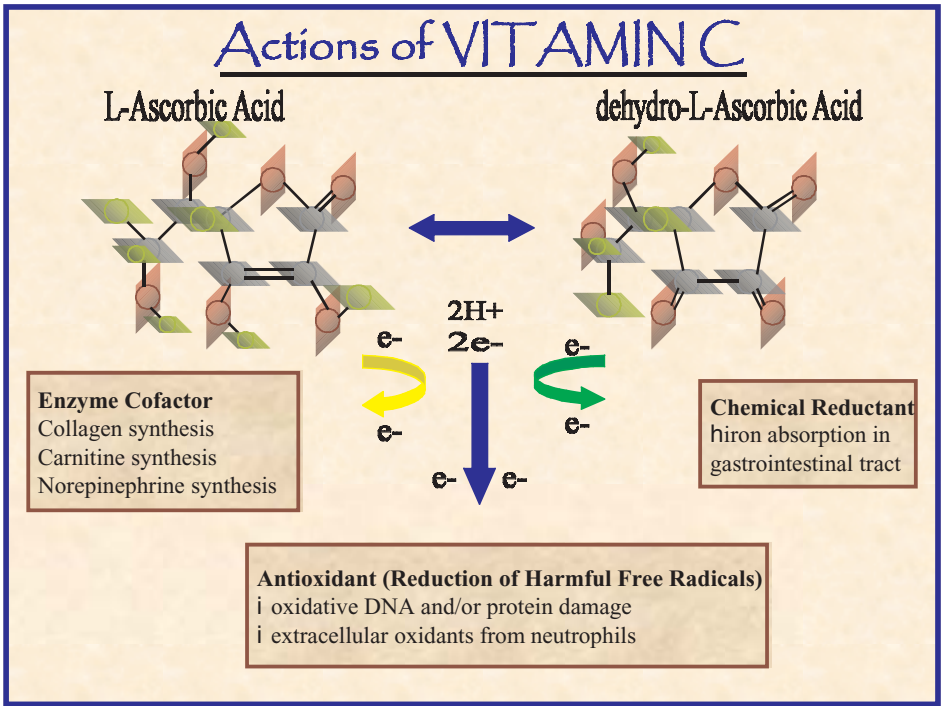


Figure 10
Actions of vitamin C. (Revised with permission from Levine M, Rumsey S, Daruwala R, Park J, Wang Y. Criteria and recommendations for vitamin C intake. JAMA 281: 1415-1423. 1999.)

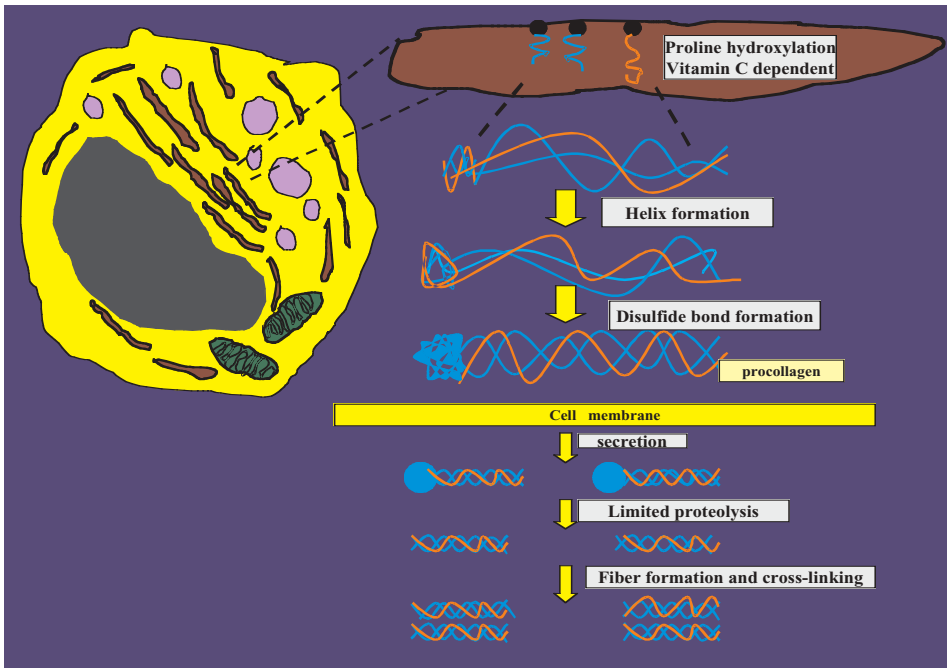


Figure 11
Normal collagen synthesis. (Revised with permission from Miller SJ, Nutritional deficiency and the skin. JAAD 21: 1-30.1989)

reports of scurvy and concomitant alcoholism (Table 1). Several factors are involved (Table 2). Many alcoholics live alone and have poor dietary intake. Alcohol is also devoid of vitamin C. Furthermore, alcohol reduces vitamin C absorption in the gastrointestinal tract.

Patients with overt psychiatric disorders such as schizophrenia,[14] depression and anorexia nervosa, (Table 3) may have unique and restrictive dietary habits that make them prone to having scurvy.

Our patient had numerous risk factors for developing scurvy: poor nutrition, male gender, lives alone, alcoholism, depression and anorexia.

Pathogenesis

Ascorbic acid is an essential vitamin. Humans, guinea pigs, non-human primates, Indian fruit bat and bulbul bird are unable to synthesize ascorbic acid from glucose due to lack of various enzymes such as gulonolactone oxidase (Fig. 9). Because of this, they require exogenous sources of vitamin C. Deficiency of vitamin C results in scurvy. Humans derive vitamin C largely from fruits and vegetables. Absorption of vitamin C from the intestines varies according to the amount ingested, decreasing with larger doses.[1] Vitamin C is eliminated via urinary excretion which increases with dietary intake.

In 1927, Albert Szent-Gyorgi isolated hexuronic acid from adrenal glands, oranges and cabbages, but it was not identified as vitamin C until 1932. Vitamin C is found highest in concentration in the adrenal and pituitary glands.

Because vitamin C is a cofactor for several enzymes, it is involved in numerous biochemical and biological functions. It is important in collagen, carnitine, norepinephrine and peptide hormone synthesis. It also acts as an enzyme cofactor in tyrosine metabolism. In addition, it increases iron absorption by acting as a chemical reductant. Furthermore, vitamin C plays an important role in folic acid metabolism. Also, vitamin C acts as an antioxidant by reducing free harmful radicals therefore affecting wound healing (Fig. 10) .

Perhaps the most important biochemical function of vitamin C is in biosynthesis of collagen, the most abundant animal protein. The clinical manifestations of scurvy are related to the function of ascorbic acid as a cofactor of proline hydroxylase in the hydroxylation of proline in procollagen. This hydroxylation results in hydrogen-hydrogen bonding that leads to triple helix formation. Eventually, it is secreted by fibroblast. Extracellularly, peptidases cleave excess amino and carboxy terminals resulting in mature collagen fibers. Underhydroxylation results in weak and easily degraded collagen polypeptides unabling them to form mature collagen, a rigid, stable triple-helical structure (Fig. 11).

This results in impaired synthesis of the basal lamina, media and adventitia of blood vessel wall and its surrounding connective tissue causing perivascular edema, protrusion of endothelial cells in the lumen and subsequent erythrocyte extravasation (Fig. 12). As a consequence, there is impaired blood vessel integrity causing hemorrhage even with slight trauma. This can result in perifollicular hemorrhage, orbital hemorrhage, hemorrhagic gingivitis, hemarthrosis, anemia, gastrointestinal bleed, hemopericardium and rarely cerebral hemorrhage.

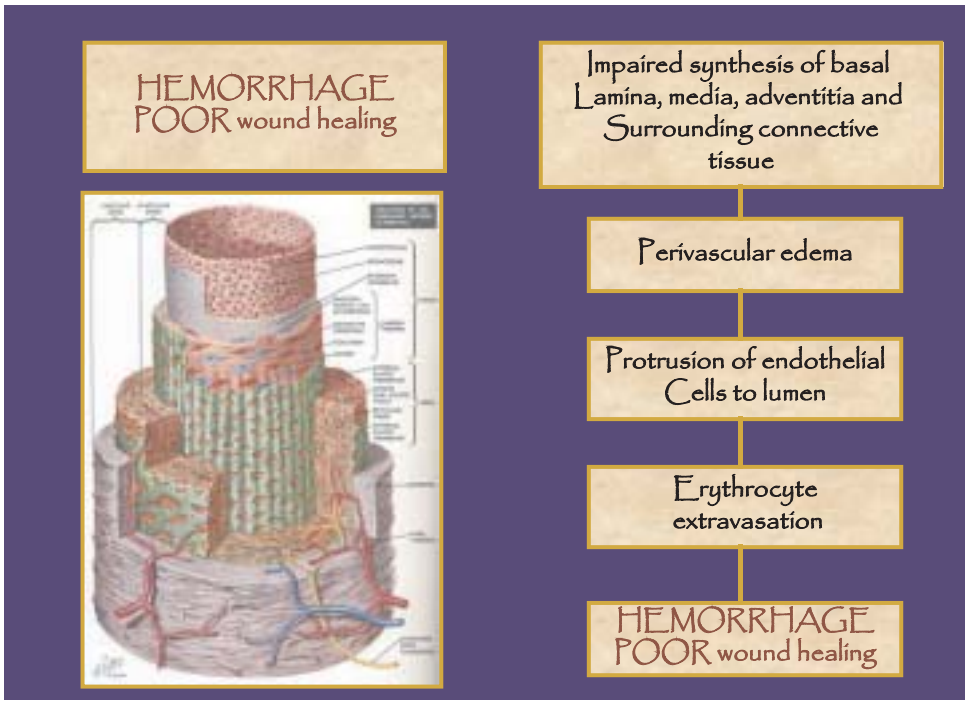


Figure 12
Impaired blood vessel integrity in scurvy resulting in hemorrhage.

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Yellow Nail Syndrome: A Case Presentation and Review of the Literature

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Dermatology Institute of North Texas in conjunction with Northeast Regional Medical Center and the Kirksville College of Osteopathic Medicine

A 59 year old African American male presented to our clinic with a chief complaint of nail fungus and slow nail growth for 6 years, which had failed to respond to treatment with oral antifungals. His past medical history was significant for hypertension, congestive heart failure, hyperlipidemia, coronary artery disease and gout. Surgical history was significant for a parathyroidectomy in 1996, abdominal aortic aneurysm repair, and a coronary artery bypass graft in 1982. His medications were losartan, verapamil, atenolol, furosemide, potassium, atorvostatin and allopurinol. Family medical history included diabetes and colon cancer, and the patient had a normal colonoscopy 2 years prior to presentation in our clinic.

As seen in figures 1 and 2, physical examination of all 20 nails revealed increased transverse curvature, yellow discoloration, subungual hyperkeratosis, onycholysis, and 1+ pitting edema of the lower extremities. DTM was positive for dermatophytes and Nickerson's was negative for yeast. A biopsy of the nail plate with PAS stain was positive for dermatophytes.

Previous therapy with terbinafine for 120 days with no improvement was noted at proximal nail folds. Review of systems was within normal limits and the patient had no constitutional symptoms. In light of the patient's congestive heart failure, itraconazole was not recommended. Patient said that the nail problems started after his parathyroidectomy. After the surgery, the nails grew much faster than usual and then abruptly stopped growing at a normal rate, then began their current state. Patient also complained of a chronic cough for the last 2-3 years.

Routine labwork abnormalities included BUN elevated at 30, creatinine elevated at 2.0, Hbg/Hct decreased at 12.2/36.5. Serum calcium was low at 7.7 possibly due to the parathyroidectomy. Urine protein electrophoresis showed random urine protein high at 245mg/g. Chest X-ray, thyroid stimulating factor, rheumatoid factor, serum protein electrophoresis, CEA, CA-125 and PSA were all within normal limits The patient's internist informed us that the patient's anemia and renal insufficiency were stable and likely due to hypertensive nephropathy. Chest X-ray was normal, as was a colonoscopy obtained 2 years prior to seeing the patient in our clinic.

Possible YNS associations in our patient included chronic bronchitis of uncertain etiology, calcium deficiency possibly secondary to parathyroidectomy and a hypertensive nephropathy. After several months of Vitamin E 1400 IU per day and calcium supplementation two of the patient's nails began to grow normally, while the rest remained unchanged.

Discussion

Yellow Nail Syndrome (YNS) is characterized by nails that are yellow and thickened with an increased transverse curvature. YNS typically affects both fingernails and toenails, and usually affects the entire nail plate. Nails have a decreased growth rate, loss of cuticle and lunula, onycholysis and periungual swelling[1]. The classic triad of YNS includes 1) characteristic nail abnormalities, 2) edema and 3) an associated medical condition as listed below. All three components of the triad need not be present for the diagnosis of YNS to be made. YNS has been associated with pulmonary conditions, malignancies, D-penicillamine, women with unequal sized breasts, thyroid disease, rheumatoid arthritis, renal conditions [1].

Malignant associations include lung cancer, laryngeal carcinoma, melanoma, Hodgkin's disease, sarcoma, lymphoma and adenocarcinoma of the endometrium[1]. Renal associations include minimal change nephrotic syndrome, xanthogranulomatous pyelonephritis, nephrotic syndrome and nephropathy with exudative pleuritis, respiratory tract disease, scleronychia and lymphangiopathy[2,3,4,5].

In the article by Yanez et al entitled "Yellow Nails and Minimal Change Nephrotic Syndrome" a case report of a 38 year old man with abnormal nails that failed to clear with Itraconazole and Amorolfine was presented. All 20 nails were thickened, yellow, opaque, with absent lunulae and increased curvature. The patient also had

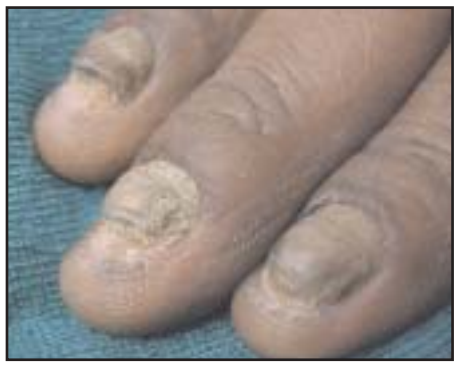

Figure 1

Figure 2

pitting edema of the lower legs and a chronic sinusitis. Labwork revealed heavy proteinuria (8.4g/24h), low serum albumin (2.7g/100mL), normal BUN/creatinine, Sed Rate of 43mm/1 hour and a urinalysis revealed 1-3 WBCs per hpf, 1-3 RBCs per hpf, scant granular casts and uric acid crystals. CT of the sinuses revealed a chronic maxillary sinusitis. Nail cultures were negative for fungus, kidney echogram was negative, renal biopsy revealed 15 glomeruli with minor mesangial enlargement consisted with minimal change disease. Treatment with vitamin E 1000 IU per day and prednisone 75mg QD and tapered after 6 months improved the yellowing and nail deformities[2].

Danenburg et al described a 74 year old female was seen for evaluation of unremitting left-sided exudative pleural/pericardial effusion. Repeated pleural cultures and biopsies were all negative, and multiple pleurocenteses were of no help. Past medical history was significant for type 2 diabetes, hyperten-

sion controlled with metformin, clonidine and nifedipine. Physical exam revealed yellow nails and 4+ pitting edema of the lower extremities. Urinalysis was positive for *Proteus mirabilis* and the sed rate was elevated at 120mm. CBC revealed a low Hgb (11.2) and MCV (77) as well as an elevated WBC (15.5) and platelets (511). CT scan revealed a left pleural effusion, large hydronephric kidney with staghorn calculus and paranephric abcesses. IVP showed no secretion from the left kidney. The patient was referred for a nephrectomy and pathology was consistent with xanthogranulomatous pyelonephritis. Following surgery prompt resolution of the pleural effusion was seen. Five months later the yellow nails improved[3].

Cockram et al. presented a 51 year old female with an 18 month history of cough, rhinorrhea, cessation of nail growth, nail yellowing, alteration of nail shape and ankle swelling. Her symptoms started after a respiratory infection. On physical examination all 20 nails had a greenish yellow discoloration, gross thickening, increased transverse curvature, onycholysis and transverse ridging. She also had pitting edema to mid calf. Labwork revealed heavy proteinuria at (6g/24hrs), low serum albumin (26g/L) and a normal BUN/creatinine. Renal biopsy showed a mesangioproliferative glomerulonephritis. Lymphangiography was within normal limits. Within a few weeks of starting treatment with furosemide and spironolactone normal nail growth returned[4].

Radenbach et al described a case of YNS that occurred in a patient with nephrotic edema due to glomerulonephritis, exudative pleuritis, respiratory tract disease, scleronycyia and widespread lymphangiopathy[5].

Conclusion

Yellow Nail syndrome is a rare nail disorder of uncertain etiology. YNS may easily be mistaken for routine onychomycosis as cultures may be positive for dermatophytes. The secondary nature of this infection becomes evident when oral antifungal therapy repeatedly fails to clear the nails. Therefore, in patients with the above clinical presentation and in whom antifungal therapies are unsuccessful, the diagnosis of YNS should be entertained. Further work-up to rule out internal and malignant associations is merited, and treatment of the underlying cause as well as Vitamin E therapy are the only known effective forms of treatment.

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Case Report: Idiopathic Scrotal Calcinosis

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Introduction

Scrotal calcinosis is a rare condition characterized by multiple, slowly growing, distinct nodular masses embedded within the dermis of scrotal skin. The pathogenesis is unclear and controversy exists as to whether the condition is idiopathic or the result of dystrophic calcification of preexisting epidermal cysts.

We report a case of scrotal calcinosis on a patient presenting with chronic multiple nodules over the scrotal skin.

Case Description

This case refers to a 46y/o who presented with a chief complaint of multiple cystic bumps on the scrotum. He reported that the bumps have been there for approximately 40 years, or as the patient stated, "they have been there all my life."

Past medical history was significant for dyslipidemia and hypertension. He denied any medications. Family history was significant for diabetes and lung cancer on the paternal side. Social history was unremarkable

Physical examination revealed multiple cystic-like nodules scattered on the scrotum. An ovoid tan-brown skin specimen, that measured 1.2 x 0.8 x 0.5, was collected and sent for biopsy and reported as idiopathic scrotal calcinosis. The patient stated he did experience itching, pain, or discharge but was aware of the lesions and wanted them removed.

Discussion

The etiology of scrotal calcinosis has been a subject of dispute. Many doubt that the condition is idiopathic based on evidence that the calcification occurs secondary to preexisting epidermal cysts. On the other hand, in several cases histology reports of the calcified nodules revealed no evidence of keratin epithelium near the calcified nodules, thereby weakening the theory of calcification secondary to a dystrophic process on preexisting epidermal cysts.

Traditionally, calcium deposition within the body is thought to occur by means of dystrophic or metastatic processes. Dystrophic calcification is often seen at sites of previous inflammation or damage to the skin. It occurs in the setting of normal serum calcium and phosphate levels, and has been associated with connective tissue disease, such as scleroderma, or polymyositis-dermatomyositis.

In contrast to dystrophic calcification, metastatic calcification is not restricted to a specific site but has a widespread distribution and is usually related to other underlying conditions such as hyperparathyroism, hypoparathyroism, or renal disease. Deposition of calcium most often occurs within visceral organs rather than skin or muscle.

The term idiopathic is reserved for cases where a causative agent cannot be identified and calcification occurs in the absence of known tissue injury or systemic metabolic defect.

Adequate evidence exists to support the premise that ruptured epithelial cysts often calcify. Furthermore, it has been asserted that the pathogenesis of scrotal calcinosis could be associated with degenerative processes of the dartoic muscle. This process, in many cases, may be the cause of scrotal calcinosis. It is this evidence that prompts many to question the use of the term 'idiopathic' when referring to the cause of scrotal calcinosis.

The debate over the cause of the condition is perpetuated by difficulty in several cases to detect a preexisting lesion, such as the report by Wright S et al of a case of scrotal calcinosis where immunohistochemical staining failed to detect any evidence of keratin in the tissue immediately adjacent to the calcium deposits. This finding was interpreted as confirmation that scrotal calcinosis is idiopathic.

The cause of the condition is most likely multifactorial. The proposition that the calcinosis is caused by preexisting epidermal cysts that rupture is a valid one and may describe the cause of the condition for only a number of the cases. For the remainder of the cases where there is difficulty in finding a preexisting lesion the term idiopathic may be appropriate.

Granuloma Annulare in a Patient with Hodgkin's Lymphoma

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Duncanville, Texas

Although granuloma annulare (GA) is a relatively common skin disorder, the occurrence of this condition with concomitant lymphoma is rare. The type of lymphoma varies and may occur either before or after the appearance of granuloma annulare[1,2]. We report a case of GA that appeared four months after the diagnosis of Hodgkin's lymphoma.

Case Report

The patient was a 65 year-old Caucasian man diagnosed with nodular lymphocyte predominance Hodgkin's lymphoma in September 2002. He presented in January 2003 after a three month history of multiple erythematous plaques, papules, and nodules on the dorsum of his hands bilaterally (Fig 1-3). A punch biopsy was taken from one of the lesions on his left hand. The pathology report described discrete areas of palisading histiocytes surrounding collections of mucin with perivascular lymphocytes. There was no evidence of lymphoma in the specimen. Granuloma annulare was diagnosed at this time.

The lesions were initially treated with a Class I topical corticosteroid cream twice daily for four weeks with minimal improvement. Topical steroids were discontinued and Tacrolimus ointment 0.1% was applied twice daily. This treatment was eventually discontinued in August 2003. After the patient underwent radiation therapy for his Hodgkin's lymphoma until May 2003, the granuloma annulare resolved completely.

Discussion

Many case reports and review articles have presented patients with both granuloma annulare and malignancy. There has been a wide variability of onset between the two conditions, with a time of onset of granuloma annulare and the discovery of malignancy varying between 18 months before to seven years following. One half of these cases had associated lymphoma as the form of malignancy[1]. Our patient presented with granuloma annulare four months after his diagnosis of Hodgkin's lymphoma.

Granuloma annulare has been linked to many different types of malignancy. It has been described as a cutaneous manifestation of Lennert's lymphoma and has been linked to B-cell non-Hodgkin's lymphoma, Hodgkin's lymphoma, and granulomatous mycosis fungoides[7]. Setoyama discussed a patient with granuloma annulare and concomitant lymphocyte predominant Hodgkin's, the same subtype as our patient[6].

The relationship between these two diseases is still unknown. Ono suggests that granuloma annulare is a lymphoma-induced reaction[8]. Whether this is the case or not, there does appear to be a link between the two diseases in some patients. In light of this possible link, patients diagnosed granuloma annulare should be considered at potential risk for underlying malignancy.

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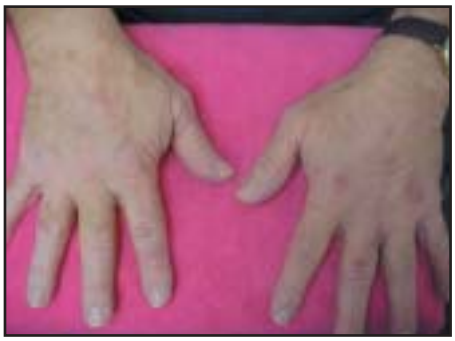

Figure 1
Bilateral Granuloma Annulare

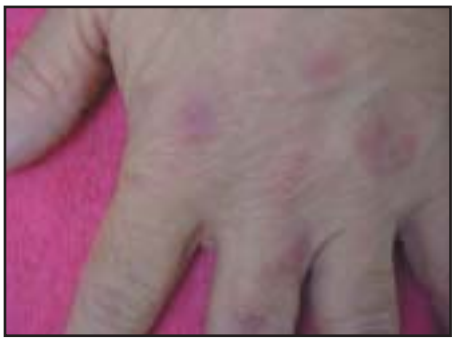

Figure 2
Granuloma Annulare of the left hand

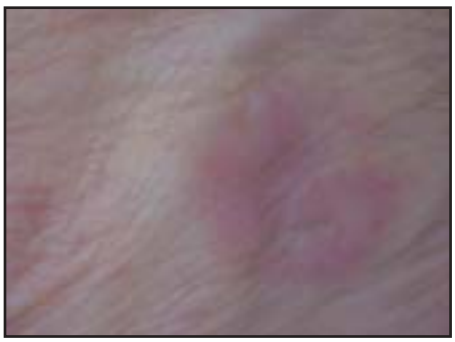

Figure 3
Close-up of Granuloma Annulare

Generalized Papular Granuloma Annulare: A Case Presentation & Literature Review

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Northeast Medical Center/KCOM, Program Director: Lloyd J. Cleaver, D.O.

