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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.

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)
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 DeRoso 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 AOAD 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 JAOCDS 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, inferiorly 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(5). The incidence of this disease in women ranges from 10-35%, with one study showing only 19.6% incidence in women(6). CNCH can affect all races, but is more common in fair-skinned individuals that have suffered sun damage(7).

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(8). 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(10). 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(11). Cartilage beneath the granulomatous and fibrotic dermis is disrupted, hemorrhagic and necrotic(12), although sometimes is appears undamaged(13). The necrotic debris of CNCH are enveloped by pseudoepitheliomatous hyperplastic epidermis(14). Because of this histopathology some authors now classify CNCH as a perforating dermatosis(15). 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.

Pathogenesis

The pathogenesis of CNCH is unclear,
Others suggest CNCH is caused by trauma which leads to chronic inflammation of the cutis and perichondrium[5]. 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[6]. The evidence supporting this theory are that studies have shown 77-99% of CNCH patients sleep on the affected ear[7-10]. This theory also seems suggestive with patients that also have systemic sclerosis and Raynaud’s phenomenon exhibiting CNCH[8]. Injury to the skin and cartilage seems to be the most important 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, suppurrative, granulomatous dermatitis into a later fibrosing dermatitis with the feature of perforating folliculitis and prurigo nodularis[9]. Another possible cause is low temperature affecting local circulation that limits blood supply and causes necrosis of the dermis and epidermis[10]. Actinic damage has also been implicated in CNCH and is a common finding, but the causal effect has not been documented[11]. The suggested cause for the pain associated with CNCH is the glomoid proliferation of small capillaries[12].

**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%[12-14]. 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[15]. Lawrence used intralaser corticosteroid injection with only a 27% cure rate[16]. The usual dosing for intralaser corticosteroids is 0.1 to 0.2 ml of triamcinolone acetonide (10-40 mg/ml)[17]. Nelson used topical Bactracin 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[20]. Taylor successfully used carbon dioxide laser ablation therapy using a Fiber Laser, 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[21]. Kromann et al reported a 31% recurrence rate using electrodesication and curettage[22]. Shave excision with curettage and desiccation has been reported to have 21% recurrence rate[23]. Wide excision of the skin and cartilage was shown a 31% recurrence rate by Newcomer et al[24]. Metzger et al showed wedge removal of skin and cartilage had a 10% recurrence rate[25].

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 burrows’ triangles. This will obtain maximal results in both comfort and appearance, while markedly reducing the likelihood of recurrence.

**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.
References

1. Winkler M. Chondrodermatitis nodularis chronica helicis. Arch Dermatol Syphilol 1915;121:278
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.
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), cephalaxin (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/µL, 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.

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. 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. Patients with full-blown AIDS may especially present with severe, extensive forms of the disease.

Epidemiology

The prevalence of psoriasis in the HIV population is estimated to be 1-3%. Psoriatic arthropathy has a prevalence of 23-50% in those with HIV and psoriasis. Twenty percent of patients with HIV-associated psoriasis have their presentation with a CD4 count greater than 400 and psoria-
Eruptive Psoriasis in a Patient with Human Immunodeficiency Virus

Pathogenesis

Psoriasis is characterized by an accelerated epidermal turnover and increased deoxyribonucleic acid synthesis (DNA) by keratinocytes. 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. An association with the Cw0602 allele in particular is seen in 79% of HIV-associated psoriasis cases.

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.

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 for 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. 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. In patients with AIDS, interferon-α, 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.

Clinical Features

The clinical manifestations of HIV-associated psoriasis are similar to those without infection. 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. Several patterns may coexist within the same patient.

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. These patients usually present in the second decade of life and often have a positive family history of psoriasis. The second group expresses psoriasis after HIV seroconversion where less common forms of psoriasis including inverse psoriasis, acral psoriasis, and pustular psoriasis are seen. 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. As mentioned earlier, the severity of psoriasis in this population tends to reflect the stage of HIV disease and worsens as HIV disease progresses.

Psoriatic arthropathy in HIV disease shows a polyarticular and asymmetric involvement. 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.

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.

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. 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. Special testing has revealed an infiltrate composed predominantly of CD8+ cells; CD4+ and Langerhans cells are depleted due to infection with HIV.

Treatment

A stepwise approach from topical to systemic therapy is the usual course of treatment. Topical preparations including corticosteroids and calcipotriol are first line treatments. 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-psoriasis has been demonstrated. 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, photaging of the skin, and nonmelanoma skin cancer. 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. 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. 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 exercised when prescribing this drug in the setting of HIV disease.