ABSTRACT

Generalized granuloma annulare is the less common subtype of granuloma annulare, typically presenting as numerous macules and papules or nodules of varying color. One third of the time there is no annular configuration. Lesions are typically non-tender and localized to the trunk and extremities. Atypical presentations like lesions located on the palms and soles, and tender lesions have been seen in patients with lymphoma and mycosis fungoides. The diagnosis and treatment may be difficult in these atypical cases as is exemplified in this case presentation.

History of Present Illness

A 53-yr-old Caucasian woman presented to the ER with complaints of low-grade fever and headache and "spots" on both of her palms developing over a two-day period. The patient complained that over the preceding 24-hours the "spots" had spread to involve her forehead, neck, arms, knees, abdomen and legs. The lesions on her palms are exquisitely painful. She denied any ill contacts. She denied having any diarrhea, vomiting, arthralgias, or myalgias. She admits to having a tick bite 6-8 weeks prior. She had just returned from visiting a relative in Omaha, Nebraska where she had been helping to clean out an old closet infested with mice feces. This occurred one week prior to becoming ill. She has been recently healthy and has a past medical history of mild COPD, dyslipidemia, and gastroesophageal reflux disease.

Physical Exam

The patient was alert and oriented to time, place and person. She looked her stated age and was a good historian. She had a low-grade temperature of 100.5 degrees Celsius. Her other vital signs were within the normal limits. She had neck stiffness and pain on cervical extension and flexion. She had shotty, non-tender anterior cervical lymphadenopathy. Her oral pharynx was slightly erythematous. She had no evidence of supraclavicular, axillary or inguinal adenopathy. There were erythematous papules scattered on her neck, chest, abdomen, back and arms and legs (Fig. 1-3). Present on both palms were pustules on an erythematous base (Fig. 4). Kernig and Brudzinski's signs were positive. Her lungs were clear to auscultation and her heart had a regular rate and rhythm without murmurs rubs or gallops. Her abdomen was soft and non-tender without any hepatosplenomegaly. The remainder of her examination was unremarkable.

Laboratory

Laboratory investigation showed a normal CBC, BMP, and coagulation studies. Lumbar puncture revealed a normal opening pressure and values. CSF culture was negative. Throat culture and blood cultures were negative. Serum antibody testing for Arbovirus IgM, and Rocky Mountain spotted fever IgG and IgM were normal. Tularemia antibody was negative as well as Ehrlichia Chaffeensis and Brucella IgG and IgM were normal. CSF viral cultures and specifically West Nile virus IgG and IgM were normal. VDRL was non-reactive. Chest x-ray and head CT were unremarkable as well.

Pathology

Two 3 mm punch biopsies were obtained each for H & E and one for a viral culture. The first punch biopsy taken from a pustule on the palm showed acute and chronic inflammation and edema of the papillary dermis- inconclusive findings. The second punch biopsies taken from two locations one on the right posterior calf and another from the right posterior shoulder revealed a vague palisading granuloma under low power (Fig. 5). Under high power the granuloma is visible. The white arrows show the outline of the granulomas, which are predominantly lymphocytes. The blue arrow shows histiocytes. The yellow shows necrobiotic collagen (Fig. 6). All special stains for microorganisms were negative.

Management

The patient received IV dexamethasone and IV Rocephin in the ER. She then was

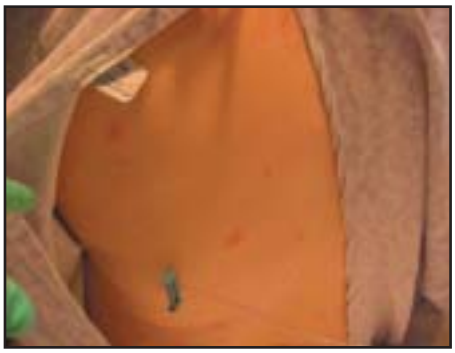

Figure 1

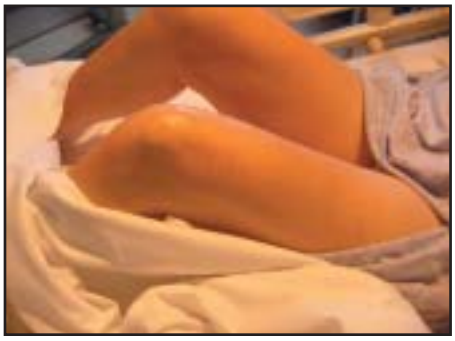

Figure 2

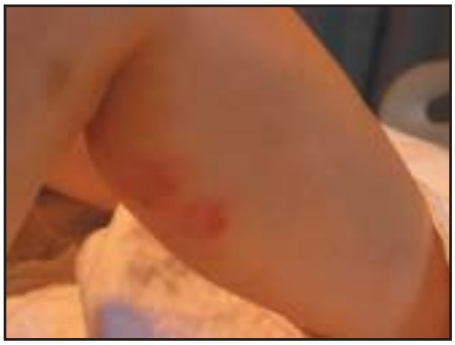

Figure 3

Figure 4

Figure 5

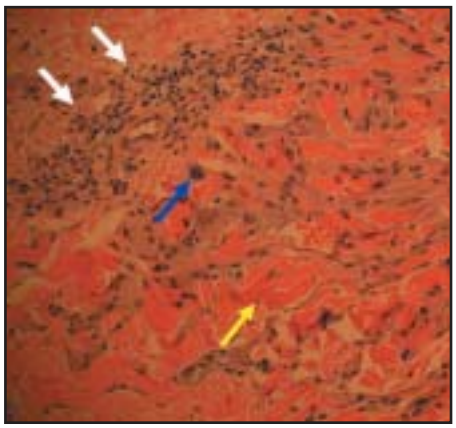

Figure 6

treated with IV Ampicillin, Acyclovir, and Doxycycline and placed in respiratory isolation in the ICU. She showed some improvement in the first 24 hours presumably due to the steroids. Her lesions worsened again over the 24-48 hours that followed. She was actually transferred to another hospital to be evaluated by an infectious disease specialist because we had no definitive diagnosis. After she was evaluated at that facility and told that she nothing infectious was causing her rash she was seen by another dermatologist who re-biopsied the papules. This time the biopsies were taken from her lower leg and her back and were consistent with granuloma annulare. The patient then received topical Temovate cream and had a course of oral prednisone for seven days with complete resolution of her lesions. She has had no recurrence to date six months later.

Discussion

Granuloma Annulare is a granulomatous dermatitis first described by Calcott Fox in 1895 as 'ringed eruption of the fingers'. It was named in 1902 by Radcliff-Crocker, as granuloma annulare.[2] Most cases of GA are localized; approximately 8-15% of cases are generalized. The term generalized implies that lesions are widely distributed over the body in contrast to being confined to one anatomic area.[6] As with the localized form it is more common in females with a ratio of approximately 2.5:1. In generalized GA however, there is a bimodal distribution in age of onset with 80% of patients presenting at ages 40-70 years and the rest presenting before age 10 years.[9] Generalized GA typically has a poor response to therapy and there is a prevalence of HLA-Bw35 seen. Lesions number in the hundreds and may be macules, papules, or nodules from skin-colored to red, yellow or tan. One third of generalized GA cases there is no annulare configuration.[8]

The lesions of GA are typically nontender. A study by Dabinski documented 2 of 100 patients that had tender lesions and none had tender lesions on the palms.[4] Furthermore, a study by Dickens et al describes 26 patients with generalized granuloma annulare and only one patient experienced some local tenderness but none of their patients had palmar lesions.[6]

The question of a possible association between diabetes mellitus and granuloma annulare is still ongoing. Due to the low incidence of generalized granuloma annulare a large-scale study national or statewide would be needed to generate enough data to make accurate conclusions regarding this. The most common lab abnormality in patients with granuloma annulare according to Dabinski's study was an abnormal ANA in 26.1% of the cases, followed by an elevated IgG in 13.5% of the cases and hypergammaglobulinemia in 11.5% of cases.[4] In the study by Dabinski et al of 100 patients with generalized GA, 45% of their patients had lipid abnormalities either hypercholesterolemia or hypertriglyceridemia or both.[4]

Generally speaking, there is no difference in the histology of localized or generalized granuloma annulare.[5] The histology of granuloma annulare is characterized by focal degeneration of collagen and elastic fibers, mucin deposition and perivascular and interstitial lymphocytic infiltrate in the upper and mid-dermis. A key finding is the presence of histiocytes in one of three patterns. Most commonly (75%) is the infiltrative or interstitial pattern where scattered histiocytes infiltrate between collagen fibers. The second most common pattern seen 25% of the time is more obvious consisting of several palisading granulomas with central connective tissue degeneration surrounded by histiocytes and lymphocytes. Mucin is present in the center of the granuloma and fibrin, neutrophils and nuclear dust as well. This is most consistent with the findings in the second set of biopsies from our patient. The last pattern is rare and consists of epithelioid histiocytic nodules that resemble cutaneous sarcoidosis.[2] Increased mucin can be seen in 70% of GA lesions. Colloidal iron or Alcian blue are two different mucin stains that can be used to detect this. Elastic tissue is reduced or absent in the histiocytic areas of 20% of generalized GA and 35% of localized GA.[2] Even with histology atypical non-annulare clinical presentations may be atypical in there histologic presentation.[5] As in our case, additional biopsies may be needed.

The differential diagnosis of non-annulare papular granuloma annulare would include arthropod bites, secondary syphilis, xanthomas and non-histiocytoses.[2] In our cases also included are viral exanthems, sarcoidosis, erythema multiforme, Sweet's syndrome, acute generalized pustulosis and other infectious diseases such as Rickettsial pox, Enteroviral infection and Monkey pox.

The etiology of GA is unclear. It has been postulated that UV light is a predisposing factor, however several studies have exposed their patients to UV light with out any recurrence of new lesions in these areas.[6] Other proposed etiologies include trauma, insect bites, tuberculin skin testing, PUVA therapy and viral infections.[2] There is one report of three children developing a papular form of GA after being bitten by the gnat Culicoides furans.[9] A more recent belief is that GA is a delayed-type hypersensivity reaction to an unknown antigen. This is based on T-cell subpopulations found in GA lesions.[2]

Localized GA is usually a benign, self-limited entity. However the generalized variety is known to recalcitrant to treatment modalities. Systemic medications are used for severe cases include nicotinamide, isotretinoin, antimalarials, cyclosporin A, chlorambucil, dapsone, and pentoxifylline. It should be noted that no large, randomized, double blind, placebo-controlled studies have been performed to support the use of these systemic medications, and most of the reports of their efficacy are anecdotal.[2] Other therapies used include systemic prednisone, potassium iodide, and methoxsalen plus ultraviolet light.[3] In addition, six of seven patients with generalized GA responded to chlorpromide (Diabinese) in one study.[10] Spontaneous resolution of GA occurs within 2 years approximately half of the time, however, there is a 40% recurrence rate. Untreated

lesions have been reported to range from a few weeks to several decades.[2] Our patient was extremely unusual in her clearing completely with a short course of oral prednisone.

Atypical clinical patterns of granuloma annulare and painful granuloma annulare lesions have been reported in patients with various types of malignant lymphoma. In a study of 13 patients with both lymphoma and granuloma annulare the clinical features of GA were atypical in most of these patients. However, the histologic features of the GA lesions were typical. Five of these patients had painful lesions on the extremities including the palms and soles. Two of these patients had generalized lesions. The painful lesions were similar to our case as they were described as erythematous nodules and papules. Painful lesions or lesions in unusual locations or both including lesions the palms, soles, and face occurred in all 13 of the patients. This finding is in direct contrast to Dickens findings of 26 patients with generalized GA without lymphoma where none of the patients had involvement of the palms or soles and four complained of pruritus, and only one had some localized tender lesions.

In five of seven patients with atypical GA lesions and lymphoma the GA developed before the diagnosis of lymphoma. The time interval from diagnosis of GA to lymphoma ranged from 4 months to 3 years. There was an overall shorter time period from development of GA to lymphoma in the more clinically atypical presentations of GA.[1]

In summary, the diagnosis of generalized granuloma annulare can be difficult, and as in our case, be missed initially. Laboratory tests are nonspecific and therefore histology is important. This is an atypical presentation of generalized papular GA. Lesions were atypical for two reasons, one, they were located in uncommon areas like the palms and two, they were exquisitely tender. In addition, the patient's rapid resolution with oral prednisone was unique, as is her lack of recurrences to date. However, as a literature search revealed this type of presentation may occur and patients with such atypical presentations should be evaluated for and monitored for lymphoma and mycosis fungoides.

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Hereditary Palmoplantar Keratoderma of the Unna-Thost Type: A Case Report and Literature Review

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ABSTRACT

Palmoplantar keratodermas are a complicated group of disorders characterized by hyperkeratosis of the palms and soles. Some of them have been associated with life threatening conditions which must be considered when evaluating these patients. A case of hereditary palmoplantar keratoderma of the Unna-Thost type is presented along with a review of the literature.

Introduction

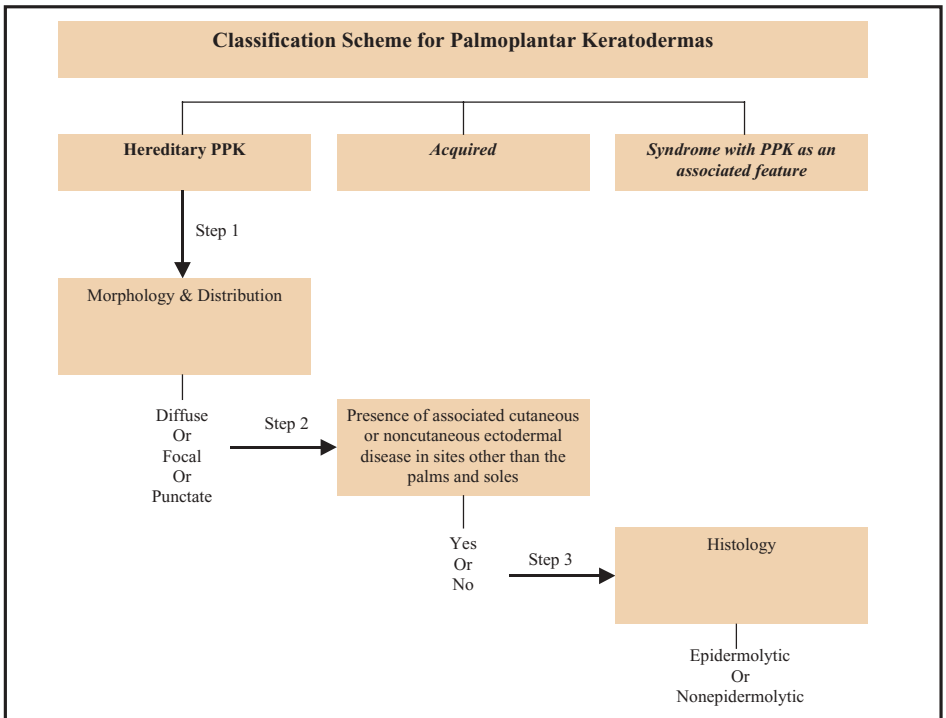
Palmoplantar keratodermas (PPK) are a group of disorders in which there is marked hyperkeratosis of the palms and soles. The PPK can be hereditary as in this case, acquired or associated with another disorder. The focus of this paper is on the hereditary PPK.

The hereditary PPK are a complex group of disorders. Historically, they have been classified in many different ways based on age of onset, inheritance pattern, morphology, severity, histology and association with other ectodermal disease [1, 2]. With new advances in molecular genetics the PPK have also been classified based on genetic mutations [3].

One of the more commonly used formats to classify the hereditary PPK is based on morphology and distribution, association with other ectodermal disease and the presence or absence of epidermolysis histologically [1] (Figure 1). The three clinical patterns seen are diffuse involving the entire surface of the palms and soles, focal involving local areas of the palms and soles most notably over pressure points and lastly punctuate in which there are small hyperkeratotic papules on the palms and soles.

Histologically, the PPK are separated into epidermolytic and nonepidermolytic. Epidermolytic PPK is characterized by orthokeratotic hyperkeratosis, large keratohyalin granules and vacuolization of the upper-mid spinous layer. Nonepidermolytic PPK is nonspecific orthokeratotic hyperkeratosis.

Some of the associated features seen in the different hereditary PPK include sensorineural deafness, periodontitis with premature loss of teeth, wooly hair, alopecia, pseudoainhum (nonspontaneous amputation of a digit), nail dystrophies, arrhythmias, cardiomyopathy, cutaneous squamous cell carcinoma and esophageal carcinoma [4-8]. With this wide range of associations, knowing which group the patient is in is important in order to determine if further workup is needed to rule out another possible underlying disorder.



Example of Classification of Diffuse Hereditary PPK:			
Step 1	**Step 2**	**Step 3**	**PPK type**
Diffuse	No other ectodermal associations	Nonepidermolytic	**Unna-Thost type PPK**
Diffuse	No other ectodermal associations	Epidermolytic	**Vörner's type PPK**

Figure 1. Classification of palmoplantar keratodermas (adapted from references 1, 11 and 22)

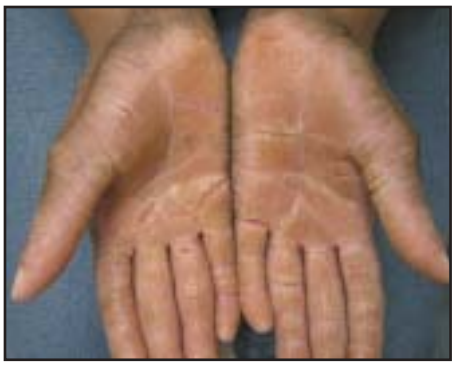


Figure 2
Symmetrical diffuse yellow waxy hyperkeratosis of the palms with fissures

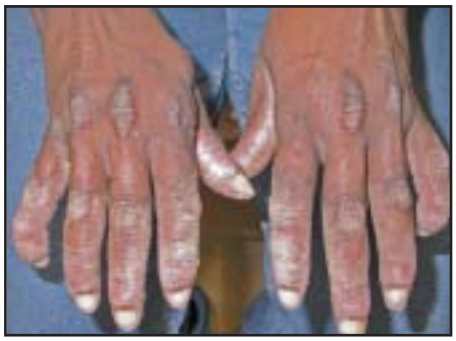


Figure 3
Hyperpigmented hyperkeratotic plaques over the metacarpal phalangeal joints and proximal interphalangeal joints

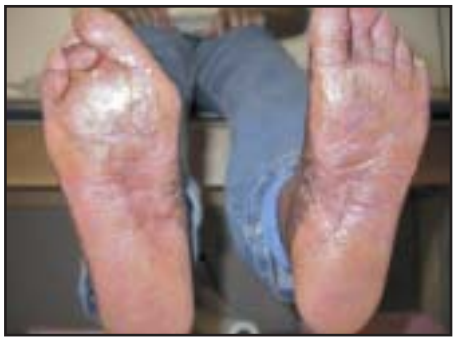


Figure 4
Symmetrical diffuse hyperkeratosis of the soles with partial sparing of the arches

Case Report

A 49 year old African American female presents to the clinic with uniform thickening of her palms and soles since shortly after birth. On examination, she was found to have symmetrical diffuse yellow waxy hyperkeratosis of the palms ending abruptly at the wrists. There are associated palmar fissures and contractures of the fingers (Figure 2). On the dorsum of her hands there are hyperpigmented hyperkeratotic plaques over the metacarpal phalangeal joints and proximal interphalangeal joints (Figure 3). Her finger tips and nails have a "parrot beak" appearance and both hands show arthritic changes. The feet reveal similar finding to the hands with diffuse hyperkeratosis which partially spares the arches (Figure 4). There is also mild symmetrical hyperkeratosis over the elbows.

Her past history is significant for hypertension, hypercholesterolemia, arthritis, chronic vertigo and a left bunionectomy. Her only hospitalization was for the birth of her daughter. She currently is on pravastatin (Pravachol), amlodipine/benazepril (Lotrel) and celecoxib (Celebrex). Family history is significant for a father, brother and niece with hereditary PPK of the Unna-Thost type.

Prior treatments included topical keratolytics, steroids and emollients which provided minimal improvement. She declined treatment with an oral retinoid because her niece had undergone treatment without any improvement.

Discussion

Hereditary PPK of the Unna-Thost type PPK is classified as a diffuse, nonepidermolytic PPK that has no other ectodermal disease associations. The Unna-Thost type (nonepidermolytic) is believed to be the most common form of hereditary PPK. However, since Unna-Thost type and Vörner's type PPK (epidermolytic) are clinically indistinguishable this is debatable [2, 9]. The underlying defect seems to be associated with keratin 1 which is one of the two main keratins found in the palmoplantar epidermis with the other being keratin 9. Keratin 1 is a type II keratin (basic, K1-K8) which is coded for on chromosome 12q13 [3, 10].

The classical presentation of this autosomal dominant disorder is symmetrical diffuse waxy yellow hyperkeratosis of the palms and soles which initially presents within the first couple years. Initially, there is erythema of the palms and soles that gradually progresses to hyperkeratosis. There is an abrupt cutoff at the wrists and there is often an area of erythema between the hyperkeratotic and normal skin. Other keratotic lesion can also be seen on the dorsum of the hands and feet or on the elbows or knees however, this is less commonly seen in this type of hereditary PPK. The hyperkeratosis of the knuckles is referred to as "cobblestone" hyperkeratosis. Some patients also have a narrowing of the pulp of the distal fingers leading to a "parrot beak" appearance of the nails and fingers [11].

Frequently, there is associated hyperhidrosis and concurrent dermatophyte infection. This often leads to malodor, maceration, peeling, pruritus and an underlying erythema which further complicates the disorder. *Trichophytum rubrum, T. Mentagrophytes, T.Verrucosum* and *Epidermophyton floccosum* are the major causes of dermatophytosis in the Unna-Thost type of PPK [12]. It is thought that activation of the immune system by *T. rubrum* may lead to the area of erythema in the transition between hyperkeratotic and normal skin in patients with PPK [13].

The workup of these patients should include a biopsy to rule out epidermolytic PPK (Vörner's type) which is clinically indistinguishable from nonepidermolytic PPK. The biopsy should be taken from a pressure point, not the periphery, to ensure the best chance of finding epidermolytic hyperkeratosis [14]. Histologically, nonepidermolytic PPK is nonspecific and can be seen in many of the keratodermas. The pathology shows orthokeratotic hyperkeratosis, acanthosis and either a normal or thickened granular layer in which the keratohyalin granules are uniformly shaped and evenly distributed throughout the cell. This is in contrast to epidermolytic PPK, in which there is also orthokeratotic hyperkeratosis but the granular layer has keratohyalin granules which are increased in size and located peripherally in the cell. Perinuclear vacuolar change with indistinct cell borders is also seen [15].

Treatment of this disorder is extremely difficult and ranges from topical therapy to surgery. The mainstay of therapy is topical with keratolytics, steroids, retinoids and emollients. Lactic acid, urea and salicylic acid are good keratolytics. Also, dermabrasion has been shown to immediately decrease the hyperkeratosis and improve the absorption of topicals [16]. Topical retinoids have been used with some success but skin irritation often limits treatment.

Other local measures include chiropody, decreasing local trauma with appropriate footwear and treating concurrent hyperhidrosis and fungal infections. Aluminum chloride and iontophoresis can be used for hyperhidrosis and itraconazole 100mg/day has been found beneficial in treating dermatophytosis [12, 21].

Oral retinoids have been used with some success but risk to benefit ratio must be considered because hyperkeratosis usually resumes shortly after stopping the medication. Currently, of the three generations of oral retinoids, the second generation or aromatic retinoids (acitretin and etretinate) are the most effective in treating disorders of keratinization [17]. The third generation retinoids (isotretinoin) are currently being studied for this use. The optimal adult dosage of acitretin for the treatment of nonpsoriatic disorders of keratinization was found to be between 20-50 mg/day with a recommended starting dose of 30-35 mg/day. Patients should be treated for 4 weeks before making dosage adjustments for maintenance. Interestingly, in a study by Blanchet-Bardon et al., 2 out of 3 patients with the Unna-Thost type PPK treated with acitretin had no change in clinically apparent disease. However, many of the other types of PPK had good response rates [18]. In one report there was a link between the keratin mutation and the effectiveness of oral acitretin and topical retinoids. Those with keratin 1 mutations (genetic cause of Unna-Thost type PPK) did not respond as well as those with K10 mutations [19]. This may help explain why only some types of PPK respond to oral retinoids.

Additional treatments include biotin and genetic counseling. Biotin in doses of 50mg/day for one month was shown to be beneficial in the treatment of patients with Unna-Thost type of PPK who had a low plasma biotin level. The beneficial effects however, were not seen in patients with normal levels of biotin [20]. Lastly, patients should be aware that the condition is genetic and can be passed on to offspring. Genetic counseling should be recommended to patients of childbearing age [21].

Conclusions

The hereditary PPK are a very complex group of disorders which may be difficult to distinguish clinically. With new advances in genetic testing it may be possible to distinguish these patients. However, since not every patient is amenable to genetic testing there are some important considerations to make when evaluating patients with hereditary PPK. A case of Unna-Thost type PPK has been presented which does not have any life threatening associations. However, since it is important to keep these in mind when evaluating patient with PPK a brief review of screening adults and children is presented.

When evaluating an adult patient with hereditary PPK it is important to note the age of onset and whether or not the PPK is focal or diffuse. Based on this, patients can be placed into two groups those with and without increased risk of esophageal cancer. If the patient has a diffuse hereditary PPK that started within the first couple years of life there is no increased risk of esophageal cancer. However, if the patient has a late onset (5-15y/o) focal hereditary PPK there could be an increased risk of esophageal cancer. In one report there was a 50% incidence by age 45 and a 95% incidence by age 65 with cancer being seen as early as age 25[8]. With this data it is imperative to recognize these patients so appropriate referral to a gastroenterologist for routine esophagogastroduodenoscopy and biopsy. The same group of patients also tends to have oral leukokeratosis which does not appear to have a malignant potential [7]. However, routine monitoring with biopsy should be obtained for suspicious lesions. The development of squamous cell carcinoma in areas of hyperkeratosis has also been reported therefore unusual or nonhealing ulcerated lesions should be biopsied [4].

When evaluating children with hereditary PPK it is important to look for signs and symptoms of cardiac abnormalities and sensorineural hearing loss. Many of the hereditary PPK are associated with cardiac abnormalities such as pulmonary stenosis, septal defects, cardiomyopathies and intraventricular conduction defects. Therefore, after thorough physical examination, electrocardiogram and echocardiogram should be obtained if warranted [5]. There are also specific hereditary PPK associated with sensorineural hearing loss. It is unclear in the literature at what age this occurs but has been seen within the first two years up to age 16 [6].

In conclusion, the hereditary PPK are a complex group of disorders. They are difficult to classify, treat and have been associated with many other diseases. When confronted with a patient with PPK, life threatening disease associations should be ruled out if indicated and treatment aimed at improving quality of life.

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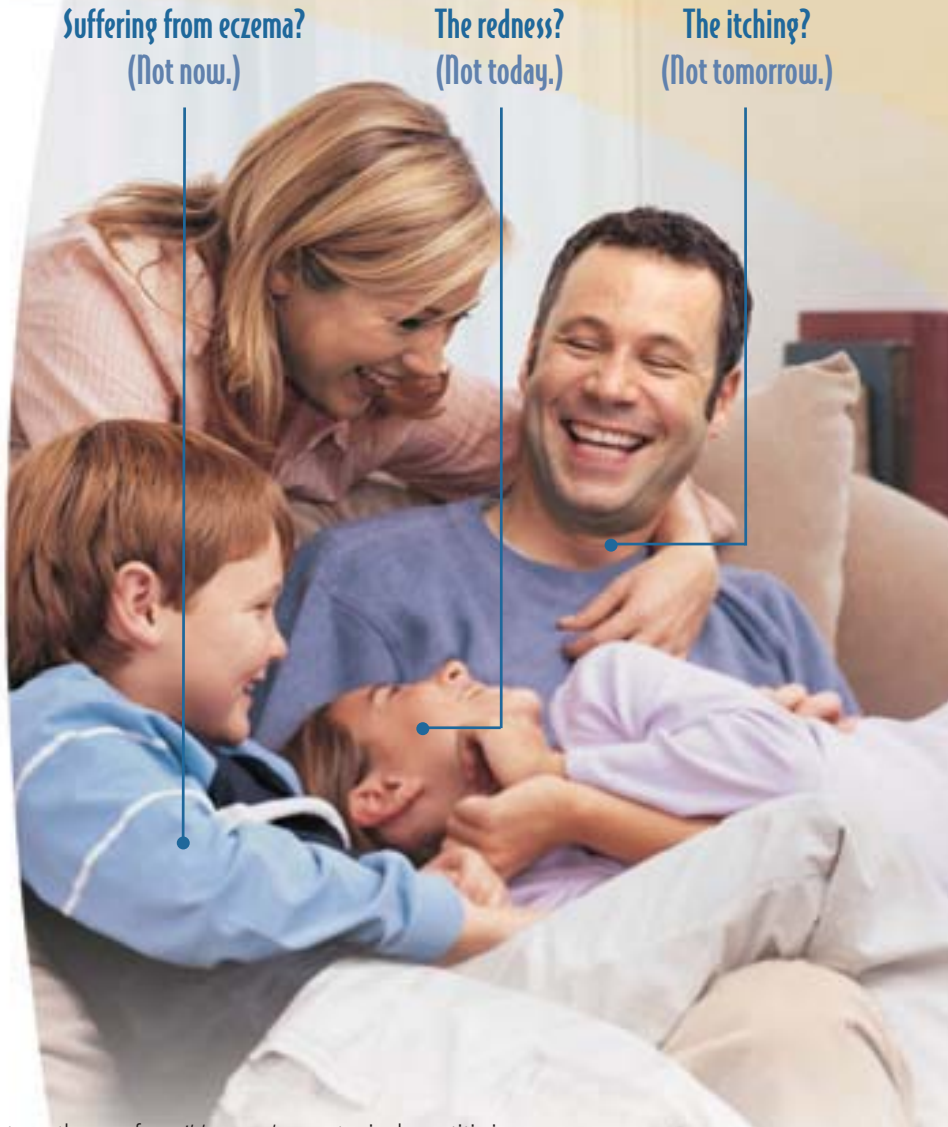

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CONTRAINDICATIONS: Elidel® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

PRECAUTIONS: General: Elidel® (pimecrolimus) Cream 1% should not be applied to areas of active cutaneous viral infections. Studies have not evaluated the safety and efficacy of Elidel Cream in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Elidel Cream, clinical infections at treatment sites should be cleared. While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with Elidel Cream may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these skin infections, the balance of risks and benefits associated with Elidel Cream use should be evaluated. In clinical studies, 14 cases of lymphadenopathy (0.9%) were reported while using Elidel Cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive Elidel Cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of Elidel Cream should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. In clinical studies, 15 cases of skin papilloma or warts (1%) were observed in patients using Elidel Cream. The youngest patient was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of Elidel Cream should be considered until complete resolution of the warts is achieved. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans *(see ADVERSE REACTIONS),* Elidel Cream shortened the time to skin tumor formation in an animal photo-carcinogenicity study *(see Carcinogenesis, Mutagenesis, Impairment of Fertility).* Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. The use of Elidel Cream in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of pimecrolimus. There are no data to support use of Elidel in immunocompromised patients. The use of Elidel Cream may cause local symptoms such as skin burning. Localized symptoms are most common during the first few days of Elidel Cream application and typically improve as the lesions of atopic dermatitis resolve. Most application site reactions lasted no more than 5 days, were mild to moderate in severity, and started within 1-5 days of treatment. *(See ADVERSE REACTIONS.)*

Information for Patients: Patients using Elidel should receive the following information and instructions:

- Patients should use Elidel Cream as directed by the physician. Elidel Cream is for external use on the skin only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
- Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using Elidel Cream.
- Patients should not use this medication for any disorder other than that for which it was prescribed.
- Patients should report any signs or symptoms of adverse reactions to their physician.
- Therapy should be discontinued after signs and symptoms of atopic dermatitis have resolved. Treatment with Elidel should be resumed at the first signs or symptoms of recurrence.
- Use of Elidel may cause reactions at the site of application such as a mild to moderate feeling of warmth and/or sensation of burning. Patients should see a physician if an application site reaction is severe or persists for more than 1 week.
- The patient should contact the physician if no improvement in the atopic dermatitis is seen following 6 weeks of treatment, or if at any time the condition worsens.

Drug Interactions: Potential interactions between Elidel and other drugs, including immunizations, have not been systematically evaluated. Due to the very low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year rat dermal carcinogenicity study using Elidel Cream, a statistically significant increase in the incidence of follicular cell adenoma of the thyroid was noted in low, mid and high dose male animals compared to vehicle and saline control male animals. Follicular cell adenoma of the thyroid was noted in the dermal rat carcinogenicity study at the lowest dose of 2 mg/kg/day [0.2% pimecrolimus cream; 1.5X the Maximum Recommended Human Dose (MRHD) based on AUC comparisons]. No increase in the incidence of follicular cell adenoma of the thyroid was noted in the oral carcinogenicity study in male rats up to 10 mg/kg/day (66X MRHD based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolic profile as by the dermal route. In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg/day (0.32% pimecrolimus in ethanol) 27X MRHD based on AUC comparisons. However, lymphoproliferative changes (including lymphoma) were noted in a 13 week repeat dose dermal toxicity study conducted in mice using pimecrolimus in an ethanolic solution at a dose of 25 mg/kg/day (47X MRHD based on AUC comparisons). No lymphoproliferative changes were noted in this study at a dose of 10 mg/kg/day (17X MRHD based on AUC comparison). However, the latency time to lymphoma formation was shortened to 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179-217X MRHD based on AUC comparisons). In a mouse oral (gavage) carcinogenicity study, a statistically significant increase in the incidence of lymphoma was noted in high dose male and female animals compared to vehicle control male and female animals. Lymphomas were noted in the oral mouse carcinogenicity study at a dose of 45 mg/kg/day (258-340X MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse oral carcinogenicity study at a dose of 15 mg/kg/day (60-133X MRHD based on AUC comparisons). In an oral (gavage) rat carcinogenicity study, a statistically significant increase in the incidence of benign thymoma was noted in 10 mg/kg/day pimecrolimus treated male and female animals compared to vehicle control treated male and female animals. In addition, a significant increase in the incidence of benign thymoma was noted in another oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus treated male animals compared to vehicle control treated male animals. No drug-related tumors were noted in the rat oral carcinogenicity study at a dose of 1 mg/kg/day male animals (1.1X MRHD based on AUC comparisons) and at a dose of 5 mg/kg/day for female animals (21X MRHD based on AUC comparisons). In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with the Elidel Cream vehicle alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, pimecrolimus, to the vehicle cream. A battery of *in vitro* genotoxicity tests, including Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an *in vivo* mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug. An oral fertility and embryofetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38X MRHD based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23X MRHD based on AUC comparisons), which was the highest dose tested in this study.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** There are no adequate and well-controlled studies of topically administered pimecrolimus in pregnant women. The experience with Elidel Cream when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. In dermal embryofetal developmental studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day (1% pimecrolimus cream) in rats (0.14X MRHD based on body surface area) and 10 mg/kg/day (1% pimecrolimus cream) in rabbits (0.65X MRHD based on AUC comparisons). The 1% pimecrolimus cream was administered topically for 6 hours/day during the period of organogenesis in rats and rabbits (gestational days 6-21 in rats and gestational days 6-20 in rabbits). A combined oral fertility and embryofetal developmental study was conducted in rats and an oral embryofetal developmental study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (2 weeks prior to mating until gestational day 16 in rats, gestational days 6-18 in rabbits) up to dose levels of 45 mg/kg/day in rats and 20 mg/kg/day in rabbits. In the absence of maternal toxicity, indicators of embryofetal toxicity (post-implantation loss and reduction in litter size) were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in the oral fertility and embryofetal developmental study conducted in rats. No malformations in the fetuses were noted at 45 mg/kg/day (38X MRHD based on AUC comparisons) in this study. No maternal toxicity, embryotoxicity or teratogenicity were noted in the oral rabbit embryofetal developmental toxicity study at 20 mg/kg/day (3.9X MRHD based on AUC comparisons), which was the highest dose tested in this study. An oral peri- and post-natal developmental study was conducted in rats. Pimecrolimus was administered from gestational day 6 through lactational day 21 up to a dose level of 40 mg/kg/day. Only 2 of 22 females delivered live pups at the highest dose of 40 mg/kg/day. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected at 10 mg/kg/day (12X MRHD based on AUC comparisons), the highest dose evaluated in this study. Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Elidel Cream may be used in pediatric patients 2 years of age and older. Three Phase 3 pediatric studies were conducted involving 1114 patients 2-17 years of age. Two studies were 6-week randomized vehicle-controlled studies with a 20-week open-label phase and one was a vehicle-controlled long-term (up to 1 year) safety study with the option for sequential topical corticosteroid use. Of these patients 542 (49%) were 2-6 years of age. In the short-term studies, 11% of Elidel patients did not complete these studies and 1.5% of Elidel patients discontinued due to adverse events. In the one-year study, 32% of Elidel patients did not complete this study and 3% of Elidel patients discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect. The most common local adverse event in the short-term studies of Elidel Cream in pediatric patients ages 2-17 was application site burning (10% vs. 13% vehicle); the incidence in the long-term study was 9% Elidel vs. 7% vehicle *(see ADVERSE REACTIONS).* Adverse events that were more frequent (> 5%) in patients treated with Elidel Cream compared to vehicle were headache (14% vs. 9%) in the short-term trial. Nasopharyngitis (26% vs. 21%), influenza (13% vs. 4%), pharyngitis (8% vs. 3%), viral infection (7% vs. 1%), pyrexia (13% vs. 5%), cough (16% vs. 11%), and headache (25% vs. 16%) were increased over vehicle in the 1-year safety study *(see ADVERSE REACTIONS).* In 843 patients ages 2-17 years treated with Elidel Cream, 9 (0.8%) developed eczema herpeticum (5 on Elidel Cream alone and 4 on Elidel Cream used in sequence with corticosteroids). In 211 patients on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity. Elidel Cream is not recommended for use in pediatric patients below the age of 2 years. Two Phase 3 studies were conducted involving 436 infants age 3 months - 23 months. One 6-week randomized vehicle-controlled study with a 20-week open-label phase and one long term safety study were conducted. In the 6-week study, 11% of Elidel and 48% of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on Elidel Cream had an increased incidence of some adverse events compared to vehicle. In the 6-week vehicle-controlled study these adverse events included pyrexia (32% vs. 13% vehicle), URI (24% vs. 14%), nasopharyngitis (15% vs. 8%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%), and diarrhea (8% vs. 0%). In the open-label phase of the study, for infants who switched to Elidel Cream from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those patients who remained on Elidel Cream. In the 6-month safety data, 16% of Elidel and 35% of vehicle patients discontinued early and 1.5% of Elidel and 0% of vehicle patients discontinued due to adverse events. Infants on Elidel Cream had a greater incidence of some adverse events as compared to vehicle. These included pyrexia (30% vs. 20%), URI (21% vs. 17%), cough (15% vs. 9%), hypersensitivity (8% vs. 2%), teething (27% vs. 22%), vomiting (9% vs. 4%), rhinitis (13% vs. 9%), viral rash (4% vs. 0%), rhinorrhea (4% vs. 0%), and wheezing (4% vs. 0%). The effects of Elidel Cream on the developing immune system in infants are unknown.

Geriatric Use: Nine (9) patients ≥ 65 years old received Elidel Cream in Phase 3 studies. Clinical studies of Elidel did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

ADVERSE REACTIONS: In human dermal safety studies, Elidel® (pimecrolimus) Cream 1% did not induce contact sensitization, phototoxicity, or photoallergy, nor did it show any cumulative irritation. In a one-year safety study in pediatric patients age 2-17 years old involving sequential use of Elidel Cream and a topical corticosteroid, 43% of Elidel patients and 68% of vehicle patients used corticosteroids during the study. Corticosteroids were used for more than 7 days by 34% of Elidel patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the patients that had used Elidel Cream and topical corticosteroid sequentially as compared to Elidel Cream alone. In 3 randomized, double-blind vehicle-controlled pediatric studies and one active-controlled adult study, 843 and 328 patients respectively, were treated with Elidel Cream. In these clinical trials, 48 (4%) of the 1171 Elidel patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8%-26% of patients treated with Elidel Cream. The following table depicts the incidence of adverse events pooled across the 2 identically designed 6-week studies with their open label extensions and the 1-year safety study for pediatric patients ages 2-17. Data from the adult active-controlled study is also included in this table. Adverse events are listed regardless of relationship to study drug.

Treatment Emergent Adverse Events (≥ 1%) in Elidel® Treatment Groups

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Elidel® Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel® Cream (N=335) N (%)	Elidel® Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel® Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and Infestations						
Upper RespiratoryTract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	<1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General Disorders and Administration Site Conditions						
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	<1%	<1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	<1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal Disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	15 (5.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	21 (7.7%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	<1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	<1%	<1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (0.4%)	<1%	3 (0.9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and Poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1%	1 (1.3%)	0
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)	<1%	<1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	<1%	0	6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.9%)	2 (2.7%)	0
Nervous System Disorders						
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

*Ages 2-17 years

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Do not freeze.

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"Herpes Gestationis" - A Case Presentation

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Case Presentation

A 32 year old female at the 20th week gestation (gravida 4, para 4) presented to the office complaining of an intensely pruritic rash that began two weeks ago on her abdomen and had progressed to her breasts and arms, sparing the face, palms and feet. Generalized small vesicles, tense bullae and secondary lesions of excoriation were noted. The patient denied any fever, chills, nausea or vomiting. Patient had never developed this type of rash with her previous pregnancies. The patient's past medical history was unremarkable. Previous surgical history was only significant for a cesarean section. Current medications included cephalexin and hydroxyzine.

An assessment of Herpes Gestationis was established. To confirm this diagnosis, three punch biopsies of normal and involved skin were done and sent for histologic and immunopathologic exams. The patient was treated with prednisone 20mg/day, topical corticosteroids and diphenhydramine. The patient returned to the office for a one week follow-up with much improved signs and symptoms. The biopsy report confirmed the diagnosis of Herpes Gestationis. The prednisone was then tapered and discontinued.

Discussion

Herpes Gestationis (pemphigoid gestationis) is a rare (1 in 50,000 pregnancies) autoimmune antibody-mediated disease that occurs either during pregnancy or the postpartum period [2,3]. The name of the disease is misleading because Herpes Gestationis has no association with the herpesvirus infection.

The onset of disease is usually during the second or third trimester (average 21 weeks gestation). The rash initially appears as edematous, erythematous, annular or polycyclic plaques, appearing in crops with tense vesicles and bullae on the abdomen and extremities, and coalesce rapidly to also involve the back and chest. Usually the face, oral mucosa, palms and soles are spared. Pruritis is intense. Duration of the lesions is variable. Seventy-five percent of patients will have a flare at delivery, but typically spontaneous resolution occurs within three months postpartum [2,4].

Herpes Gestationis may occur for the first time during any pregnancy, but once it has occurred, it tends to reappear in subsequent pregnancies earlier and more severely. There also may be recurrences with the use of oral contraceptives or with menses leading to a protracted course; "conversion to Bullous Pemphigoid" [3,4]. Herpes Gestationis may also occur in association with hydatidiform mole and choriocarcinoma.[1,3,4].

The etiology of Herpes Gestationis remains uncertain. There is evidence that supports

Herpes Gestationis as an autoimmune process. There is a genetic predisposition with 90% of patients expressing class II antigens [alleles HLA-DR3 (61-80%), HLA-DR4 (52%) or both (43-50%)] and most carry a class III antigen (C4 null allele) [4]. Herpes Gestationis appears to be mediated by an Ig-G1 subclass and the antigenic target is a 180-kd hemidesmosomal glycoprotein which is the bullous pemphigoid antigen (BPAg2) [2,4]. African American women rarely manifest Herpes Gestationis [4]. This is theorized to be secondary to the low incidence of HLA-DR4 in African Americans[4]. There is also an increased risk of developing Graves Disease in patients with a history of Herpes Gestationis[1]. There is no other maternal health risks in Herpes Gestationis.

Herpes Gestationis has been associated with prematurity and small-for-gestational-age neonates, but without any increased fetal morbidity and mortality [3]. The newborn fetus will have cutaneous involvement approximately 10% of the time, most likely secondary to passive transfer of Herpes Gestationis antibody [2,3,4]. The cutaneous eruption is self-limited and resolves spontaneously within days to weeks.

Upon histopathologic exam of the bullous lesions, you see subepidermal edema and inflammatory dermal infiltrate with eosinophils and spongiosis [4]. The characteristic direct immunofluorescence feature is a linear bandlike deposit of C3 along the basement membrane zone with concurrent IgG deposition [2,4].

Oral corticosteroids with starting dosages of 20-40mg/day are usually required for control [1,2,3,4]. The dosage is then gradually tapered. The use of topical corticosteroids are helpful for mild cases. Pyridoxine has been reported to have helped. Azathioprine has also been used for disease that is steroid-dependent or steroid-resistant [1]. Case studies have indicated some benefit from tetracyclines in postpartum Herpes Gestationis, but their effectiveness requires further investigation[4].

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Unusual Hypermelanosis of Anonymous Origin

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ABSTRACT

Hypermelanosis due to physical stress can have a unique distribution in the skin. In this report I am describing a young arabic female who presented with generalized hyperpigmentation which was more pronounced over bony prominences of the vertebral column, the left clavicular area and the costal bones of the chest.

Introduction

Melanoderma associated with mechanical factors have been reported frequently in the Japanese literature.[1,2] It is caused by prolonged mechanical friction, pressure, and chronic irritation. It is not gender specific and genetic factors are questionable. Here I am reporting a young healthy female with generalized hyperpigmentation which was reinforced over bony prominences.

The Case

A 19-years old Arabic female presented with generalized hyperpigmentation on the trunk which was more obvious at the bony prominences of the vertebral column, the left clavicular bones and the costal bones of the chest. The problem started since three years as gradual skin darkening especially on the above mentioned areas with no change in the skin surface. There was no associated symptoms. Past medical history, drug history including systemic and topical treatments and family history for similar condition was negative. Questioning about the patient daily habits including body scrubbing , nylon towels use, tight clothings, nylon textiles and type of bed was irrelevant On examination of the skin there was diffuse hyperpigmentation with darker patchy lesions of blurred borders over the spinous processes of the vertebral column extending from the neck spines to the sacral area (figure 1) The surface was not indurated. Similarly the area over the left clavicular bone and the costal bones were also affected with hyperpigmentation but the extremeties were free (figure 2). In addition the patient was of thin asthenic body type. Laboratory evaluation including complete blood count, liver function tests, endocrinological profile of adrenal gland were all within normal limits. A biopsy from the hyperpigmented lesion on the back showed flattened epidermis with no signs of vacuolar interface changes. In the papillary dermis there were mild perivascular mononuclear inflammatory cell infiltrate and prominent melanophages (figure 3). S-100 protein stain showed normal quantity of melanocytes. PAS and congo red stains were negative excluding the presence of amyloid.