Effective antiretroviral therapy has also shown improvement of cutaneous lesions in this patient population, supporting the role of HIV in the pathogenesis of psoriasis. Zidovudine (AZT) was the first antiretroviral shown to be useful for the treatment of HIV-associated psoriasis in a dose-dependent fashion. 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. Other antiretrovirals from case reports that have shown improvement of psoriasis in HIV patients include the following: lamivudine, ritonavir, saquinavir, and nevirapine.

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. Often, flares of HIV-associated psoriasis can be accompanied by skin infection. It is therefore important to identify and treat all known infections.

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.

References:

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, non-tender 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 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, hydrophobia, or following organ transplant.1

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).6 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 MEDF 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 dermatofibroma.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.2 Dermatofibroma may be confused with keratoacanthoma, nodular fasciitis, neurofibroma, Kaposi’s sarcoma, keloid and melanocytic nevus.2 Histology

Dermatofibroma is also known as benign fibrous histiocytoma, histiocytoma, or scirrhus hemangiom.2 Gross examination reveals 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...
The dermal tumor is poorly demarcated on both sides, where spindle cells infiltrate between collagen. 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. There is proliferation of fibroblasts and histiocytes in the reticular dermis, arranged as short intersecting fascicles. Dermatofibromas are positive for Factor XIIIa, vimentin, and muscle-specific actin. In contrast to dermatofibrosarcoma protuberans, dermatofibromas are negative for S-100 and CD34.

**Underlying Diseases**

Multiple dermatofibromas have been associated with altered humoral and/or cellular immune system, including systemic lupus erythematosus, Sjögren’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. Niyama et al reported MEDF in a 48 year-old female with SLE. 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. One patient who developed MEDF had both SLE and Sjögren’s syndrome. Newman and Walter reported MEDF in 3 female patients with SLE who were treated with prednisone, azathioprine, or both. 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.

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. 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. Alpha-interferon exerts a wide range of effects on the production of many cytokines including interleukin 1, interleukin 2 and tumor necrosis factor. 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. 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. 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.

The only case strongly associated with diabetes mellitus and necrobiosis lipoidica occurred in a 36 year-old Caucasian female. 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
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. 10 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 cyclophosphamide 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 cyclophosphamide and prednisolone.

Cohen reported a 45 year-old male with pemphigus vulgaris and ulcerative colitis, who developed 23 dermatofibromas on his legs. 26 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. 2

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, immunodeficiencies, or following immunosuppressive therapy.

References

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**STUDIES**

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There are no contraindications for the use of LoproX Shampoo, except for those inherent in the use of other antifungal agents.

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Seborrheic dermatitis may be present in infancy, but no clinical studies have been done in patients younger than 16 years.

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There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women.

**Adverse Reactions**
In 626 patients treated with LoproX Shampoo twice weekly in two pivotal clinical studies, the most common adverse events were irritation, itching, and burning. Other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder.

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**Prescription 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 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 there were no known drug allergies.

Topical fluocinonide cream (Lidx) 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. 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, however, bilateral distribution has been reported. Occasionally the eruption may be seen on the neck, face or trunk. 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.

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 during the eruption.
Lichen striatus following botulinum toxin type A (Botox) injection

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.

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.

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.

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 and environmental factors have each been considered to play a role. Initially the linear pattern of cell migration during embryogenesis, perivascular and perieccrine lymphocytic infiltrate is seen. Closer view of the moderately intense perivascular and perieccrine lymphocytic infiltrate at the dermal-epidermal junction.

Closer view of the moderately intense perivascular and perieccrine lymphocytic infiltrate is see.
periecrine 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.5

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.2,3,4 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.

References


LAWLOR, ADLER 21
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, scatted 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. PLCA is classically grouped into macular and lichen amyloidosis. The two forms are identical histologically and can only be differentiated clinically.2

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.2 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.3 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-
PLCA has also been described in hyperpigmentedlichenified ano-sacral variant that often occurs in association with bishapic 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 epidermis1,2 (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.1,2 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, consisting of environmental factors and genetic predisposition.1 As noted previously, it is postulated that chronic local injury to the epidermis causes damage to epidermal keratinocytes2 (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.2 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 keratinocytes 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 sulf oxide, and cyclosporine have shown only mild efficacy in treatment of the disease.2

**Acknowledgements**

I would like to thank Dr. Andrew Hanly and Dr. Evangelos Poulos at Global Pathology Laboratory Services for providing the histological images in this Case Report.

**References:**
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 pre-served head lice.13

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 becomes 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.14

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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 café 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.
Head lice infestation is a worldwide problem, although the infestation rates may be variable. 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. 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); Wales, 4.1%; Turkey 9.42%; northern Jordan 13.4%. In Australia, 21% of the 456 pupils who participated in the survey had active infestation. Similarly, in a study in Israel, 11.2% of the children were infested with living lice and eggs while 23.4% had nits only. 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.