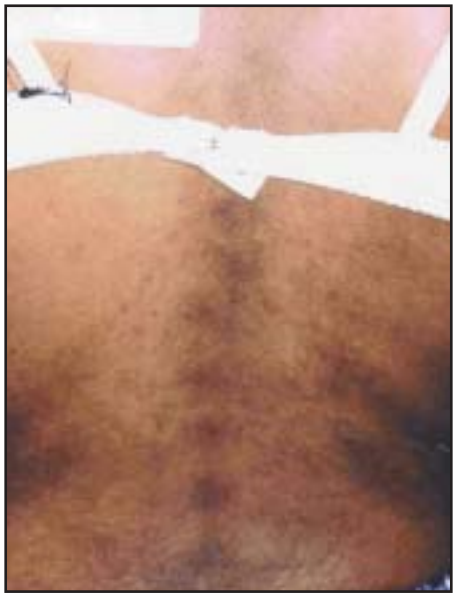

Figure 1
Diffuse hyperpigmentation of the back with darker patches over bony prominences of the vertebral column and the lower costal ribs.

So our patient was diagnosed as a unique case of unusual hypermelanosis of the trunk. A trial of treatment with topical hydroquinone cream as a bleaching agent for 3 months proved to be ineffective. She is now followed up periodically in the clinic for evaluation of the condition.

Discussion

Melanoderma associated with mechanical factors have been reported frequently in the Japanese literature.[1,2,3,4] It was thought to be precipitated by physical stress such as exposure to prolonged mechanical friction, pressure, heat, rubbing and chronic irritation.[5,6,7,8,9] In fact some authors considered friction melanosis as a dinstinct pigmentary disorder.[9,10] Besides some people are more susceptible to this type of melanosis especially skin type III-IV. In Mexico, friction melanosis was seen in the clavicular zone, the outer aspects of the arms and forearms, the back and the anterior aspects of the legs because of the use of bath pads for rubbing.[11,12] Hyperpigmentation due to performance of a precise rituals within a religious context were also reported in muslim men called prayer nod-

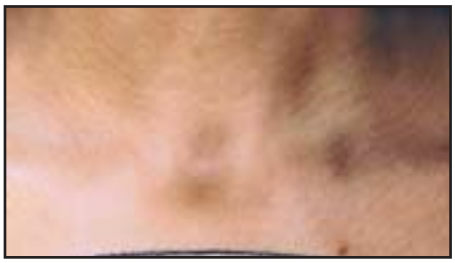

Figure 2
Similar lesions over the left clavicular bone.

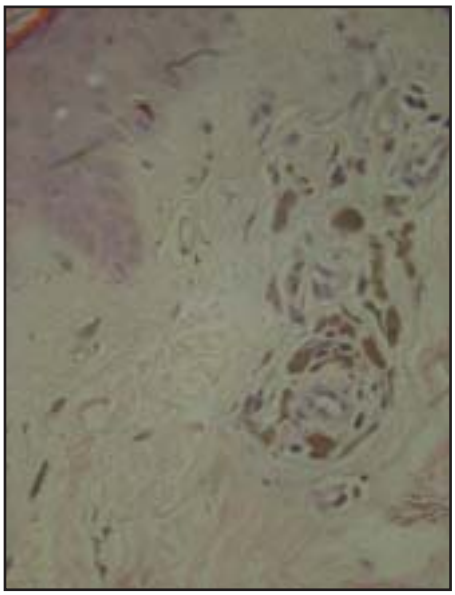

Figure 3
Histologic features of the hyperpigmented lesion showing flattened epidermis and prominent melanophages. (H&E, X40).

ules and in Talmudic male students in jewish.[13,14] Histologically no specific findings were documented, some have found flattened epidermis, necrosis of isolated keratinocytes with vacuolar interface changes and incontinence of pigment in the form of free melanin or inside melanophages in association with a superficial perivascular lymphocytic infiltrate.[12] While others found epidermal hyperplasia and diffuse hyperpigmentation at the base of the epidermis with no melanophage or interface dermatitis or inflammatory infiltrate.[14] Macular amyloidosis was also found in other reports which was not documented in our case.[10] It is believed that the histopathologic changes are variable because this is a dynamic process with the late stage characterized by postinflammatory hyperpigmentation.[11] It is important to stress that this condition is not gender specific and genetic factors are in question. Environmental factors and the duration of the stimulation are definitely important in any susceptible person. Here I am reporting a young arabic female who had hyperpigmentation similar in distribution to that reported in Japanese females and Davener's dermatosis but with no clear history of regular body scrubbuing or heavy physical exertion. It could be that the patient was being continuously exposed to minimal degree of skin irritation (for example certain type of textiles) causing subclinical dermatitis and resolving with postinflammatory hyperpigmentation but this does not explain the exagerated hyperpigmentation over bony prominences in some areas of the trunk. On the contrary, it is possible that this type of hypermelanosis represents a specific pigmentary disorder in genetically susceptible individuals as in our patient and the two siblings reported by Naimer and his colleagues.[14] Further studies are needed to determine factors related to this disease and individuals who are susceptible to such pigmentary changes.

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Photodynamic Therapy for Intra- Epidermal Squamous Cell Carcinoma: Preliminary Results With Histopathologic Correlation

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ABSTRACT

Photodynamic therapy is an established method of treating multiple actinic keratoses. After a review of the literature we examined the effectiveness of PDT in treating squamous cell carcinoma in situ based on histopathologic examination of biopsies performed prior to and 6 weeks after PDT in three patients. Therapy resulted in two complete clearances and one treatment failure at six weeks. While PDT offers the potential of cure while sparing the morbidity of excisional surgery, optimization of the procedure is needed to achieve a cure rate comparable with surgery.

Introduction:

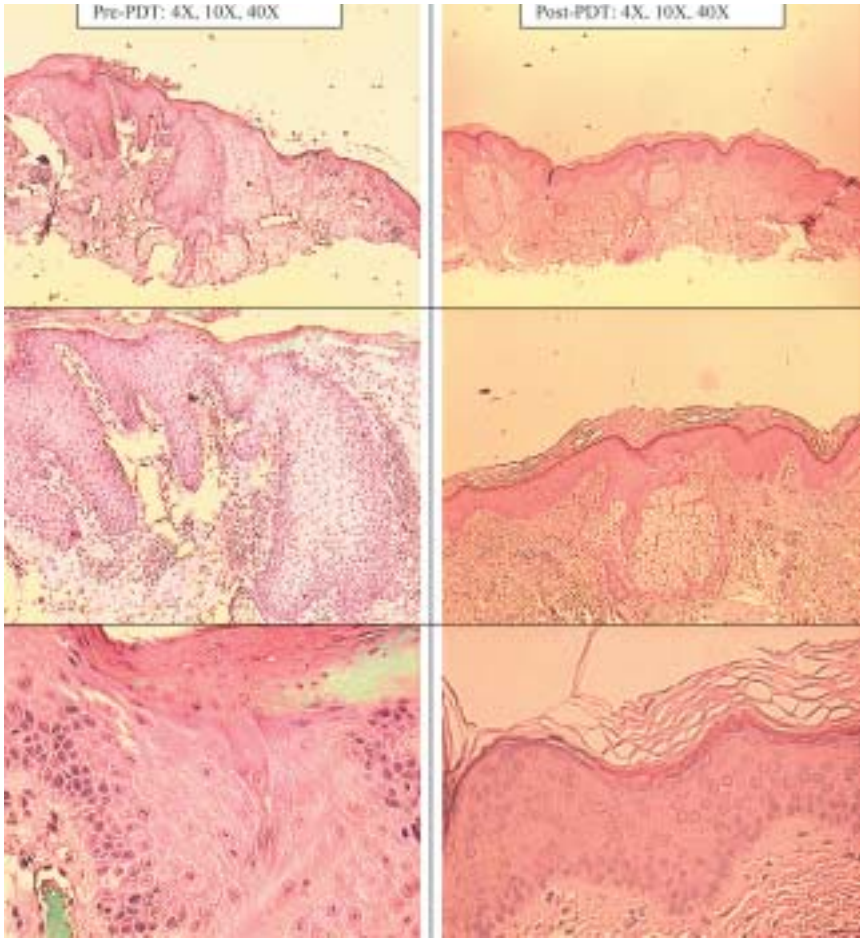
Squamous cell carcinoma in situ is a common lesion that causes significant morbidity and potential mortality to our society. Histological features include full thickness epidermal and adnexal carcinoma without dermal invasion. Development into invasive squamous cell carcinoma occurs in 26% of cases with subsequent metastasis in 16%1. The ideal treatment option would offer a high cure rate and low morbidity and cost. Of the many modalities available to the clinician, surgical excision or mohs surgery offers the highest cure rate at or above 95% but may not be applicable to very large or multiple lesions. Radiation therapy and electrodesiccation with curettage have been shown to be nearly as effective as surgery, but are operator dependent and carry significant morbidity2. Topical 5-fluorouracil and imiquimod have proven useful for field treatment of actinic keratoses and more recently superficial carcinomas such as basal cell carcinoma and squamous cell carcinoma in situ 3-5. The rate of cure for topical therapies, however, remain lower that those of surgical modalities.

Photodynamic therapy (PDT) is the use of a photosensitizer to facilitate selective O2 radical induced intracellular damage and apoptosis. In 1999, the use of topical aminolevulinic acid (ALA) and blue light gained approval by the FDA for the treatment of multiple actinic keratoses of the face and scalp. Aminolevulinic acid is a naturally occurring rate limiting reaction product of heme and porphyrin synthesis. The uptake of ALA into a cell provides the substrate which the cell's own biochemical machinery uses to produce large amounts of protoporphyrin IX (PpIX). PpIX then acts as the photosensitizer by accepting light energy and creating singlet O2 species, leading to cellular oxidative injury and eventual death. The deranged lymphatic drainage and higher metabolic rate of dysplastic lesions favors the partitioning of ALA to cancerous lesions. Studies of ALA-PDT have demonstrated 80-100% clearance of actinic keratoses1. A search of the literature for ALA-PDT use in squamous cell carcinoma in situ produced several studies reporting 88-100% initial clearance and 69-89% clearance at 12 months 6-10. We decided to evaluate the effectiveness of this modality on biopsy proven squamous cell carcinoma in situ by histopathologic examination.

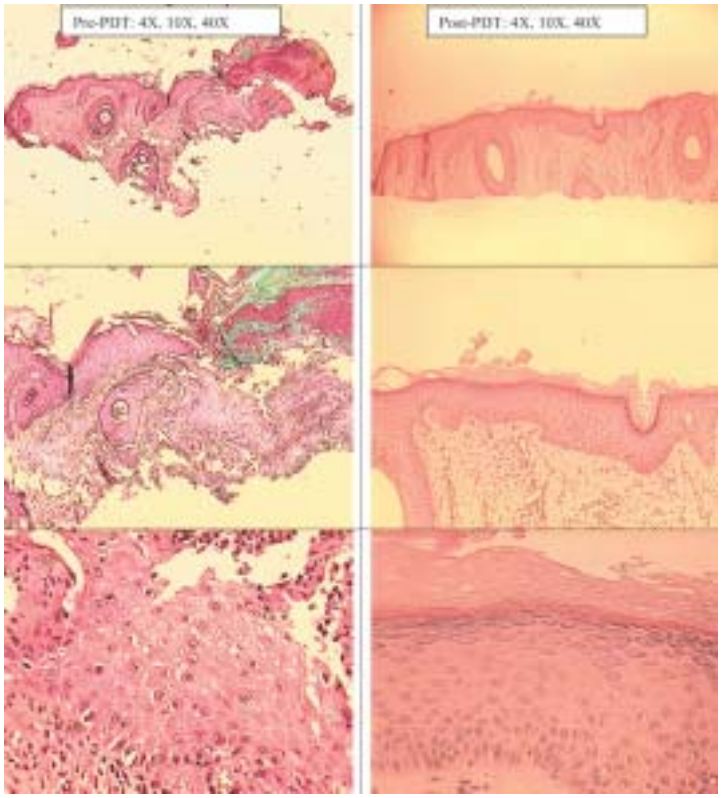
Methods:

Three patients with documented squamous cell carcinoma in situ who were reluctant to or had refused surgical excision were offered this experimental therapy. After informed consent was granted, the patients agreed to follow up biopsy and

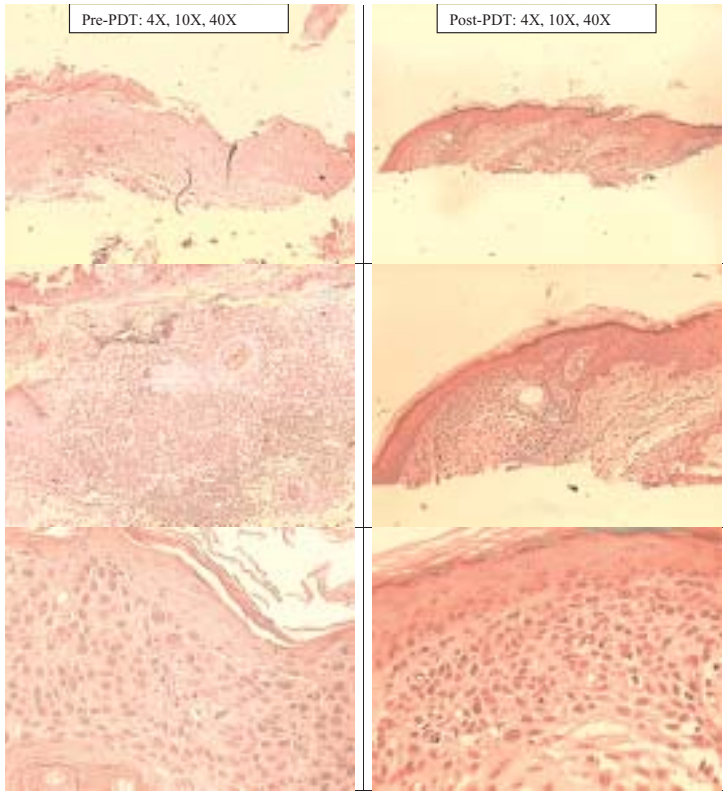
Patient 1



Patient 2



Patient 3



further treatment if required. Endpoints were planned for 6 weeks, 6 months, and 12 months. The lesions were photographed, and a triple application of 5-aminolevulinic acid HCL (Levulan) was applied at both 18 and 4 hours prior to a 16 minute illumination with blue light (10 J/cm2).

Results:

All three patients tolerated the procedure well. There was complete clinical cure in all three patients at six weeks. Examination of the biopsy specimens from both patients 1 (posterior neck) and 2 (mesolabial) reveal complete clearance of squamous cell carcinoma in situ. The histophotomicrographs demonstrate the return of an ordered epidermis as well as an improvement in dermal collagen appearance. While the biopsy status post treatment of patient 3 (ear) shows clearance of the squamous cell carcinoma in situ, it revealed basal cell carcinoma. This lesion was subsequently treated with electrodesiccation and curettage. 6 and 12 month follow up for all three patients have been planned.

Discussion:

Photodynamic therapy as a modality for treatment of squamous cell carcinoma in situ has the potential of sparing the morbidity of excisional surgery but as of now cannot offer a cure rate that is comparable. Variables being examined to increase the effectiveness of this therapy include choice of sensitizer, skin preparation and occlusion, incubation time, and illumination source. In our study, the initial results reveal 2/3 histopathologic cure at 6 weeks and one treatment failure. This failure was possibly due to inclusion of a collision tumor in which the initial biopsy failed to reveal the basal cell carcinoma. In our practice we will continue to utilize ALA-PDT for field treatment of actinic keratoses but remain hesitant for its use for thin non melanoma skin cancers until higher cure rates have been documented.

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Multiple Symmetrical Lipomatosis: A Case Report and Review

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ABSTRACT

Multiple Symmetrical Lipomatosis (MSL) is a rare metabolic condition characterized by the abnormal growth of fatty masses around the face, back of the head, neck, upper arms, abdomen and back in a specific distribution. It usually affects both sexes, particularly those with an alcoholic background, with a male to female ratio of 15:1. Treatment consists of excision of the masses, although there is a chance of recurrences. This article will discuss a patient's case in detail. Additionally, a review of the literature and treatment modalities associated with MSL will be discussed.

Case Presentation:

A 38-year old Caucasian male was referred to the dermatology clinic by his gastroenterologist for evaluation of non-pruritic and non-tender symmetrical nodules on his shoulders, chest, abdomen and lower back of 3 months duration. Prior to this, the patient was otherwise healthy but reported a 10-pound weight gain and GI upset for about one month. The patient was been seen by the gastroenterologist for work up, which showed slightly elevated liver function enzymes, which were attributed to the patient's alcohol intake. The patient was negative for Hepatitis B and C. CT scan of the abdomen and pelvis were also unremarkable. The patient does not smoke, but reports an alcohol intake of 2-3 drinks a night for many years. The patient has no medication allergies and currently takes Paxil and Chlordiazepoxide, both for anxiety. Past medical history is significant for ventricular tachycardia status post ablation and idiopathic infertility. His family history is remarkable for ovarian cancer in his mother and thyroid disease in his father. No family members have had similar skin lesions.

Physical examination revealed bilateral, symmetrical soft, subcutaneous non-tender nodules involving his shoulders, chest, abdomen and lower back with no epidermal changes. A 6mm punch biopsy was performed on the right abdomen, which revealed a normal skin specimen without enough tissue to confirm a lipoma.

Laboratory test results were as follows: Amylase 58 (nl 25-115 G/L), Lipase 227 (nl 114-286 U/L), total protein 7.9 (nl 6.4-8.2 g/DL), Alk phosphatase 80 (nl 50-136 U/L), Bilirubin total 2.0 (nl 0.0-1.0 mg/DL), Bili Direct 0.4 (nl 0.0-0.3 mg/DL), Bili Indirect 1.6 (nl 0.0-1.0 mg/DL). Iron and thyroid studies were normal.

The clinical and histopathologic differential diagnosis consists of Multiple Symmetrical Lipomatosis, Familial Lipomas, Lipodystrophy, Weber-Christian panniculitis, nodular fasciitis, Adiposis Dolorosa, Gardner's Syndrome and liposarcoma. Given the clinical and histological findings the consensus was that the patient has Madelung's Disease or Multiple Symmetrical Lipomatosis.

Discussion:

MSL, Multiple Symmetrical Lipomatosis, also known as Benign Symmetric Lipomatosis, Madelung's Disease and Lanois-Bensaude Syndrome is a metabolic condition characterized by the growth of fatty masses around the face, back of the head, neck, upper arms, abdomen and back in a specific distribution.

In 1880, Otto Madelung described the classic "horse collar" cervical distribution of the lipomatous tissue. Ten years later, Lanois and Bensaude further defined this syndrome as multiple symmetric unencapsulated fatty accumulations.[1,2,3] It is because of the lack of membranous capsule as well as the absolute symmetry that the condition is often dismissed as simple obesity.

Lipomas are slow growing, almost always benign adipose tumors that present as nonpainful, round, mobile masses with a characteristic soft, doughy feel. Microscopically, lipomas are composed of mature adipocytes arranged in lobules usually surrounded by a fibrous capsule. Occasionally a nonencapsulated lipoma infiltrates into muscle, which is then referred to as an infiltrating lipoma..[4,5,6,7]

MSL affects adults from 30 to 60 years of age with the highest incidence reported in males and in particular those with an alcoholic background.[1,8] The incidence is highest in the Mediterranean area.[9,10] Up to 90% of the patients with Madelung's Disease have associated alcoholism. The lipogenic, antilipolytic, and decreased lipid oxidation effects of alcohol may play a role in the development of adipocyte hyperplasia in a susceptible person.[1] Associated disorders described in MSL include hyperuricemia, diabetes mellitus, hypothyroidism, liver disease, polyneuropathy, abnormal glucose tolerance, hyperlipidemia, and malignant tumors.[1,11]

Two patterns of distribution of lipomatous tissue have been identified. In the type I pattern, which affects primarily men, the circumscribed protruding masses affect the nape of the neck, supraclavicular and deltoid regions. In the type II variant, affecting both men and women, lipomatous tissue diffuses and extends down over the trunk and the proximal part of the extremities, giving the patients the appearance of simple obesity.[1] Because of the symmetry, regular physical exam may not identify the

Table I. Differences between lipomatosis and lipomas

	Lipomatosis	*Lipomas*
Clinical lesions	Diffuse and symmetric	Single or multiple tumors
Infiltration of adjacent tissues	Present	Generally absent
Connective tissue capsule	Absent	Present

(Modified from Ogawa A, Nakamura H, Takahashi H. J Oral Maxillofac Surg. 1988;46:502-4.)

condition. The location of the masses, a history of weight gain, even in a reduced calorie intake, extreme fatigue and muscle aches are indicators that there is a need for further investigation. Over the years, the fat deposits achieve a large size, become cosmetically deforming, and in advanced cases, cause dyspnea and dysphagia.[9,12]

Histologic examination shows that cells in the abnormal lipomatous areas are indistinguishable from those in normal fat, although the adipocyte in MSL are smaller and multivacuolated suggesting a possible origin in brown fat.[1,8]

Treatment:

Weight loss and abstinence from alcohol are still recommended; however, they do not reverse or stop the progression of the disease once it is established.[9] Most lipomas are best left alone, but rapidly growing or painful lipomas can be treated with a variety of procedures ranging from steroid injections to excision of the tumor. Conservative surgical therapy is indicated to relieve functional impairment and to improve cosmetic deformities.

Nonexcisional treatment of lipomas includes steroid injections and liposuction. Steroid injections result in local fat atrophy, thus shrinking of the lipoma. Injections are best performed on lipomas less than 1 inch in diameter. A one-to-one mixture of 1% Xylocaine and Kenalog, in a dosage of 10mg per mL, is injected into the center of the lesion. Response is expected to occur with 3 to 4 weeks. Liposuction can be used to remove small or large lipomatous growths.[4,13]

Small lipomas can be removed by enucleation. After an incision is made over the lipoma, a curette is placed inside the wound to free the lipoma from the surrounding tissue. Once freed, the tumor is enucleated through the incision using the curette. Sutures are usually not needed and a pressure dressing is applied to prevent hematoma formation.[4]

Larger lipomas are best removed by excisions that follow the skin tension lines. Dissection is performed beneath the subcutaneous fat to the tumor and tissue cutting is performed under direct visualization using a no.15 scalpel or scissors around the lipoma. Care must be taken to avoid cutting nerves or blood vessels that may lie beneath. Once the lipoma is dissected from the surrounding tissue, it is delivered as a whole. Hemostasis is achieved using hemostats or suture ligation. The dead space created beneath the skin is closed using buried, interrupted 3-0 or 4-0 Vicryl sutures. The wound is generally checked in 2-7 days and the sutures removed after 7 to 21 days depending on location.[4]

Complications of Lipoma Excision[4]

1. Surgical Infection/ Cellulitis/ Fasciitis
2. Ecchymosis
3. Hematoma Formation
4. Injury to Nerves with permanent paresthesia/ anesthesia
5. Injury to vessels/ vascular compromise
6. Deformity
7. Scarring
8. Muscle Injury
9. Fat Embolus
10. Osteomyelitis

In conclusion, we have presented a 38 year old male who was diagnosed with Multiple Symmetrical Lipomatosis, MSL. MSL is a rare disorder that is associated with abnormal lipid distribution in a symmetrical fashion around the face, neck, abdomen and back. A defect in fat cell lipolytic pathways is a suggested mechanism for the accumulation of adipose tissue. We have presented a review of literature on Multiple Symmetrical Lipomatosis and various treatment options available. Hopefully, through further reports, a common unifying theme may become apparent that will explain its pathogenesis. Once this is known, perhaps we will have more effective treatment options.

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A Word About Malignant Melanoma

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ABSTRACT

Malignant melanoma is very dangerous because it can occur anywhere in the body and has a great tendency to metastasize. Biochemical and genetic changes secondary to ultra-violet B radiation from the sun lead to the formation of melanoma cells. Sunscreen use has no effect.

Dermatologists, unfortunately, are not usually familiar with these biochemical and genetic changes.

The purpose of this article is to acquaint practitioners with some alternatives available to prevent the onset, growth and spread of melanoma and to provide the genetic and biochemical rationale for their use.

Alternative remedies mentioned include diet, caffeine, green tea, quercetin, tocotrienols, vitamin E, omega-3-fatty acids, curcumin, boswellia, melatonin, PPAR gamma agonists, milk thistle, genestein, butyrate, alpha lipoic acid, N-acetylcysteine, vitamins K, A, and C, selenium, taurine, glycine, L-carnitine, honey and astragalus. Of course there are many others that have not been included. It would be impossible to be totally complete.

At least, the article should give the practitioner the basic tools needed to evaluate the true effectiveness of a vitamin or supplement.

There are many pre-malignant and rare skin cancers to study, but I will just concentrate on melanoma. The three most common skin cancers, simply put, vary from the non-metastasizing basal cell carcinoma, to the dangerous squamous cell carcinoma, that can slowly metastasize and the ominous malignant melanoma.

Ultra-violet B (UVB) radiation from the sun has been implicated in all three. If one can determine the actual specific causes of the cancers, prevention becomes much easier.

Cancer can be seen as a result of a genetic process causing the unregulated proliferation of a given cell combined with the loss of differentiation and apoptosis (programmed cell death). i.e. There are genes that specifically inhibit cell division and act as a "brake" to stop the cells from wild reproduction. One is known as the cyclin-dependent kinase inhibitor gene, CDKN2A/p16INK4A that is inactivated by the melanoma cells. Another gene, p21CIP1, also an inhibitor gene, is induced by treating the melanoma cells with histone deacetylase inhibitors, namely butyrate and phenylbutyrate. [1]

These will be discussed later.

Exposure to UVB radiation promotes the formation of cyclooxygenase- 2 (COX-2) and other inflammatory cytokines and ornithine decarboxylase (ODC) in the keratinocytes of the skin. These promote carcinogenesis. Melanoma cells have actually been induced in normal melanocytes by combining UVB radiation with basic fibroblast growth factor, stem cell factor and endothelin-3 within four weeks exposure. [2]

There are extremely competent dermatologists who can identify and remove suspicious skin lesions in a flash. Unfortunately, when questioned about prevention they can only offer sun avoidance and sunscreen lotions.

Sunscreen however, does not prevent melanoma. A quantitative review of the world-wide literature published from 1966 to 2003 reported "no association was seen between melanoma and sunscreen use." The user of sunscreen may obtain a false sense of security resulting in increased sun exposure and therefore an increased risk. [3]

The basic reason for this "letter" is to inform the reader that there are many other avenues, aside from chemotherapy, that can prevent the onset, prevent the spread, and even promote the elimination of melanoma.

The frightening thing about melanoma is that it can start in areas where the sun doesn't shine. Melanoma has started in the esophagus, small intestine, urinary bladder, rectum and other locations. It can spread anywhere including the heart and brain. Prognosis is poor unless it is caught in an early stage, either in-situ or with less than 0.75 mm. penetration.

Prevention depends on removing as many exciting factors (such as the sun) and adding as many inhibiting factors found tolerable.

The easiest way to prevent melanoma is through the diet. A strong inverse relationship between high intakes of polyunsaturated fatty acids (especially omega-3 type) and melanoma was noted. Conversely, women who have two or more drinks a day of alcoholic beverages (20 grams of alcohol) had 2.5 times the risk of melanoma as non-drinkers. Antioxidants (beta-carotene, vitamin E, and zinc) were effective in reducing the incidence. [4]

Caffeine has been shown to reduce the incidence of skin cancer due to UVB exposure. It has been shown that caffeine suppressed the progression of quiescent cells into the cell cycle. This may be due to the inhibition of cell growth signal-induced activation of cdk4, which may be involved in blocking carcinogenesis in vivo. [5] It also inhibits solid tumor development, invasion and growth of pulmonary metastases induced by melanoma cells as well as high-grade tissue sarcoma. [6] Caffeine was an effective inhibitor of metastatic activity. These effects were related to the depletion of glutathione and increased lipid peroxidation in the melanoma cells associated with increased glutathione S-transferase activity. [7]

Exposure to UVB also causes increased interleukin-10 (IL-10). IL-10, an immunosuppressive cytokine derived from T2 lymphocytes, suppresses the immune responses the body needs to defend itself from cancer cells. Green tea contains (-)-epigallocatechin-3-gallate (EGCG), one of the most potent of the green tea polyphenols. Drinking green tea reduced erythema, oxidative stress and infiltration of inflammatory leukocytes in the skin caused by UVB exposure. It also reduced IL-10 and increased IL-12. IL-12 increases immune responses. Green tea, therefore, can be used to prevent photo-aging, melanoma and non-melanoma skin cancers. [8]

Quercetin, a flavonoid class of polyphenols, is found in apples, onions, and tea. It has been shown to inhibit melanoma growth, invasion and metastases. Quercetin is available in health food stores, etc. It is usually combined with bromelain to increase its absorption and bio-availability.

Quercetin directly reduces protein kinase C (PKC) activity and may block the invasion of melanoma cells by inhibiting promatrix metalloproteinase-9 (pro-MMP-9) via the PKC pathway, causing cell cycle arrest. [9,10] Quercetin was able to inhibit the

proliferation, growth, and invasion of melanoma cells after 48 hours exposure. This was accomplished by causing remarkable apoptosis in the cells. Furthermore, quercetin markedly inhibited the expression of the anti-apoptotic protein Bcl-2. [11]

Elevated levels of Bcl-2 are associated with many cancers including breast cancer. Therefore anything that can block Bcl-2 would be good to treat any cancer.

Isoprenoids are mevalonate-derived constituents of fruits, vegetables, and cereal grains. They can suppress the growth of melanoma cells in vitro and in vivo. Orange oil, which is 90% D-limonene, and its derivative, perillyl alcohol (found in lavender oil) both have anti-cancer properties.

d-gamma tocotrienol, a member of the vitamin E family, that is derived from heated rice bran, was able to reduce melanoma growth by 50%. Tocotrienols can also lower cholesterol and LDL levels probably because they also inhibit HMG-CoA reductase activity. D-alpha tocopherol (vitamin E) and other tocotrienols also suppressed melanoma cell growth but to a lesser extent. [12,13]

Fish lipid oil [omega-3-fatty acids containing eicosopentanoic acid (EPA) and docosohexanoic acid (DHA)], can reduce the invasiveness and lung metastases of melanoma cells. They reduce the metastases by converting tumor cells into benign cells. Arachidonic acid, which is found in high quantities in red meat, is the source of COX-2 and 5-lipoxygenase (5-LIPO). Arachidonic acid is also produced by the action of delta-5- desaturase on dihomo gamma linolenic acid (which is derived from gamma linolenic acid) (GLA). COX-2 and 5-LIPO are required for the invasive and metastatic qualities of melanoma and other tumor cells. EPA blocks the action of delta-5-desaturase decreasing the production of arachidonic acid and subsequently reducing the levels of COX-2 and 5-LIPO. Therefore you can see why EPA would have an anti-cancer effect. [14]

DHA is available alone or combined with EPA. DHA, but not EPA, causes cell cycle arrest and apoptosis in melanoma cells. [15]

The active ingredient of the spice turmeric is curcumin. Curcumin is antioxidant and anti-inflammatory. In this study, it was cytotoxic to melanoma cells by inducing apoptosis. [16] Curcumin also significantly inhibited MMP-2 and down-regulated focal adhesion kinase (FAK) activity, resulting in effective anti-metastatic activity. [17,18] I found it very exciting digging out the actual mechanisms of curcumin's actions. Once the basic science is understood it can be applied to many other unrelated conditions.

Curcumin inhibits NF kappa B activity and induced nitric oxide synthase (iNOS). These are both cancer promoters. It also increased P53, P21, P27 and checkpoint kinase-2, all of which are cancer inhibitors on a genetic level. Curcumin also downregulated constitutive iNOS in melanoma cells. That "curcumin should be considered further as a potential therapy for melanoma" was the conclusion of the University of Texas MD Anderson Cancer Center in Houston, TX. [19]

Furthermore, Melanoma cells are associated with P53, either the wild type or the mutant type of genetic abnormality. Since melanoma cells with the mutant P53 gene are strongly resistant to conventional chemotherapy, curcumin may overcome this chemo-resistance. [20] Curcumin is available in health food stores, etc.

Combinations of curcumin with other polyphenols are also effective in stopping the spread of the melanoma cells. Combined with catechins, the combinations were even more effective in stopping spread to the lungs. Other polyphenols that inhibited lung tumor nodule formation were rutin, epicatechin (from green tea), naringin and naringenin (from grapefruit). Curcumin increased the life span of the test animals 143.85%. [21]

Melanoma cells produce topoisomerase II, an enzyme necessary for cell division. Blocking this enzyme is an effective way to kill the melanoma cells. In fact, the antineoplastic agent, etoposide has this action. Curcumin also is a topoisomerase II poison that can only add to its effectiveness. And it is safe. [22]

Boswellia is a plant that yields boswellic acids. Boswellia stops the growth of melanoma cells and induces differentiation. It also inhibits topoisomerase II that is produced in the melanoma cells. It is well tolerated, with no significant toxicity or side effects. It is considered a good candidate for the prevention of primary melanoma, invasion, and metastases. [23]

Melatonin, a derivative of tryptophane, that is produced by the pineal gland in the brain, can inhibit the growth of cancer cells. At very low doses melatonin had a mild stimulatory effect on melanoma cell growth. At intermediate doses it was oncostatic and at high doses it demonstrated clear, lethal, oncocidal action and killed melanoma cells.[24]. A high dose would be considered 20 mg. a day given at bedtime. Reduction of tumor growth in vivo was also demonstrated by melatonin. This effect was due to the increase in intracellular antioxidant enzymes, catalase and glutathione peroxidase. MT-1 melatonin receptors discovered in melanoma cells were responsible for the dramatic antiproliferative effects observed in patients treated with melatonin.[25]

The endothelin system, consisting of 3 peptides, 2 peptidases and 2 G-protein coupled receptors, is widely distributed in the body. Endothelin has been implicated in the proliferation and dissemination of tumor cells and recent studies have shown that antagonists might inhibit growth and produce cell death in human melanoma cells. [26]

Endothelin-1 (ET-1) induces the synthesis of IL-6 and heat shock protein. (HSP). IL-6 also promotes the production of HSP. Inhibitors of PKC suppressed ET-1 induced accumulation of HSP27. [27] Quercetin is a PKC inhibitor and, as such, may inhibit production of HSP thereby inhibiting cancer cell growth.

Peroxisome proliferator-activated receptor (PPAR) gamma agonists significantly suppressed the secretion of endothelin and so are helpful in controlling melanoma. The most well known group of PPARgamma agonists are the thiazolidinediones (TZD).

These include the anti-diabetic drugs called pioglitazone and rosiglitazone. These TZDs are also valuable against ASHD and hypertension. [28]

Gamma tocopherol, and to a lesser extent alpha tocopherol, fractions of vitamin E are also PPAR gamma agonists.

DHA, previously mentioned, is an omega-3 polyunsaturated fatty acid that can also activate PPAR gamma.

Heat shock protein (HSP) is overexpressed in melanoma cells. HSP, known as a chaperone protein, regulates the folding of proteins needed for cell proliferation and protects melanoma cells from stress such as hypoxia or pH changes. Blocking HSP90, which is important to the survival of melanoma cells, would therefore be important. [29]

HSP90 is also essential for the integrity of the telomerase complex. Telomerase prevents the shortening of the chromosomes that occur with each cell division. The production of telomerase by melanoma cells assures their immortality as well as protecting them from mutations. A progressively shortened chromosome will cause a cell to die by apoptosis. Some common telomerase inhibitors include green tea, garlic, curcumin, butytrate, silibinin (from milk thistle) [30] and ellagic acid(derived from strawberries).

Chronic activation of HSP is a normal defense response to cellular stress, but when it is prolonged, can induce or promote carcinogenesis. Repeated exposure to mobile phone radiation acts as repetitive stress increasing HSP that in turn can result in cancer. [31] Thus we can see a relationship between the use of mobile phones and melanoma, as if we didn't have enough to worry about from the sun. There are many different HSPs and their blockage must be specific. HSP73 is increased in primary melanomas in proportion to the Breslow thickness. [32]

As mentioned before, quercetin can block PKC, decreasing ET-1 and thereby reducing HSP. Quercetin also inhibits heat shock factor (HSF) activation, which in turn

prevents the induction of HSP. [33]

Genestein, an isoflavone derived from soy products such as tofu and soy sauce, is a protein tyrosine kinase (PTK) inhibitor. Cells that have been deactivated by PTK inhibitors fail to promote HSP27 under the influence of IL-6. [34]

Butyrate, a short chain fatty acid, is also a histone deacetylase (HDAC) inhibitor. Nucleohistones are combinations of DNA and histone. To be active in cell division, this combination must be separated by the enzyme histone deacetylase. Butyrate inhibition of this deacetylation process results in super-acetylation that prevents cell division. Butyrate has been effective in suppressing the growth of primary and metastatic uveal melanoma in all cell lines. [35] Butyrate also causes cell differentiation and apoptosis and an increase in tumor necrosis factor alpha (TNFalpha). [36] Butyrate is available in health food stores, etc.

Another short chain fatty acid, alpha lipoic acid, is an HDAC inhibitor. Whereas butyrate causes G0/G1 arrest, alpha lipoic acid elevates p27Kip1. They both have pro-apoptotic effects but by different mechanisms. Therefore, alpha lipoic acid would also be also effective against melanoma. [37] HDAC inhibitors can also be used to enhance the activity of retinoic acid (RA) when it is used on RA-responsive melanoma cells. [38]

Butyrate and alpha lipoic acid, both HDAC inhibitors, are also effective against squamous cell carcinoma. [39]

Vascular endothelial growth factor (VEGF) is the most potent angiogenic growth factor identified to date. It is associated with growth and metastases of solid tumors including melanoma. Melanoma cells produce elevated levels of VEGF with primary melanoma, local recurrence, and above all, with metastatic melanoma.

N-acetylcysteine (NAC) inhibits production of VEGF in three human melanoma cell lines. [40] NAC acts by inducing genetic changes that arrest cell division in the cancer cells. Specifically, "NAC induces p16(INK4a) and p21(WAF1/CIP1) gene expression and prolongs cell-cycle transition through G(1) phase." This is important because it shows that the anti-cancer activity of NAC is separate from its antioxidant properties. [41]

NAC was able to inhibit the creation of tumorigenesis but did not affect malignant conversion. [42]

NAC is an important source of intracellular glutathione (GSH) and it was found that elevated levels of GSH inhibited tumor progression and may prevent formation. [43]

Genestein, an isoflavone derived from soy products such as tofu and soy sauce, has been found effective in inducing morphological changes in melanoma cells as well as inhibiting cell proliferation. Its action is associated with its ability to block PTK [44] and to increase P53 and decrease the content of c-Myc within the cancer cells. [45] It also has the ability to increase the activities of cytotoxic T cells and natural killer (NK) cells. [46]

Vitamin K can affect anti-cancer action at the level of PTK and c-Myc. Vitamin K3 (menadione) as well as K1 and K2 have all been shown to have anti-cancer affects leading to cell cycle arrest and cell death. [47] Deep green vegetables (such as broccoli, spinach and romaine lettuce) and soybean oil are the best sources of vitamin K1. Vitamin K2 is found in cheese [48,49] and K3 is the synthetic form. They are all fat-soluble.

Vitamin A possesses both wound healing and anti-tumor actions. Vitamin A supplementation has resulted in decreased tumor growth and metastases in animals with melanoma. The group of animals that received the vitamin A supplement had a 100% survival compared to the non-supplemented group. Vitamin A has demonstrated a potential preventive and therapeutic role in the treatment of melanoma. [50]

Ginsenosides, derived from Ginseng (Panax ginseng), induced differentiation in melanoma cells and teratocarcinoma cells, changing them to normal melanocyte-like cells or parietal endoderm-like cells [46] Modulation of PKC isoforms were involved in this process. [51]

Vitamin C increases intracellular reactive oxygen intermediates. It also down-regulates IL-18, which is highly expressed in melanoma cells. The killing effect that large doses of vitamin C has on melanoma cells is due to its increasing the reactive oxygen species in the cells and acting as a pro-oxidant. Therefore NAC, which is a powerful antioxidant, will nullify its effects and should not be given together with mega-doses of vitamin C. [52,53]

Selenium, in its active form as selenomethionine or combined with soy protein, has been shown to decrease growth and metastases of melanoma cells. [54,55]

Milk thistle extract containing silymarin and silibinin caused regression of established skin tumors by up-regulating p38 mitogen-activated protein kinase (p38MAPK). It could be an effective agent for both prevention and intervention of human skin cancer. [56]

Quercetin and green tea also exert their cancer-preventive effects by differential responses on mitogenic signaling and cell cycle regulators such as increasing p21, p27 and decreasing CDK4 and cyclin-1. [57]

Taurine acts as an important osmolyte in the skin required for keratinocyte hydration. It has antioxidant effects, protects cells from UVB-induced stress and has effects on cell proliferation. [58,59] These actions would therefore protect against melanoma formation as well as wrinkles. There you have a 2 for 1 benefit. (Taurine will also lower cholesterol levels, and by increasing the levels of gamma aminobutyric acid (GABA), acts as an anti-convulsant and anti-tremor agent).

Glycine also increases GABA levels so it is well characterized as an inhibitory neurotransmitter. Dietary glycine, available as a large percentage of Jello, is also produced in the body as a result of choline being metabolized to betaine and then to glycine. [60] Aside from its anti-inflammatory action, glycine also prevents the growth of melanoma cells in vivo. [61] Choline is found in lecithin and as phoshatidylcholine supplements. Betaine is also available as a supplement.

L-Carnitine inhibited the growth of melanoma cells in a dose dependent manner. The action of L-carnitine was associated with its effect on PKC activity. [62]

The bad news is that many different malignancies are related at biochemical and genetic levels. This can be seen when considering ODC, PTK and 5-LIPO. These three have all been previously mentioned in this letter as stimulators of melanomas. They have also been implicated in the promotion of pre-neoplastic lesions relevant to colon cancer. The good news is, all three promoters are inhibited by phenylethyl caffeate, (PEK), phenylethyl-3-methyl caffeate (PEMC), and phenyethyl dimethyl caffeate (PEDMC). All these three inhibitors are present in HONEY. [63] Now isn't that sweet.

One final thought: Surgical resection of primary and/or metastatic tumors is associated with suppression of the host's immunity. This not only has an immediate effect in the post-operative period but also has ultimately affected survival. It is important that, at these times, every effort be made to stimulate the patient's own immunity. This can be done by administering the immunostimulant taurolidine. [64]

It has been shown that astragalus, the Chinese herb, is a potent immune stimulant, and its use as a biological response modifier should be considered. [65]

There are many other modalities available to treat melanoma that I have omitted. This is because, to be complete, I would have to write a book. To understand the treatment, it helps to understand the basic mechanisms that control the growth, differentiation, metastases, etc. that are usually controlled at genetic levels. Once familiar with genetic terminology, all that has to be done is to throw the name of the supplement, together with the controlling genetic marker, into a reference library, such as PubMed or Medline, etc. to discover if it has value.

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Surgical Pearls

Jay S. Gottlieb, D.O., F.O.C.O.O.

How I did it..... ..

After resection of a tumor on the upper nasal dorsum. Repair of the resulting defect.

Tumor:

Squamous Cell Carcinoma

Procedure:

Resection. Pathology for clear margins. Repair 48 hours later.

Flap:

Superiorly based forehead flap, based on ipsilateral supratrochlear artery.

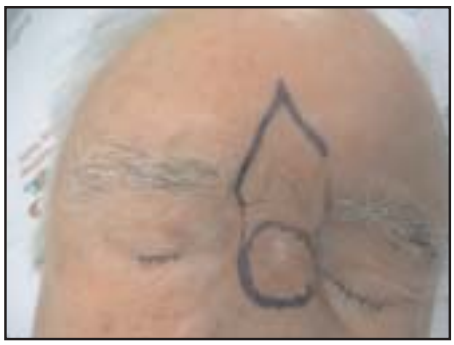

Figure 1
Planned Resection

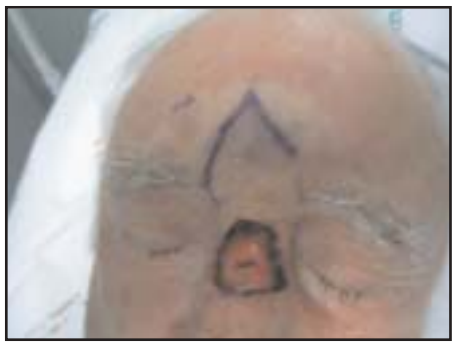

Figure 2
Resection

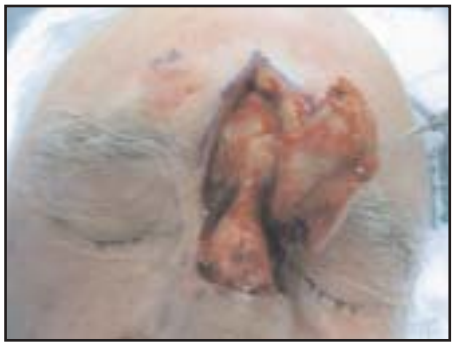

Figure 3
Midline Forehead Flap

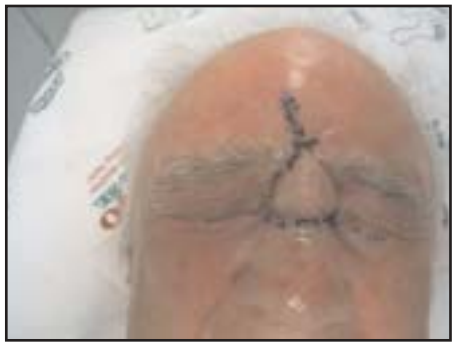

Figure 4
Immediate Closure

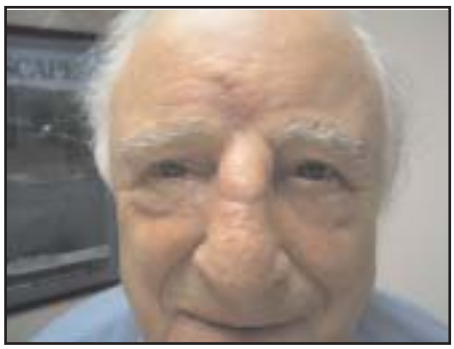

Figure 5
3 Weeks Post Op

Figure 6
16 Weeks Post Op

Dermatology Lexicon Project

Dermatologists have the unprecedented opportunity to apply their expertise to a comprehensive dermatology terminology to improve communication, image indexing, computerized medical records, and research.

Who: Dermatology Lexicon Project

What: Open Comment Period

When: 9.1.04 – 10.31.04

Where: www.dermatologylexicon.org

How: All it takes is 30 minutes to ensure all skin diseases are included, suggest synonyms and identify rare and orphan diseases for version 1.0.

For more information e-mail
jennifer_byrnes@urmc.rochester.edu

This project has been funded in whole or in part with Federal funds from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institute of Health, Department of Health and Human Services and with Funds from The Carl J. Herzog Foundation, Inc. under Contract No. NO1-AR-1-2255.