A cross-sectional survey of three primary schools in Guerrero, Mexico reported a prevalence of head lice infestation ranging from 18 to 33%. 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%.

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. 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.

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
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 38.8% (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),
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.

**Treatment Strategies**

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

**Mechanical removal**

**Drug List**

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

**Pediculicides**

The choice of a pediculicide can be challenged by widespread insecticide resistance. 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. 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. 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. 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 mamalian 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. 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). 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.

**Potential toxicities and side effects**

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 use of a lubricant such as olive oil or hair conditioner. Other lubricating agents include petrolatum, mayonnaise and other essential oils such as those from the leaves of Lippia multiflora. Use of these agents were found more effective when used in an enclosed system to suffocate the lice. Further data are needed to fully assess the safety and efficacy of these alternative therapies.

**Eradication of infestation by wet combing**

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. Wet combing treatment is repeated every 3-4 days for several days.
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%). 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 infection 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.

**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.

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**

Special thanks go to the organizers and the volunteers of the Nicaraguan Medical Missions 2003, the members of the Christian Medical Association of the University of Miami School of Medicine. Acknowledgement also goes to Marceline Fiorini, Christie Dinkla, Alexandra Smith, Dr. Jose Arroyo and Dr. Robert Kirsner.

**References**


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Patients should not donate blood during or 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 ejaculation volume of 10 mL, the amount of drug transferred in semen would be 0.15 ng/mL of a single 25-mg capsule. Thus, although it appears that acitretin is not absorbed following oral ingestion, there is a small risk to a fetus while a male patient is taking the drug or after it is discontinued, the non-effect limit for teratogenicity in women and teratogenic effects associated with acitretin are unknown. The available data are as follows: There have been 25 cases of reported conception when the male partner was taking acitretin. The non-effect limit for conceptions in these cases. Of these, 9 reports were retrospective and 4 were prospective (noting the pregnancy was reported as knowledge of the outcome).

= Timing of prenatal acitretin treatment relative to conception:

Delivery of healthy newborn Spontaneous abortion Induced abortion

<table>
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<th>Accts of conception</th>
<th>0</th>
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<th>0</th>
<th>0</th>
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</thead>
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<td>0</td>
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<tr>
<td>Discontinuation -4 months prior</td>
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<td>0</td>
<td>0</td>
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</tbody>
</table>

**WARNINGs**

**Precautions:** For Patients: Soriatane should be used with caution in patients with a history of or predisposition to thyroid disease. If the patient develops symptoms suggestive of hypothyroidism or hyperthyroidism, therapy should be discontinued until the condition is more fully evaluated. Patients should be informed that acitretin can cause hyperlipidemia. If the patient develops symptoms suggestive of hyperlipidemia, therapy should be discontinued until the condition is more fully evaluated. Patients should be informed that acitretin can cause hyperglycemia. If the patient develops symptoms suggestive of hyperglycemia, therapy should be discontinued until the condition is more fully evaluated.

= High blood lipids or triglycerides have been noted in patients with hyperlipidemia.

= The use of acitretin in patients with hyperlipidemia should be discontinued if the lipid abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hyperglycemia should be discontinued if the glucose abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypertriglyceridemia should be discontinued if the triglyceride abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypercholesterolemia should be discontinued if the cholesterol abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hyperuricemia should be discontinued if the uric acid abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypertension should be discontinued if the blood pressure abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with diabetes mellitus should be discontinued if the blood glucose abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypothyroidism should be discontinued if the blood thyroid stimulating hormone (TSH) abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hyperthyroidism should be discontinued if the blood thyroid stimulating hormone (TSH) abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypoglycemia should be discontinued if the blood glucose abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hyperglycemia should be discontinued if the blood glucose abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypertriglyceridemia should be discontinued if the blood triglyceride abnormality persists after the drug has been discontinued.

= The use of acitretin in patients with hypercholesterolemia should be discontinued if the blood cholesterol abnormality persists after the drug has been discontinued.

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Sorbitane (sorbitan)
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 mucosa, 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.
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 bruising 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.
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 deficiency 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
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. 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 enabling 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, hematrhosis, anemia, gastrointestinal bleed, hemopericardium and rarely cerebral hemorrhage.

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

References:
1. Hirschmann JV,
YELLOW NAIL SYNDROME: A CASE PRESENTATION AND REVIEW OF THE LITERATURE

By Dan Ladd Jr. DO, Rick Lin, DO, Bill V. Way, DO
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, Hgb/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 periongual swelling. 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.