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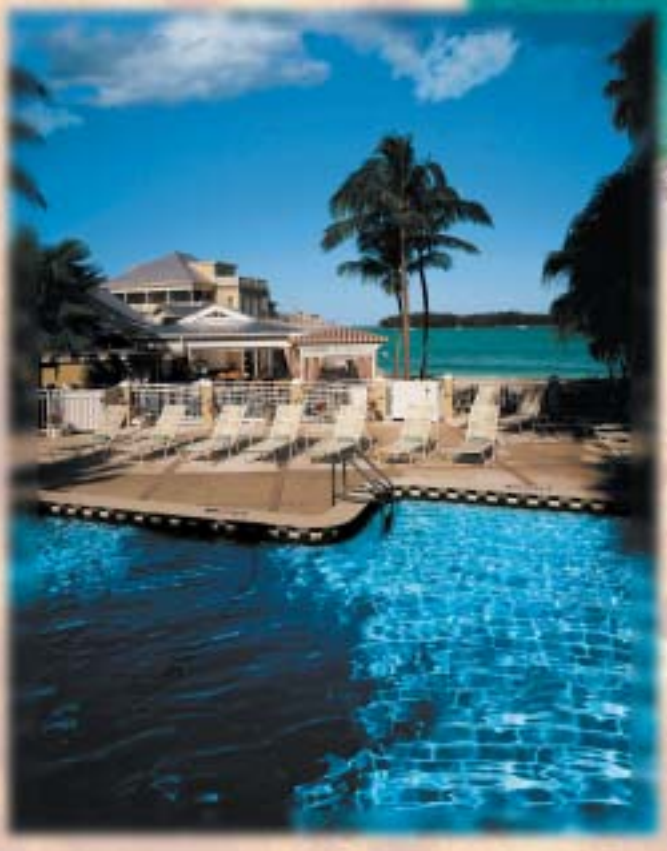

Dermatosis Papulosa Nigra With Mucosal Involvement

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Dermatology Department, Demmam, Saudi Arabia

ABSTRACT

Dermatosis papulosa nigra is a common skin condition in dark skin race. Clinically, it presents with black to dark brown pinhead size papules over the cheeks and forehaead. In this report a patient with dermatosis papulosa nigra with unusual mucosal involvement is being described.

Key words:

Dermatosis papulosa nigra, pigmented nevi, verrucae planae.

Introduction:

Dermatosis papulosa nigra (DPN) is a condition that was first described by Aldo Castellani in 1925.[1,2] It is seen frequently in the Negroid race.[3] Clinically, the patient will present with light brown to black pinhead size papules located on the cheeks mainly. In this report I am describing a patient who had a classical presentation of DPN with involvement of tongue mucosa which is the first to be reported in the literature.

The Case:

A 21-year-old Saudi Arabian female presented to our clinic with 4 years history of pinhead size pigmented papules affecting the face, both forearms and dorsum of the hands (figure 1). The condition started gradually over the forehead and the cheeks then it progressed to affect the forearms and dorsum of the hands with no associated symptoms. Five months ago the patient noticed the appearance of hyperpigmented irregular patch on the dorsal mucosal surface of the tongue without alteration in taste sensation (figure 2). Past medical history, drug history and family history for similar condition was negative. On examination of the skin there was scattered black to dark brown papules of 2 mm in diameter over the forehead fanning to the cheeks and the forearms. The neck, trunk and lower limbs were not involved. Isomorphic phenomenon was not detected. Examination of the buccal mucosa showed hyperpigmented patches with irregular border affecting the dorsal surface of the tongue with no change in its surface. The gums and teeth were normal. So at that time our differential diagnosis included: DPN, pigmented nevi, verrucae planae and fibroepitheliomas. Basic laboratory tests including complete blood count, liver function tests, renal function tests and adrenal function tests revealed normal results. Punch biopsy from lesion in the left forearm showed mild acanthosis, increase in pigment in the basal cell layer and few melanophages are present in the upper dermis with mild papillary dermal edema and lymphohistiocytic infiltrate (figure 3). So our final diagnosis of this condition was dermatosis papulosa nigra with mucosal involvement.

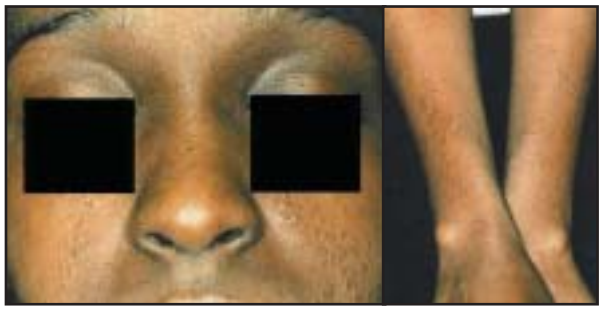

Figure 1: Small pigmented papules on the face and both forearms.

Discussion:

It was first observed by Aldo Castellani in 1925 while visiting Jamaica and Central America and he named this condition dermatosis papulosa nigra.[1,2] It is frequently seen in the Negroid race.[3] The incidence among blacks can reach up to 77%[4] and in a recent study by Dunwell et al it was found to affect 1.59% of their studied population which was 95.6% of afrocaribbean race.[4] Occasional cases among Mexicans, Filipinos, Vietnamese, and Europeans have been described in the literature.[5] Females usually predominate approaching 2 to 1 compared to males. Clinically, adult patient will present with light brown to black, well-circumscribed, smooth and rounded or pedunculated to filiform papules measuring 0.1 to 0.5 cm in diameter most densely located on the cheeks with gradual fanning toward the forehead and neck. There is a gradual increase in size and number of the papules, peaking during the sixth decade The papules are generally asymptomatic unless traumatized. In this patient the clinical presentation was classical except for the tongue mucosal involvement which is the first to be reported in the literature. Histological examination of early lesions of DPN shows acanthosis with broadening and downward projection of the rete pegs, increase in mitotic figures and pigment in the basal cell. As the papule matures, the acanthotic center becomes more pronounced with fusing of the rete pegs. Melanophages are present in the upper dermis with mild papillary dermal edema and lymphohistiocytic infiltrate may be

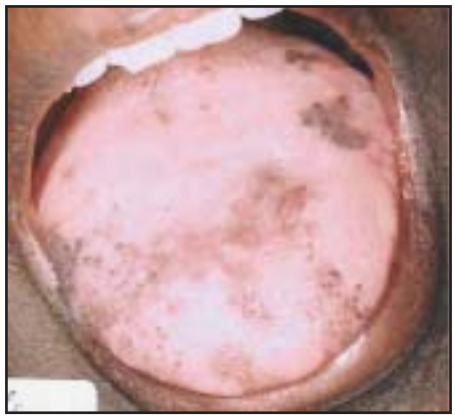

Figure 2: Scattered pigmented lesions on the tongue mucosal surface.

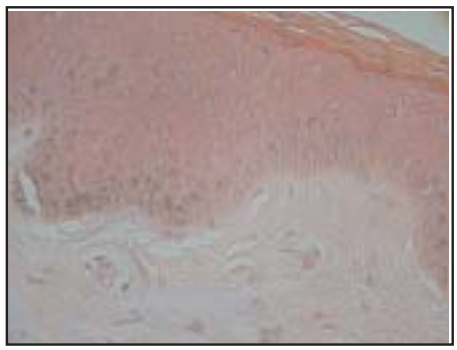

Figure 3: Microscopic view of the lesion showing acanthosis, increased pigment in the basal layer, few melanophages and edema of the papillary dermis (H&E stain, X40).

present.[6] The differential diagnosis of DPN includes pigmented nevi which are less numerous, smoother, and have a distinctive histopathology; adenoma sebaceum in blacks which can only be identified by pathologic examination; verrucae planae which are usually less pigmented and show signs of the isomorphic (Koebner) phenomenon; basal cell nevus in which the histopathology is diagnostic; fibroepitheliomas (skin tags) are common on the eyelids and periorbital areas but tend to be more pedunculated. The pathogenesis of dermatosis papulosa nigra is not yet identified but there appears to be a genetic basis and the appearance at puberty with slow progression suggests a hormonal effect on the pilosebaceous apparatus.[6] In fact, approximately one half of affected individuals report at least one family member with this problem with no associated medical conditions[6] but in our case family history was negative. DPN is usually treated with various destructive modalities including light abrasive curettage, light electrodesiccation, cryosurgery, shave excision, chemical cautery and the CO2 laser in the ultrapulsed mode. Our patient preferred not to have any of those treatment modalities because she was satisfied with her appearance as long as the condition is benign.

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Dermatologic Manifestations of Dilantin Hypersensitivity Syndrome: Case Presentation and Review

Kevin T. Belasco, D.O., M.S.*, Bill V. Way, D.O., FAOCD, and Rick J. Lin, D.O., M.P.H. *****

ABSTRACT

Dilantin hypersensitivity syndrome (DHS), also called phenytoin syndrome, is a serious drug reaction with cutaneous and systemic findings. A case of DHS with generalized cutaneous eruption, sepsis and multi-organ failure in a 37-year old African American is described. This paper presents a life-threatening case of DHS and reviews the uses, mechanism of action, and side effects of phenytoin. We also discuss the range of clinical presentations and laboratory findings associated with dilantin hypersensitivity syndrome. This clinical entity is often severe in its consequences but successful management is possible if it is detected early and consultation with a dermatologist is made early on.

Case Report:

History

A 37-year old African American male with a history of a seizure disorder, pulmonary edema, and anoxic encephalopathy secondary to a cardiac arrest presented to the hospital from a nursing care facility with fever of 103.3° F, septic shock, acute renal failure, and a generalized rash. Family history was not known and the patient was obtunded at the time of admission. Patient had been on phenytoin for 2 months at the nursing home prior to the admission to the hospital. Blood tests revealed leukocytosis (13.7, normal 4.5 – 11.0 x 10^3/ ul), neutropenia (27%, normal 45 to 75%), and bandemia (39%, normal 0 – 7%) with negative blood cultures drawn on the day of admission. Lab tests also revealed elevated ammonia (114, normal 1 – 35 _M/L) consistent with acute hepatic encephalopathy; AST and ALT were markedly elevated at 724 and 1075 respectively (normal 8 – 20 IU/L), consistent with hepatic failure. Bilirubin was elevated at 3.0 (normal, 0.3 – 1.9 mg/dL), alkaline phosphatase was elevated at 346 (normal 40 – 125 IU/L), and BUN/Cr was 54/2.5 (normal 7 – 26 mg/dL and 0.6 – 1.2 mg/dL, respectively), suggesting pre-renal azotemia and acute renal failure.

The patient was transferred to the ICU and subsequently placed on vancomycin, cefepime, and levofloxacin (Levaquin). The patient was maintained on dilantin for seizure prophylaxis. Labs were repeated and revealed marked leukocytosis (53.3 x 10^3/ul) and creatinine extremely elevated (106 mg/dL). Total bilirubin also increased markedly to 16.4, AST and ALT remained elevated. Eosinophils were elevated at 5.0% (normal 1 – 4%). A generalized rash was noted in the nursing notes from the time of admission; ten days later, a dermatologist was called for consultation.

Physical Examination & Clinical Impression

On physical examination, the patient was found to be comatose, responsive only to slight touch on the upper eyelids with a reflex-like jerking motion. Overall examination of the skin revealed extensive erythroderma with desquamation on the face, especially on the lips and ears, as well as the torso and extremities (Figures 1-5). Desquamation was also noted in the scrotal as well as the back and gluteal cleft region. Examination of the eyes revealed scleral icterus with periorbital and facial edema.

The clinical impression at the time of examination was adverse drug reaction, specifically, the Dilantin Hypersensitivity Syndrome, with sepsis, multi-organ system failure, and features consistent with nascent toxic epidermal necrolysis. The recommendation was made to discontinue the phenytoin immediately and to retain body heat by covering the body with moisturizers. Moisuturizers were also applied to protect areas of denuded skin susceptible to bacterial infection. Supportive care was also recommended; valium was substituted for phenytoin to control seizures. Strict avoidance of phenytoin, carbamazepine, and phenobarbital was recommended. Diphenhydramine was continued and a trial of systemic corticosteroids, 1 mg/kg/day was considered. Prognosis was deemed extremely poor and the patient expired the following morning.

Discussion and Review

Phenytoin: Use in Dermatology, Mechanism of action, and Cutaneous Side Effects

Phenytoin (Dilantin) is a highly effective and widely prescribed anticonvulsant agent used in the treatment and management of epileptic seizures. Phenytoin has been used in dermatology for the management of stress ulcers and –albeit with mixed results- for the treatment of junctional and dystrophic epidermolysis bullosa[1]. In vitro studies dating as far back as the 1970s suggest that phenytoin inhibits collagenase, an enzyme found at the basement membrane[2]. This offers a plausible explanation for the mechanism of phenytoin in the reduction of blister counts in epidermolysis bullosa, and its efficacy in the maintenance of collagen integrity and wound healing.

Phenytoin has also been used to treat a variety of collagen vascular disorders; it has been used with limited success in linear scleroderma (in coup de sabre) and pachyonychia congenita[11]. In addition, phenytoin has been used to treat lichen planus, rheumatoid arthritis, and neuropathic pain in diabetics[12]. Along with carbamazepine, phenytoin was the first anticonvulsant to be shown in controlled clinical trials to relieve paroxysmal attacks in patients with trigeminal neuralgia[13].

In addition to its mechanism in neuromuscular sodium-channel blockade and inhibition of collagenase activity, phenytoin suppresses cortisol, induces the cytochrome P450 enzyme system in the liver, stimulates steroid clearance, and suppresses cytotoxic natural killer T cells[10]. These effects of phenytoin in immune function and surveillance may partially explain the cutaneous side effects of this drug.

The most common cutaneous side effect of phenytoin is gingival hyperplasia, which occurs to some degree in approximately one-half of patients on long-term therapy and interestingly, is not dose-related. Long-term phenytoin therapy can also induce lip enlargement and a coarsening of the facies. Hursutism occurs in over 10% of children receiving phenytoin, usually within 3 months of initiating therapy[10]. Hair growth occurs on the extensor aspect of the arms and on the trunk and face; this

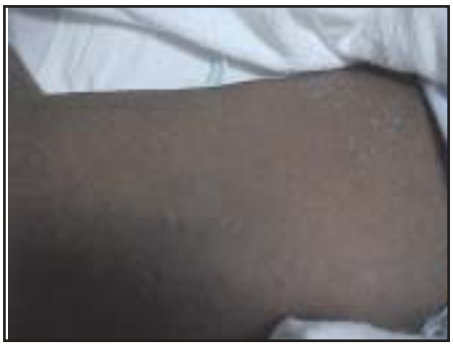

Figure 1

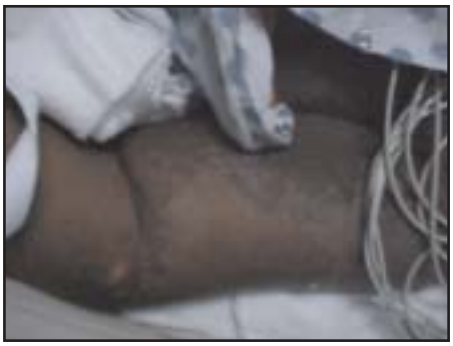

Figure 2

Figure 3

side effect usually resolves within 1 year of discontinuing phenytoin. Studies linking phenytoin use with acne and altered rates of excretion of sebum have yielded mixed results. Phenytoin-induced lupus, by contrast, is well-documented in the literature[14]. Phenytoin has also been associated with lupus in children. Phenytoin-induced linear IgA bullous disease has also been reported in the literature[9].

Generalized nodular cutaneous pseudolymphoma has been described in association with phenytoin[3]. This clinical entity is distinct from DHS and is usually seen with long-term therapy. In pseudolymphoma, lymph nodes display focal necrosis with eosinophilic and histiocytic infiltrates that destroy the normal parenchyma[3]. Unlike DHS, pseudolymphoma syndrome remits without relapses. Generalized cutaneous eruptions following phenytoin administration are variable. Phenytoin-related reactions in the skin range from maculopapular, follicular or pustular eruptions to severe desquamative reactions

Figure 4

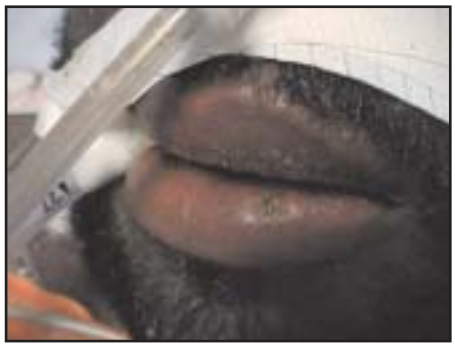

Figure 5

including Stevens-Johnson syndrome and toxic epidermal necrolysis[6]. Fixed drug reactions have also been reported following use of phenytoin[6].

Hypersenstivity Reactions to Dilantin

Most hypersensitivity reactions to phenytoin are mild and resolve spontaneously if the drug is discontinued by the patient. For example, a reversible and often mild morbilliform, maculopapular eruption secondary to phenytoin occurs in as many as ten percent of patients who take the drug[6]. In contrast to these reversible and generally benign effects, a distinct and often severe hypersensitivity reaction to phenytoin has been recognized since 1950. That year, a report entitled Dilantin sensitivity: report of a case of hepatitis with jaundice pyrexia, and exfoliative dermatitis was published in the New England Journal of Medicine[15]. Dilantin hypersensitivity syndrome has been reported in all age groups from preadolescence to the elderly. The incidence of DHS ranges from one in 1,000-10,000 exposures[4]. It is also seen in patients who have been exposed to other aromatic anticonvulsants including carbamazepine, phenobarbital, and primidone (Mysoline)4. DHS is characterized by a classic pentad of fever, rash, lymphadenopathy, facial edema, and hepatic injury, though many of these findings are frequently absent. Anemia, diarrhea, and nephritis may also be present. A "strawberry tongue" may also be noted with or without pharyngitis[4]. These potential findings point to the importance of thoroughly examining the patient's oral mucosa, tongue, and mouth.

The majority of reported cases of DHS have occurred in African-Americans. The skin eruption is classically described as erythematous follicular papules and pustules, though it may present as a morbilliform rash involving the face, trunk, and extremities. If untreated, the cutaneous eruption may progress to erythroderma or toxic epidermal necrolysis with extensive desquamation[6]. Note that the morbilliform rash associated with DHS does not spare the palms and soles. Discontinuation of the offending agent and early recognition of DHS is crucial to prevent a deleterious –even fatal- outcome.

Dilantin hypersensitivity syndrome usually occurs within three months of initiation of therapy and may occur as early as 2 weeks after starting the drug[4]. Relapses may occur even months after the drug has been discontinued and the serum levels of phenytoin are zero. Because the phenytoin may already have been discontinued, the patient may not report its use to the physician after developing DHS. The delayed onset of DHS explains why the diagnosis is often missed; the leukocytosis may lead the clinician to assume that an infection, such as cellulitis, is the culprit, rather than a reaction to the phenytoin. Patients usually have normal therapeutic phenytoin levels in the early stages of DHS5.

There are no fixed criteria by which DHS is diagnosed; a thorough history to ascertain any current or recent use of anticonvulsants is, of course, a first step in the clinical work-up of DHS. DHS should be suspected based on the findings of fever, skin eruptions, tender, generalized lymhadenopathy, and evidence of hepatocellular insult (i.e., elevated transaminases) in patients who have taken phenytoin, carbamazepine, or mysoline (recall that phenobarbital is the active metabolite of mysoline). The degree of hepatic injury in DHS is variable, and there may be only slight elevation of transaminases. Hepatosplenomegaly may occur in approximately half the cases of DHS. Massive hepatic necrosis is believed to be a key contributing factor to mortality in DHS patients. The clinician must also recall that serum levels of the anticonvulsant do not correlate with the likelihood of DHS, and are therefore not of diagnostic value in this syndrome. Evidence of cholestasis (jaundice, elevated alkaline phosphatase, both of which were seen in this case study) will also aid the clinician in arriving at the diagnosis of DHS.

Patients with DHS often complain of sore throat, malaise, joint pains (arthralgias), and/or diarrhea. The skin eruption of DHS is classically –though not always- pruritic. There is no specific histopathologic finding

associated with DHS. Eosinophils are sometimes found in the skin specimens; significant desquamation may occur during the healing from the skin eruption, sometimes progressing to Stevens-Johnson syndrome or toxic epidermal necrolysis. Post-inflammatory hyperpigmentation may occur without scarring[6].

Leukocytosis is almost universally seen in DHS, with white counts as high as 50,000 or more, as seen in our patient. As in the case of this patient, DHS may occur concomitantly with sepsis. Eosinophilia may also be found, though it may be slight (as in this patient) or marked (as high as 50%).

Accidental re-exposure or continued exposure of sensitized patients to phenytoin remains a major cause of mortality in patients with DHS[6]. Challenge with phenytoin can be dangerous in a patient who has previously been sensitized to the drug but has since discontinued the agent[4]. The mechanism of DHS is unknown but it has been hypothesized that when the drug binds to T cells, an antigenic complex is formed and recognized as "nonself"; this triggers an immune-mediated reaction analogous to graft-versus-host disease (GVHD), whereby the entire body is subject to immune dysregulation6.

Because the aromatic anticonvulsants are metabolized to hydroxylated products such as arene oxides, these compounds may represent the toxic triggers of DHS; genetic defects in the enzyme epoxide hydrolase, which breaks down these arene oxides, may be the pathophysiologic basis for DHS[10]. A genetic predisposition has not been established but seems reasonable in light of the fact that phenytoin levels remain normal in DHS; accumulation of the toxic metabolites of the aromatic anticonvulsants, rather than the parent drug, may account for the cutaneous and systemic findings.

Therapy & Management

Systemic steroids have been used with mixed results in the management of DHS. For example, one series of five patients treated for DHS quickly responded to dosage equivalents of 60 mg prednisone daily, only to relapse when the corticosteroid was discontinued abruptly or even tapered over two weeks[6]. Corticosteroid administration has not proved efficacious in controlled studies and management with systemic corticosteroids remains empiric4. One source states that systemic corticosteroids, starting at 1 mg/kg/day, should be used for at least one month[10]. Patients with DHS should receive supportive care, including fluid hydration, as well as antihistamines and topical corticosteroids to affected areas. Extreme care must be taken when tapering off systemic corticosteroids so as not to trigger a relapse.

Summary

In summary, our patient developed DHS with sepsis, multi-organ failure, and generalized desquamation of the skin with erythroderma following exposure to phenytoin. The need for early and rapid consultation with the dermatologist is highlighted by the severity of cutaneous symptoms and the delay in discontinuation of the offending agent with a fatal outcome. Fever, generalized rash, facial edema, hepatic injury, leukocytosis, and eosinophilia, all hallmarks of DHS, were present in this patient.

Generalized drug reaction must be considered in all patients who present with these constitutional symptoms and associated lab findings. All generalized skin reactions with systemic symptoms merit a dermatology consult and consideration of skin biopsy. In our patient, neither a skin biopsy nor a drug screen was necessary. Consultation with a dermatologist, however, was crucial in arriving at an accurate diagnosis. In summary, this case illustrates the importance of a thorough physical examination and early recognition that the dermatologist must be involved early on in the management of suspicious skin eruptions.

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Eruptive Xanthoma Occurring With Type III Hyperlipidemia: A Case Report and Review of the Literature

Carissa Summa, D.O., Igor Chaplik D.O., Charles Gropper, M.D., Cindy Hoffman, D.O., Richard Hwang, M.D.

ABSTRACT

Xanthomas are lesions characterized by accumulations of lipid-laden macrophages. Eruptive xanthomas can be a reflection of lipid metabolism or local cell dysfunction. Lesions are yellow-orange to red-brown papules surrounded by an erythematous halo appearing in crops commonly on extensor surfaces of extremities, flexural creases, and buttocks. A case of a 35 year-old male with hypertriglyceridemia developing eruptive xanthomas is presented. In addition, clinical and histologic features of eruptive xanthomas, associated conditions, normal lipid metabolism, proposed pathogenesis, and clinical features are reviewed.

Case Report

A 35 year-old Hispanic male was seen as a consultation in the St. Barnabas Nursing Home for a two-week history of a rash. The lesions began on the elbows and spread to palms and extensor forearms. No treatment was being used for the rash at the time of presentation.

The patient had a known history of hypertriglyceridemia for two years prior to presentation for which he received no treatment. His past medical history included acquired immune deficiency syndrome (AIDS), dementia, diabetes mellitus, hypertension, and psychosis. He denied any allergies to medications. He was taking Insulin, Metformin (Glucophage), Sertraline (Zoloft), Aspirin, Zidovudine, Rabeprazole (Aciphex), Clonazepam (Klonipin), Temazepam (Restoril), Enalapril (Vasotec) and Olanzapine (Zyprexa). He was a resident of St. Barnabas Nursing Home facility, admitted to smoking one pack per day of tobacco and an ex-intravenous drug abuser.

A comprehensive cutaneous examination revealed multiple, discrete yellow to red papules and plaques, ranging in size from 0.2 cm to 1.6 cm on the elbows, palms, forearms and legs bilaterally (Figures 1 & 2). Few scattered lesions were noted on the upper arms and anterior chest. No oral lesions were present. Laboratory studies at presentation revealed total cholesterol of 397 mg/dl, triglycerides of 1852 mg/dl, high-density lipoprotein (HDL) of 29 mg/dl and low-density lipoprotein (LDL) unable to be calculated with triglycerides greater than 450 mg/dl. At one year and again at three months prior to the rash, triglycerides were 355 and 854 mg/dl, respectively.

The clinical differential diagnosis at that time included eruptive xanthomas, granuloma annulare, perforating collagenosis or other perforating diseases, and sarcoidosis. A 3 mm punch biopsy was performed

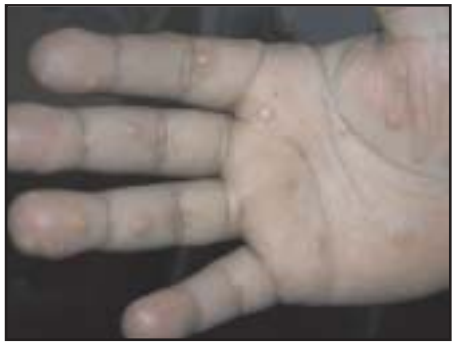


Figure 1.
Multiple well defined yellow, dome-shaped papules with surrounding erythematous halos on right palmar hand.

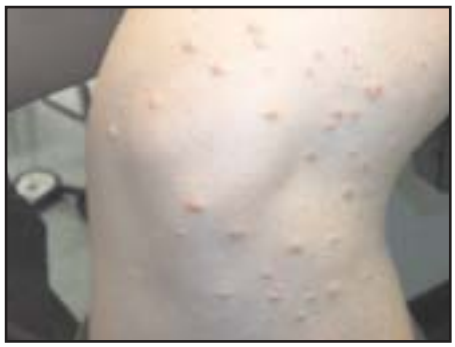
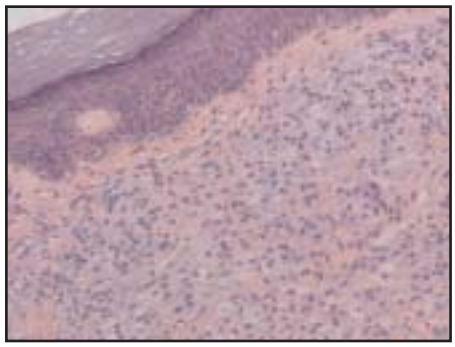


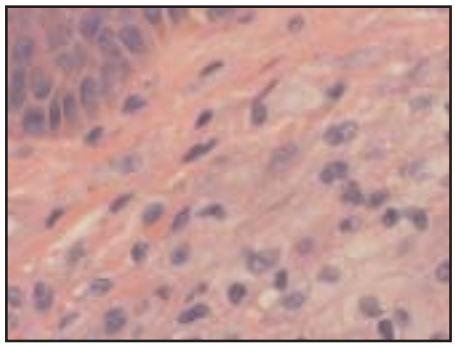
Figure 2.
Lesions on right medial knee.

from a left arm lesion. Histologically, a diffuse interstitial histiocytic infiltrate was present. Histiocytes appeared foamy confirming the diagnosis of xanthoma. Cleft-like spaces between collagen bundles represented extracellular lipid not yet engulfed by histiocytes indicating the acute nature of the eruption. There was a lack of Touton giant cells also alluding to the acute presentation (Figures 3 & 4). These findings were considered characteristic of eruptive xanthomas.

Therapy with Atorvastatin (Lipitor) 20 mg once daily was initiated in our clinic. Subsequently, the triglycerides decreased to



Figures 3.
H & E stain of 3 mm punch biopsy at 100X showing an interstitial histiocytic infiltrate and lipid deposition in the dermis. Note the lack of Touton giant cells.

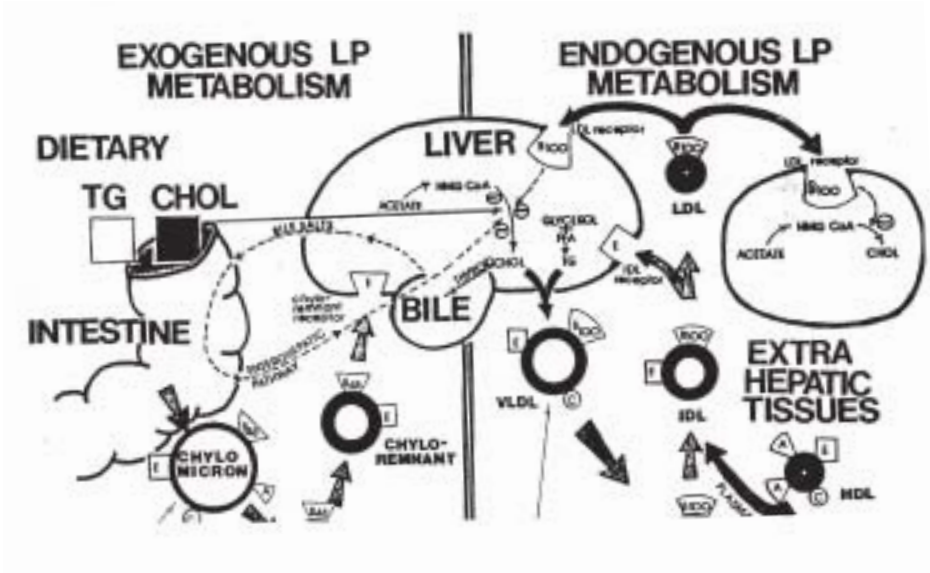


Figures 4.
H & E stain at 400X with foamy histiocytes and cleft-like spaces between collagen bundles representing extracellular lipid.

1675 mg/dl and total cholesterol to 336 mg/dl two weeks later. At five months of therapy, triglycerides were 299 mg/dl and total cholesterol 245 mg/dl with complete resolution of lesions.

Comment

An understanding of normal lipoprotein metabolism is essential to appreciate xan-



thoma formation (refer to Figure 5). Lipoprotein particles, which include LDL, HDL, very low-density lipoprotein (VLDL) and chylomicrons, function as transporters of lipids in plasma. Triglycerides and cholesterol are carried in the core of the particle, whereas apoproteins and phospholipids compose their outer surface.[3]

In the exogenous pathway of lipoprotein metabolism, dietary fat is incorporated by intestinal cells into the large lipoproteins called chylomicrons. Chylomicrons travel through lymphatics and enter the bloodstream in capillaries of adipose and muscle tissue. Apolipoproteins on the chylomicron surface activate lipoprotein lipase on capillary endothelium. Lipoprotein lipase then hydrolyzes the triglycerides in the chylomicron core into fatty acids and monoglycerides. The resulting lipoprotein remnants are then cleared by the liver.[3, 4]

The endogenous pathway transports newly synthesized or recycled triglycerides and cholesterol and accounts for most of the lipoproteins in plasma. VLDL is secreted by the liver, travel like chylomicrons to capillaries of adipose and muscle tissue, where triglycerides are hydrolyzed by lipoprotein lipase. The remaining lipoprotein remnants are removed by the liver or converted to LDL. The resultant cholesterol is delivered to cells via uptake of the lipoproteins by LDL receptors in the liver and other tissues.[3,4]

Eruptive xanthomas appear as crops of yellow papules, nodules or plaques with a characteristic erythematous halo on the buttocks and extensor arms and legs most commonly. They also may arise over antecubital and popliteal fossae, axillae, lips, eyelids, and ears.[1] Acutely, inflammatory components such as erythema, pruritus, and pain may be associated findings. In areas of trauma, keobnerization frequently occurs.[2] Lesions usually resolve spontaneously over weeks and may result in hypertrophic scars.

Eruptive xanthomas occur almost exclusively in the setting of hypertriglyceridemia and chylomicronemia, with the most common primary causes being types I, III and V hyperlipidemia.[5] Type I hyperlipidemia is caused by lipoprotein lipase deficiency. It is typically seen in children who develop eruptive xanthomas, lipemia retinalis, and pancreatitis. Triglycerides are frequently greater than 1000 mg/dl. Type V hyperlipidemia or familial hyperlipoproteinemia is caused by overproduction of VLDL and chylomicrons. It occurs in adults and may be associated with diabetes mellitus, hypertension, hyperuricemia, pancreatitis, and/or polyneuropathy. Triglycerides are greater than 500 mg/dl. Types I and V is not associated with premature atherosclerosis. Type III hyperlipidemia or familial dysbetalipoproteinemia is caused by decreased clearance of VLDL and chylomicrons. It is associated with eruptive xanthomas on the elbows and palmar creases. Patients typically have increased cholesterol and triglycerides both greater than 250 mg/dl, increasing their risk of premature atherosclerosis.[3,4]

Chylomicronemia is also commonly caused by secondary hyperlipoproteinemia from uncontrolled diabetes mellitus, alcohol ingestion, or exogenous estrogens. These conditions cause decreased lipoprotein lipase activity and increased hepatic production of VLDL. Chylomicrons are then less able to effectively compete with VLDL for lipoprotein lipase. Eruptive xanthomas have also been reported in association with nephritic syndrome, Von Gierke's disease, chronic pancreatitis, Langerhans cell histiocytosis, hepatic cholestasis, oral corticosteroids, isotretinoin, and hypothyroidism. [1,6,9]

The exact process of how xanthomas form is not fully elucidated, but possible mechanisms for the formation of hypercholesterolemic xanthomas have been proposed.[1] Increased production of lipoproteins by way of any of the conditions discussed occurs first. It is suggested that lipoproteins, when found in high concentrations, permeate dermal capillary walls and are engulfed by histiocytes. Macrophages are thought to possess specialized surface receptors, which aid in the recognition and uptake of the lipoproteins.[7] Trauma and inflammation also lead to increased leakage of the particles from vessels into surrounding tissues with subsequent deposition.[8]

Treatment of eruptive xanthomas includes treatment of the underlying condition. Currently, there are several agents to treat increased cholesterol and hypertriglyceridemia. The most frequently used medications are the HMG-CoA reductase inhibitors, also known as "statins". Atorvastatin (Lipitor) is among the most widely used in this class of drugs and was our treatment of choice for this patient. These medications reduce LDL cholesterol, total cholesterol, triglycerides, and apolipoprotein B and increase HDL cholesterol. Symptomatic treatment of the pruritus with topical corticosteroids and oral antihistamines is often needed acutely, as well.

In conclusion, eruptive xanthomas most commonly occur in the setting of hypertriglyceridemia and chylomicronemia due to various conditions. This patient most likely had Type III hyperlipidemia (familial dysbetalipoproteinemia) due to his history of hypertension and diabetes mellitus and family history of hypertriglyceridemia. Treatment of these patients should be initiated as soon as the diagnosis is made and lesions will likely resolve in the following few weeks. Referral to a primary care physician is recommended for a complete lipid profile work-up.

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"What *really* irritates me is acne medicine that doesn't deliver the results I want"

It's time for TAZORAC®

The results are worth it

TAZORAC®
(TAZAROTENE) 0.1%
cream

Patients like the results.

It's time for TAZORAC®

Patients like the results in everyday clinical practice with TAZORAC® Cream 0.1%[1]:

- **77%** increase in patient satisfaction at weeks 10–12 (n = 167)
- **68%** of patients reported they were satisfied/very satisfied at weeks 4–6 (n = 185)

Patients like the results in a double-blind clinical study with TAZORAC® Cream 0.1%[2]:

- **84%** reported a highly favorable/favorable impression at week 12 (n = 76)
- **76%** rated acne severity as none/trace/mild at week 12—compared to only 33% at baseline (n = 76)

Patient treated with TAZORAC® Cream 0.1% once daily. Photographs are completely unretouched. Results may vary.

TAZORAC® Cream 0.1% is indicated for acne vulgaris.

Because retinoids may cause fetal harm when administered to pregnant women, TAZORAC® Cream is contraindicated in women who are or who may become pregnant. Women who can become pregnant should use adequate birth control measures when TAZORAC® Cream is used.

The most frequent adverse events reported during clinical trials with TAZORAC® Cream 0.1% for the treatment of acne vulgaris were seen in 10% to 30% of patients and included, in descending order, desquamation, dry skin, erythema, and burning sensation. Events occurring in 1% to 5% of patients included pruritus, irritation, face pain, and stinging.

Please see adjacent page for brief summary of prescribing information.

1. Data on file, Allergan, Inc. [BEST trial]. 2. Data on file, Allergan, Inc. [T-219].

TAZORAC® (TAZAROTENE) 0.1% cream

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TAZORAC®
(tazarotene) Cream, 0.1%

BRIEF SUMMARY (For full prescribing information, see package insert)

INDICATIONS AND USAGE: TAZORAC® (tazarotene) Cream 0.1% is indicated for the topical treatment of patients with acne vulgaris.

CONTRAINDICATIONS:

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05% gel administered **topically** during gestation days 6 through 17 at 0.25 mg/kg/day resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed **topically** with 0.25 mg/kg/day tazarotene gel during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. Systemic exposure ($AUC_{0\text{-}24h}$) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 4.0 and 44 times, respectively, the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

As with other retinoids, when tazarotene was given **orally** to experimental animals, developmental delays were seen in rats; and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 3.5 and 85 times, respectively, the maximum exposure ($AUC_{0\text{-}24h}$) in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation day 7. A low incidence of retinoid-related malformations at that dose were reported to be related to treatment. That dose produced an $AUC_{0\text{-}24h}$ that was 11 times the max $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

There were thirteen reported pregnancies in patients who participated in the clinical trials for topical tazarotene. Nine of the patients were found to have been treated with topical tazarotene, and the other four had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy for nonmedical reasons unrelated to treatment. The other eight pregnant women who were inadvertently exposed to topical tazarotene during clinical trials subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

TAZORAC® Cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. (see also PRECAUTIONS: Pregnancy: Teratogenic Effects).

TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS:

Pregnancy Category X. See CONTRAINDICATIONS section. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period.

PRECAUTIONS:

General: TAZORAC® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC® Cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC® Cream. Patients with sunburn should be advised not to use TAZORAC® Cream until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC® Cream and ensure that the precautions outlined in the Information for Patients subsection of the full package insert are observed.

TAZORAC® Cream should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established.

Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC® Cream.

Drug Interactions: Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® Cream is begun.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

A long term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure ($AUC_{0\text{-}12h}$) at the highest dose was 13 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Tazarotene was found to be non-mutagenic in the Ames assays using Salmonella and E. *coli* and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an $AUC_{0\text{-}24h}$ that was 6.3 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an $AUC_{0\text{-}24h}$ that was 11 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum $AUC_{0\text{-}24h}$ in acne patients treated with 2 mg/cm^2 of tazarotene cream 0.1% over 15% body surface area.

Pregnancy: Teratogenic Effects: Pregnancy Category X:

See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

Nursing mothers:

After single topical doses of ^{14}C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of tazarotene cream have not been established in patients with acne under the age of 12 years.

Geriatric Use:

Tazarotene cream for the treatment of acne has not been clinically tested in persons 65 years of age or older.

ADVERSE REACTIONS:

In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity, or photoallergy.

The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne, occurring in 10-30% of patients, in descending order included desquamation, dry skin, erythema, and burning sensation. Events occurring in 1 to 5% of patients included pruritus, irritation, face pain, and stinging.

OVERDOSAGE:

Excessive topical use of TAZORAC® Cream 0.1% may lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General).

TAZORAC® Cream 0.1% is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.

Rx only

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Celecoxib Induced Acute Generalized Exanthematous Pustulosis: A Case Report

Schield Wikas, D.O., Monte Fox, D.O., Ritu Bansal, Charmaine Jensen, D.O.

A 71 year old Caucasian male presents with a 4-day history of an explosive "pus-like rash" on his trunk, that is spreading to his face and thighs. He admits to pruritus and irritation. He also complained of redness, itching and burning sensation of his eyes. He admitted to having fever, myalgias and arthralgias one week prior to presentation, which have now resolved. Upon further questioning, he received celecoxib (Celebrex) fifteen days ago for arthritis on his shoulder after not responding to a cortisone injection during the previous day. In addition, he was started on ciprofloxacin (Cipro) for the rash, one day prior to presentation.

His past medical history is significant for seasonal allergies, hyperlipidemia and hypertension. He denied any history of psoriasis, eczema or any dermatological condition. His medications include loratadine (Claritin), atorvastatin (Lipitor), lisinopril (Zestril), hydrochlorothiazide/triamterene (Dyazide) and ciprofloxacin (Cipro). He has no known drug allergies. His past surgical history is positive for prostatectomy. His family history is significant for cataracts, glaucoma, arthritis, cancer and hypertension.

He is retired. He denied tobacco and alcohol consumption.

Objective examination revealed a well-appearing 71 year old Caucasian male in no acute distress. On his anterior neck, there were scattered, multiple, discrete pustules, some of which are coalescing into lakes of pus (Figure 1 and Figure 2).

There were also widespread pustules on his face specifically on his bilateral preauricular regions. Some pustules had overlying yellow crust. (Figures 3 and 4).

His chest revealed isolated 4mm perifollicular pustules on an erythematous base (Figure 5). There were also scattered ill-defined erythematous plaques and patches on his chest, abdomen and back.

Examination of his lower extremities revealed multiple erythematous macules coalescing into patches, some of which had a dusky center (Figure 6).

Examination of his oral, conjunctival and genital mucosa revealed no abnormalities. He had no palmar, plantar or nail involvement.

Biopsies were performed and revealed to be consistent with Acute Generalized Exanthematous Pustulosis.

Celebrex was discontinued. The patient was treated with triamcinolone acetonide 0.1% ointment for symptomatic relief. He returned two weeks later with resolution of symptoms.

Discussion

Once classified as pustular psoriasis von Zumbusch type, AGEP is a rare disease first suggested by Beylot et al. in 19801 as a separate entity due to its acute, non-relapsing characteristics and association with various drugs (TABLE 1). Roujeau et al.[2], through retrospective analysis, showed that the majority of 63 cases of AGEP had resulted from drug reactions with _-lactams (28 cases) and macrolide antibiotics (11 cases). Other antibiotics (6 cases) and drugs (10 cases) were implicated, as well as exposure to mercury, in which the latter appears to cause a hypersensitivity reaction leading to AGEP[3]. In this study, 11 patients were also found to have a history of psoriasis[4], but sarcoidosis, autoimmune

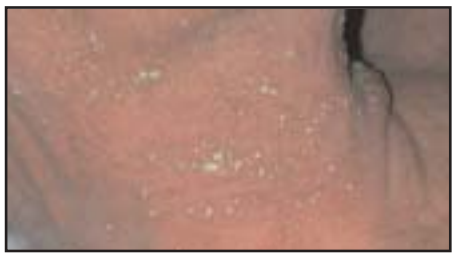

Figure 1.
Anterior neck. Scattered, multiple discrete pustules, some of which are coalescing into lakes of pus, on a background of erythematous and edematous skin.

Figure 2.
Close-up of anterior neck. Discrete pustules with some coalescensce on a background of erythematous skin.

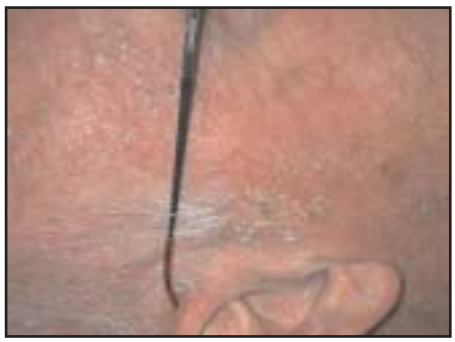

Figure 3.
Right preauricular region. Discrete pustules with overlying yellow crust.

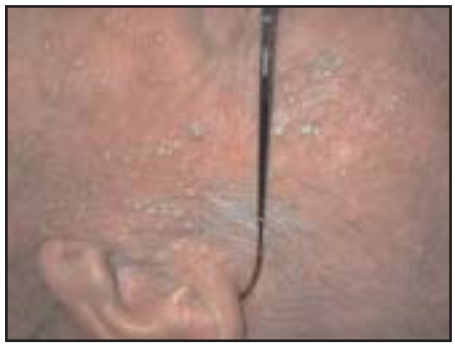

Figure 4. Left preauricular region and scalp. widespread small pustules on an erythematous base.

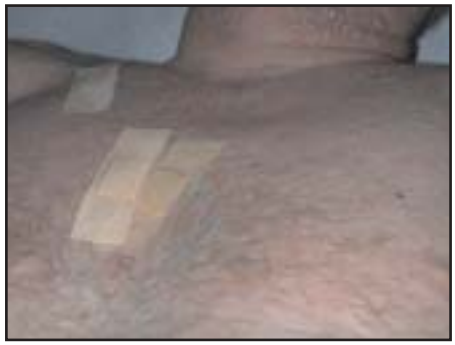

Figure 5. Central chest. Scattered, isolated 4 mm perifollicular pustules on an erythematous base. Ill-defined erythematous plaques and patches.

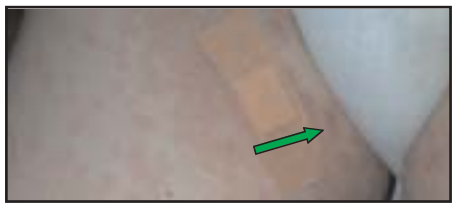

Figure 6. Right inner thigh. Multiple erythematous Circular to oval macules coalescing into patches, some of which have dusky centers (arrow).

Table 1. Drugs Responsible for AGEP[8]

Antibiotics		Others
_ lactams		Nonsteroidal antiinflammatories
Penicillin		Bufexamac (topical use)
	Ampicillin	Diclofenac
	Amoxicillin	Antalgics and antipyretics
	Bacampicillin	Acetylsalicylic acid
	Penicillin	Paracetamol
Cefalosporin		Antimalarial agents
	Cefactor	Chloroquine
	Cefalexin	Hydroxychloroquine
	Cefazolin	Mefloquine
	Cefradine	Antiparasitics
	Ceftazidine	Piperazine
	Cefuroxime	Pyrimethamine
Other		Calcium channel blockers
	Imipenem	Diltiazem
Macrolides		Nifedipine
	Azithromycin	Angiotensin-converting enzymes
	Erythromycin	inhibitors
	Josamycin	Enalapril
	Pristinamycin	Anti-arrhythmics
	Roxithromycin	Nadoxolol
	Spiramycin	Quinidine
Other antibiotics		Anti-convulsants
Cyclines		Carbamazepine
	Doxycycline	Phenytoin
	Oxytetracycline	Tricyclic antidepressors
Quinolones		Amoxapine
	Ciprofloxacin	Anxiolytics (benzodiazepine)
	Enoxacin	Clobazam
	Norfloxacin	Miscellaneous
	Pipemidic acid	Acetaminophen
Others		Acetazolamide
	Chloramphenicol	Allopurinol
	Clindamycin[9]	Aminoglutethimide
	Isoniazid	Buphenine
	Streptomycin	Calcium dobesilate
	Vancomycin	Carbutamide
Sulfonamides		Disulfiram
	Cotrimoxazole	Ferrous fumarate
	Trimethoprim	Furosemide
	Sulfasalazine	Hydrochlorothiazide10
Oral antifungal agents		Icodextrin11
	Itraconazole	Sulbutiamine
	Terbinafine	

thyroiditis, inflammatory bowel disease, and multiple sclerosis all have been found as underlying diseases in patients with AGEP[5]. AGEP has been seen to evolve from viral infections parvovirus B19 and enterovirus, but most still agree at least 90% of AGEP cases studied were associated with the ingestion of drugs especially of the antibacterial class of aminopenicillins[3].

Characterized by an acute onset and fever above 38_C, AGEP involves a cutaneous eruption with numerous, occasionally hundreds of small (<5mm), nonfollicular subcorneal pustules often accompanied by a dermal vasculitis[4]. Pustules are found on edematous erythematous skin, causing widespread pruritus and burning with eruption usually beginning on the face and in skin creases. After a couple of hours, the eruption continues to the trunk and eventually to the lower extremities. Mucocutaneous features of AGEP include facial edema, purpura on lower limbs, vesicles or blisters, mucous membrane erosions of mouth and tongue, and occasionally, some erythema multiforme-like atypical targets.

The mean interval time between drug ingestion and eruption is 9.7 days with resolution of pustules occurring spontaneously in under 15 days. Superficial desquamation in an annular pattern follows a couple days after resolution begins. Neutrophilia greater than 7 X 103/_L is present and mild-to-moderate eosinophilia is found in about one third of cases[6].

It is unknown whether the cortisone injection prior to the ingestion of celecoxib had any precipitating effect on the development of AGEP in our patient. But nonsteroidal anti-inflammatory medications, which tend to have a high rate of cutaneous side effects, have been implicated with AGEP in the past[7]. In conclusion, we propose that celecoxib be added to the list of medications causing AGEP and physicians be aware of its association.

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Nephrogenic Fibrosing Dermopathy: A Case Report

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ABSTRACT

Nephrogenic fibrosing dermopathy is a condition that was first reported in 1997 by investigators from the University of California in San Francisco[1]. There have been approximately 140 reported cases as of May 2004[2]. This scleromyxedema-like disorder presents in patients with renal disease. Characteristic skin changes develop after renal insufficiency, hemodialysis, or renal transplant in these patients. However, neither the underlying cause nor the duration of the kidney disease appears to play a role in the development of nephrogenic fibrosing dermopathy. Cases are currently being investigated and monitored by Dr. Shawn Cowper and The NFD Registry at Yale University.

Introduction

Nephrogenic fibrosing dermopathy (NFD) is a recently defined idiopathic disorder characterized by fibrotic skin plaques in patients with renal disease[1]. The disorder, formerly called "scleromyxedema –like cutaneous disease", was first described by investigators at the University of California in San Francisco in 1997[1]. Three years later, Cowper S. et al, described 14 patients who had undergone either hemodialysis or renal transplant and then developed thickening of the skin[3]. These patients on H&E showed an increase in dermal fibroblast-like cells. There was collagen remodeling and mucin deposition. The term "nephrogenic fibrosing dermopathy" was then proposed to replace the prior term. Since then, the Nephrogenic Fibrosing Dermopathy Registry Project at Yale University has documented 140 reported cases of the disorder[2].

Numerous reported cases have demonstrated the variance in presentations. Although the disorder was first described in a cluster of patients who had either undergone dialysis or transplant, the disorder has since been seen in many other patients with renal impairment[3]. The causes of renal insufficiency that are associated with the skin manifestations are vast[4]. Cowper notes that restoration of normal renal function usually leads to improved skin manifestations, however, return of normal kidney function does not necessarily assure improvement in all cases. Furthermore, the severity of renal impairment does not appear to correlate with the severity of the cutaneous eruptions[4]. Spontaneous resolution of symptoms as well as skin change improvement with aggressive dialysis have been noted in some patients[5, 4].

Erythematous, confluent papules, patches or raised plaques are common with islands of sparing within the indurated plaques[4, 5]. Mackay et al described four patients having plaques with irregular edges and irregular finger-like or amoeboid projections[5]. Patients typically present with symmetric skin tightening of the limbs and/or trunk[4]. Unlike other fibrotic disorders, the face appears to be spared[6, 5]. The skin becomes textured with a peau d'orange appearance[4]. Progressive hardening of the skin leads to skin contractures causing decreased ability to flex and extend the joints[2]. Debilitating outcomes and inability to ambulate without assistance often result[5].

Patients have a wide range of initial presentations. Common complaints include stiffening of the skin, muscle weakness, decreased mobility, myalgias, pruritus, a tingling or burning sensation, sharp pain, or patients may be asymptomatic[4, 5]. According to Cowper, the condition is evenly distributed among men and women; a wide age distribution is also noted but the majority of cases appear to occur in the middle aged[2]. The reported cases encompass great racial diversity and many ethnic backgrounds[4].

Diagnosis can be made by histopathological examination of a skin biopsy specimen. Incisional or punch biopsy are acceptable[4]. NFD pathology reveals three primary characteristics, as described by Cowper: (1) An increase in the number of dermal fibroblasts, (2) an increase in dermal mucin deposits, and (3) dermal change in the normal pattern of collagen bundles[2]. In addition, the specimen may demonstrate an increase in the number of subcutaneous spindle cells that can extend into the fascia and muscle[4]. Fragmented elastic fibers have also been noted[6].

Case Report

At the age of 24, our patient had developed end stage renal disease as a complication of vesicoureteral reflux caused by congenital abnormalities. He was treated with hemodialysis for a few months before switching to peritoneal dialysis with which he was treated for one and a half years. One month before presentation he switched back to hemodialysis because of inadequate dialysis and uremia.

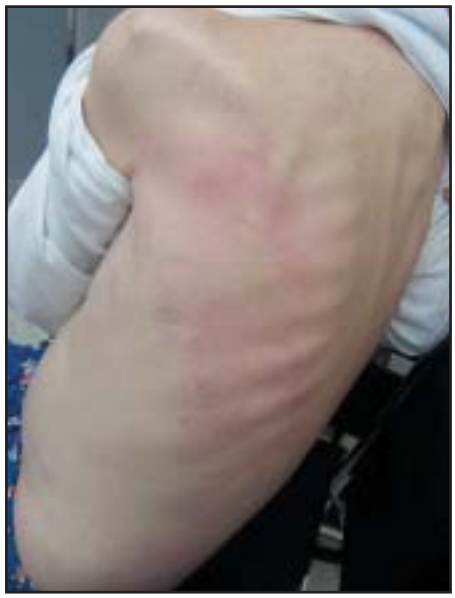

Figure 1

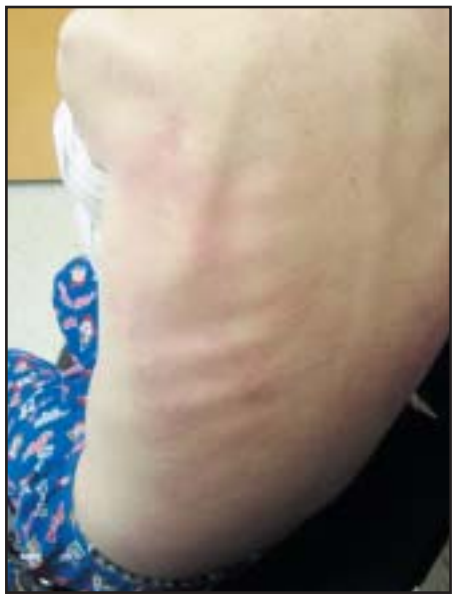

Figure 2

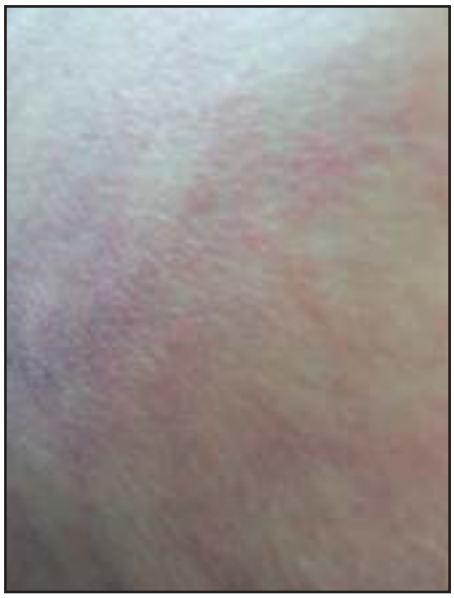

Figure 3

Figure 4

Figure 5

Several months prior to switching from peritoneal dialysis to hemodialysis, he developed superficial skin ulcerations of his proximal lower extremities and anterior chest wall. Biopsy of the lesions was suggestive of calciphylaxis but not diagnostic. There was also evidence of diffuse pulmonary calcification. At the time, Sensipar (cinacalcet) was started and he was changed from calcium-containing binders to Renagel (sevelamer). These changes and aggressive local wound care were followed by prompt resolution of the lesions.

At the age of 26, this white male presented with symmetrical rash over his entire back and elbows which reportedly felt tight and itchy. The areas of involvement

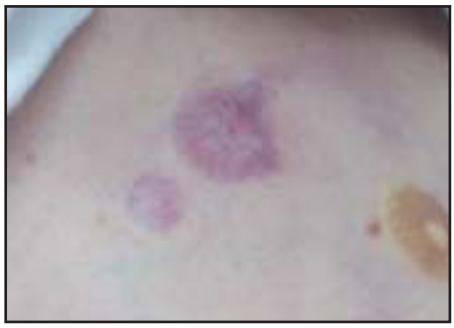

Figure 6

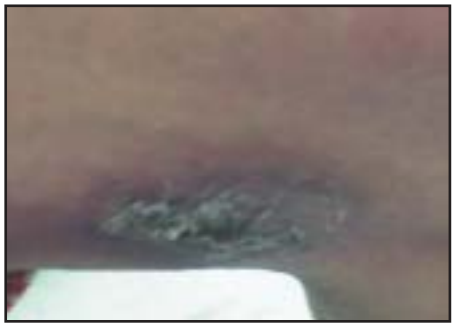

Figure 7

seemed to change with time and come and go. The patient denied having any systemic symptoms with the exception of lethargy from his anemia.

The affected areas were slightly red, raised, pruritic and blanched. The skin on the flanks was indurated, erythematous, and plaque like. The skin also displayed atrophy, tightening and an irregular texture of both flanks. Many of these areas had irregular projections out of the plaques with adjacent areas of perfectly normal appearing skin. There was no skin breakdown in contrast to his previously diagnosed calciphylaxis lesions that had presented initially as patches of ulceration. A 4mm punch biopsy, 6mm in depth from the affected skin site was obtained.

At the time of presentation with the NFD lesions, the patient was anemic, but this was slowly responding to treatment with Erythropoeitin. Transfusion was being avoided because of the potential for renal transplantation. He had undergone no vascular procedures and had no known thrombotic conditions. Approximately 6 weeks after diagnosis of NFD, the patient died of complications associated with bowel ischemia and perforation.

Discussion

This patient's clinical presentation and histopathological findings are consistent with previously reported findings of NFD. It is of interest to note the length of time this patient had been undergoing dialysis prior to the onset of his NFD symptoms. This makes it increasingly apparent that NFD does not necessarily have a correlation with dialysis but rather with the underlying renal insufficiency. Cases reported by Streams et al and Mackay et al both demonstrate great variance between the length of time (onset) on dialysis and the eruption of cutaneous findings[6, 5]. This further supports the hypothesis that NFD is not a manifestation of the dialysis itself but rather from some other component of the underlying renal impairment that triggers the cutaneous manifestations.

It would also be of interest to examine the possibility of an association between calciphylaxis and NFD. Our patient seemed to have a condition of systemic calcification leading to ischemic lesions of his legs, chest, and ultimately his small bowel. Until more cases of NFD are reported and researched, the possible relation of NFD with this patient's systemic calcification condition can not be determined.

Histological Findings

The skin biopsy was examined using H&E staining which showed increased stellate shaped dermal cells. This increased number of dendritic cells was found amongst the collagen bundles from the papillary dermis and extended to the base of the punch biopsy. There was also a sparse perivascular, mononuclear cell infiltrate. Sections labeled with immunoperoxidase technique for factor XIIIA revealed an increased number of factor XIIIA positive dermal dendrocytes throughout the dermis. Sections labeled for CD117 showed a normal number of mast cells in the dermis. Section stains Giemsa stain also revealed a normal number of mast cells in the dermis. In combining the clinical picture with the histological specimen, a diagnosis of nephrogenic fibrosing dermopathy was made.

Treatment

With so few reported cases to date and lack of concrete treatment data, no universally agreed upon treatment regimen has been established for NFD[4]. Many of the treatment modalities are centered around those used to treat scleromyxedema[7]. Attempted or currently investigated treatments include oral and topical steroids, retinoids, histamine blockers, photophoresis, plasmapheresis, radiation therapy, psoralen UV light, immunosuppressive medications, and physical therapy for contractures[4, 8]. In the above case, our patient was treated with triamcinolone ointment and atarax.

Many treatment efforts are aimed at improvement of underlying renal dysfunction. However, resolution of renal impairment does not necessarily result in resolution of NFD[4]. In a case report by Hancox, the patient's NFD did not appear to improve when normal renal function was restored[9].

Conclusion

Many more cases of nephrogenic fibrosing dermopathy are likely going unidentified or unreported. A challenge lies ahead in educating practitioners on this relatively new condition and exploring controlled treatment modalities within the context of the underlying renal impairment.

Verification of cases and collection of epidemiological data is an undertaking of Yale University with the Nephrogenic Fibrosing Dermopathy Registry Project. The International Center for NFD Research (ICNFDR) at Yale University can be reached at http://www.icnfdr.org [2].

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Actinic Keratosis Management: A Combination Approach with 20% Aminolevulinic Acid and Cryotherapy.

Don A. Anderson DO, Christian B. Anderson DO, PharmD, RPh

ABSTRACT

Topical 20% aminolevulinic acid (ALA) photodynamic therapy (PDT) was recently approved by the FDA for the treatment of actinic keratoses (AK). ALA is a new type of photosensitizer that can be used in PDT. This treatment involves the application of a pro-drug, ALA, which is metabolized by proliferating cells into the photosensitive, photoactive product protoporphyrin IX. Upon excitation of the protoporphyrin IX (405nm-650nm) with an appropriate external light source (device generating visible blue light at approximately 420nm), singlet oxygen is generated and the resulting limited inflammatory response results in the destruction of the AK.

This innovative therapy has become the treatment of choice in our clinics for AK patients with extensive disease (over 15 lesions on the face and/or scalp), history of multiple cutaneous malignancies, severe underlying photo-damage, and those who are immunocompromised. Our approach is markedly different than published protocols in that we apply ALA broadly over the affected skin rather than to discrete lesions, and we use post-treatment cryotherapy for remaining, typically hyperkeratotic, individual lesions.

In general, our patient base is predominately Fitzpatrick I-III skin types. The majority of these patients have diffuse and severe actinic damage. We use a broad application of 20% ALA as a single uniform coating to all affected skin within our target area, similar to the broad based approach of 5-FU therapy. A second (double) application of ALA is applied to lesions of significant clinical concern. Patients with a history of more than 6 herpes simplex outbreaks per year are given anti-viral prophylaxis prior to PDT. The value of prophylaxis is unclear as we have had no related outbreaks. To accommodate patients with both face and scalp lesions the blue light source is oriented to cover both areas simultaneously. Patients with severe disease may require a second course of ALA PDT, however they are a minority, representing approximately 1 out of 75 patients treated.

To date we have treated over 1600 patients utilizing this technique and have achieved impressive AK reduction and patient satisfaction has been high. A summary of our patient management approach will be presented in detail including but not limited to: patient selection, pain management, post-treatment management, use of adjuvant therapy and outcome data.

Introduction[1-10]

There are several therapeutic choices in the treatment of actinic keratoses (AK). These include 20% aminolevulinic acid (ALA) combined with photodynamic therapy (PDT), cryotherapy, 5-flurouracil cream and lotion (5-FU), diclofenac sodium 3% gel, curettage, dermabrasion, and trichloroacetic acid (TCA)/glycolic acid chemical peels.

The introduction of PDT with 20% ALA offers a novel, safe, effective, and convenient approach to management of actinic keratosis. We believe treatment with 20% ALA/PDT demonstrates a reduction in the number of side effects compared with other treatment options, thus increasing patient satisfaction and compliance.

Our approach is broad based-single application 20% ALA/PDT to all cosmetic units within the face and scalp followed by adjunctive cryotherapy to residual hyperkeratotic lesions 4 weeks post treatment with PDT. This is contrary to published protocols which suggest application to discrete non-hyperkeratotic actinic keratoses of the face or scalp.

The rationale for our approach is primarily related to our desire to treat both clinical and sub-clinical lesions simultaneously, thus reducing the frequency and number of treatments traditionally required while improving the overall outcome for this chronic condition. Since the inception of our approach, 36 months prior to this review, we have successfully treated over 1600 patients with broad based,single application 20% ALA/PDT and are pleased to note that to date no more than 2% of these patients have needed retreatment with 20%ALA/PDT. Needed retreatments are due to poor response, non-uniform application of ALA, and/or patient inability to complete 1000 seconds of BLU-U exposure.

Methods[6-13]

Method of Treatment

– Pre-Tx: Wash with Cetaphil ® immediately prior to ALA application. Leave the skin slightly moist after drying.

– Drug application: Mix ALA per Kerastick ™ package insert and apply to entire cosmetic unit as a single uniform coat. Double coat clinically evident lesions using spot applications. Typically one Kerastick ™ is required for the entire face with an additional applicator for the scalp.

– Incubation Time: 14 to 18 hours with strict UV avoidance.

– Light Treatment: BLU-U light source (420nm), 1000 second exposure.

– Pain Management: Refrigerated air during BLU-U exposure per Cryo 5 ® manufacturer instructions, face wash and ice packs immediately after.

– Post –Tx Care: Regular moisturizer of choice, when healed physical sunscreen SPF 15+.

– 4 Week Follow-up: Apply cryotherapy for remaining, typically hyperkeratotic, individual lesions.

Selection criteria include patients with extensive disease (over 15 lesions on the face and/or scalp), history of multiple cutaneous malignancies, severe underlying photo-damage, and those who are immunocompromised. Patients with any form of porphyuria are excluded. Those with a history of more than 6 herpes simplex outbreaks per year are given famciclovir 500 mg every 12 hours starting 24 hours prior to treatment an continued for 4 days after PDT.

Pain management during PDT is achieved with the use of a Zimmer® Cryo 5 Unit supplying refrigerated dry air to the surface of the treated area(s) Ice packs are directly applied to the treated area(s) and

Table 1 - Treatment Data Summary

Category	Number of Treatments	Severity of Disease	Incubation Time (hrs.)	UV Time (min.)	PDT Reaction	Improvement	Pt. Satisfaction
All	297	S = 147 MO = 149 MI = 1	14-18 = 279 <14 = 17 Unk = 1	>16 = 267 <16 = 29 Unk = 1 Mean = 15.9	S = 171 MO = 121 MI = 3 Unk = 2	Clear= 101 Marked= 89 Moderate= 46 Modest= 46 MIN= 9	High = 202 Med = 64 Low = 22 Unk = 9
Face	86	S = 26 MO = 60 MI = 0	14-18 = 78 <14 = 8	>16 = 77 <16 = 9 Mean = 15.3	S = 52 MO = 33 MI = 0 Unk = 1	Unk = 6 Clear= 42 Marked= 22 Moderate= 10 Modest= 7 MIN= 4	High = 64 Med = 11 Low = 7 Unk = 4
Scalp	17	S = 16 MO = 1 MI = 0	14-18 = 15 <14 = 2	>16 = 17 <16 = 0 Mean = 16.4	S = 10 MO = 6 MI = 1	Unk = 1 Clear= 1 Marked= 8 Moderate= 3 Modest= 5	High = 10 Med = 6 Low = 1
Extremities	43	S = 29 MO = 14 MI = 0	14-18 = 43 <14 = 0	>16 = 42 <16 = 1 Mean = 16.2	S = 6 MO = 36 MI = 1	Clear= 7 Marked= 11 Moderate= 12 Modest= 12 MIN= 1	High = 29 Med = 11 Low = 3

titrated to patient need. Menthol containing cream followed by frequent applications of emollient cream are applied, as needed, to hydrate the treated skin throughout the healing period. Once peeling is complete physical sunscreen, SPF 15+, is utilized until general erythema abates.

During PDT and the immediate 2-4 hours after, patients experience significant erythema and variable intensities of tolerable pain, followed by 24-48 hours of erythema with gradual disappearance of pain culminating in prolonged desquamation during days 3-12.

Method of Retrospective Review

Our intent is to provide an unbiased assessment of our approach to the treatment of actinic keratoses using a combination approach with 20% ALA/PDT and cryotherapy.

After linking scheduled PDT appointment codes and chart numbers, 1011 patient charts were identified as our population base. 31.5% of these, 318 charts, were then randomly selected by an independent contractor and set aside for review. Comprehensive review of the medical records in entirety resulted in 297 separate patient cases. A total of 21 charts were excluded from the sample; 14 due to same day cancellations and 7 patients were lost to follow-up.

The scoring system used in the chart review was defined as follows:

Severity of Disease (number of AK within the treated area): Minimum (MI) = <15, Moderate (MO) =15-30, Severe(S) = 30+.

Incubation Time = time between drug application and when light treatment was started.

UV Time = time of light treatment.

PDT Reaction = minimum (MI), moderate (MO), severe (S).

Improvement = clear 96+%, marked 76-95%, moderate 51%-75%, modest 26-50%, min 25% or less.

Pigmentation = after complete healing any pigmentation - yes/no, if yes degree/list maximum amount (minimum, moderate, severe)

Persistent Pigmentation = if pigment developed, did it persist - yes/no.

Persistent Erythema = Yes/NO, If Yes, minimum, moderate, severe.

Scarring = yes/no, if yes describe.

Pt. Satisfaction = high, medium, low.

Results

A total of 297 treatments were reviewed. The majority of these subject had facial areas treated, however many patients also had chest, arm and scalp areas treated. The patients ranged in age from 29 to 97 years of age and included a relatively even mix of both males and females, all with Fitzpatrick skin type's I-III. As this was a retrospective review, discrete categories of data analysis were not defined ahead of time. Consequently, four broad categories were defined a) all treatments reviewed, b) face only, c) scalp only and d) extremities. Similarly, we did not document the specific timing of therapy and in some cases, patients were treated twice for the same concern (14 of the 297 treatments reviewed). In most cases this was done for lack of therapeutic benefit.

Most patients were classified as having severe or moderate actinic keratosis. In general, ALA PDT was administered per the package insert with 14 to 18 hour drug incubation and about 1000 seconds of light exposure but with broader areas of ALA application. Healing appears more rapid than conventional broad based therapies like 5-FU, with most patients looking significantly better by 2 weeks and returning back to baseline after 4 weeks. A typical patients' healing course is detailed in Figure 1 No evidence of scarring, persistent erythema or pigmentation change has been noted in any patient to date. For all treatments reviewed, clearing (96+ % resolution) was seen in one third of all cases, and in about half of the cases limited to the face. Clearing or a marked response (76% or better improvement) was found in about two thirds of all cases and in three quarters of the cases limited to the face. Scalp and

extremities did not enjoy as dramatic a response to the therapy as detailed in Table 1, consistent with many other AK therapies. Lastly patient satisfaction was rated as high in 68% of the cases treated and moderate to high in 90% of the cases.

Conclusions

– AK Clearance: Broad based application of ALA/PDT is effective in treating a large number of lesions, reducing the need for adjunctive therapies, providing small retreatment rates, and enhancing suppression in growth of recurrent clinically relevant lesions.

– Facial Applications: the most common anatomic area treated, had complete clearing in 75% of the cases, with most patients having moderate to severe disease.

– Compliance: The in-office nature of the procedure ensures compliance and provides a more rapid healing time that of other broad based therapies like 5-FU.

– Follow up treatment with cryo-therapy, as a limited spot treatment, provides an easy means to readily clear any residual lesions after broad area ALA/PDT.

– Patient Satisfaction: was high with 90% of the patients rating the therapy as High or Moderate..

– Cosmesis: No scarring or hyperpigmentation has been encountered and patients appeared to enjoy an overall improvement in skin quality.

– Pain Management: Our suggested approach may help produce tolerable pain thus enhancing patient compliance and better post-therapy healing.

This regimen markedly reduces appearance of new actinic keratoses. Anecdotally, the decrease afforded our patients/ is at least equivalent to 5-FU, and nearly as good as with 25 or 35% TCA peels. Cosmesis is similar to TCA peels however, continued improvement and longevity seems to be better. Our confidence in our approach continues to grow as patient satisfaction remains high and the need to retreat patients remains a small fraction of our population base.

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