Malignant associations include lung cancer, laryngeal carcinoma, melanoma, Hodgkin's disease, sarcoma, lymphoma and adenocarcinoma of the endometrium. Renal associations include minimal change nephrotic syndrome, xanthogranulomatous pyelonephritis, nephrotic syndrome and nephropathy with exudative pleuritis, respiratory tract disease, sclerodactyly and lymphangiopathy.

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 Amorolfin was presented. All 20 nails were thickened, yellow, opaque, with absent lunulae and increased curvature. The patient also had 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.

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 abscesses. 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.

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 at (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.

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

**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.

**References:**

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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 hyperparathyroidism, hypoparathyroidism, 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 dartos 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.
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. 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. 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. 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. Setoyama discussed a patient with granuloma annulare and concomitant lymphocyte predominant Hodgkin’s, the same subtype as our patient.

The relationship between these two diseases is still unknown. Ono suggests that granuloma annulare is a lymphoma-induced reaction. 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.

References

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 supravacular, 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
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. Most 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. 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. 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.

The lesions of GA are typically non-tender. A study by Dabinski document 2 of 100 patients that had tender lesions and none had tender lesions on the palms. 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.

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 for 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. 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.

Generally speaking, there is no difference in the histology of localized or generalized granuloma annulare. 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. 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.

Even with histology atypical non-annulare clinical presentations may be atypical in there histologic presentation. As in our case, additional biopsies may be needed.

The differential diagnosis of non-annulare granuloma annulare would include arthropod bites, secondary syphilis, xanthomas and non-histiocytoses. 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. Other proposed etiologies include trauma, insect bites, tuberculin skin testing, PUVA therapy and viral infections. There is one report of three children developing a papular form of GA after being bitten by the gnat Culicoides furans. A more recent belief is that GA is a delayed-type hypersensitivity reaction to an unknown antigen. This is based on T-cell subpopulations found in GA lesions.

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, isoretinoin, antimalarials, cyclosporin A, chlorambucil, dapsone, and pentoxifylline. It should be noted that no large, randomized, double blind, placebo-controlled studies have performed to support the use of these systemic medications, and most of the reports of their efficacy are anecdotal. Other therapies used include systemic prednisone, potassium iodide, and methoxsalen plus ultraviolet light. In addition, six of seven patients with generalized GA responded to chlorpromide (Diabetic) in one study. 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. 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.

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.

References
**HEREDITARY PALMOPLANTAR KERATODERMA OF THE UNNA-THOST TYPE: A CASE REPORT AND LITERATURE REVIEW**

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Philadelphia College of Osteopathic Medicine, Philadelphia, PA

**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. With new advances in molecular genetics the PPK have also been classified based on genetic mutations.

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 (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 keratin 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. 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.

**Classification Scheme for Palmoplantar Keratodermas**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>PPK type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>No other ectodermal associations</td>
<td>Epidermolytic</td>
<td>Vörner’s type PPK</td>
</tr>
<tr>
<td>Focal Or Punctate</td>
<td>Presence of associated cutaneous or noncutaneous ectodermal disease in sites other than the palms and soles</td>
<td>Yes Or No</td>
<td>Nonepidermolytic</td>
</tr>
</tbody>
</table>

**Example of Classification of Diffuse Hereditary PPK:**

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>PPK type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>No other ectodermal associations</td>
<td>Epidermolytic</td>
<td>Unna-Thost type PPK</td>
</tr>
<tr>
<td>Diffuse</td>
<td>No other ectodermal associations</td>
<td>Nonepidermolytic</td>
<td>Vörner’s type PPK</td>
</tr>
</tbody>
</table>

Figure 1. Classification of palmoplantar keratodermas (adapted from references 1, 11 and 22)
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. The underlying defect seems to be associated with keratin 1 which is one of the two main keratins found in the palmar plantar epidermis with the other being keratin 9. Keratin 1 is a type II keratin (basic, K1-K8) which is coded for on chromosome 12q13.

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.

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. Trichophyton rubrum, T. Mentagrophytes, T. Verrucosum and Epidermophyton floccosum are the major causes of dermatophytosis in the Unna-Thost type of PPK. 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.

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. 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.

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. 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 anditraconazole 100mg/day has been found beneficial in treating dermatophytosis.

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. The third generation retinoids (isoretinoin) 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 clinical appearance. However, many of the other types of PPK had good response rates. 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. 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. 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.

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. 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. 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.

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 intra-ventricular conduction defects. Therefore, after thorough physical examination, electrocardiogram and echocardiogram should be obtained if warranted. 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.

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.

References

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“HERPES GESTATIONIS” - A CASE PRESENTATION

Robert A. Norman, D.O., MPH, FAAD
Dyan J. Harvey-Dent, D.O.

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 cephalaxin 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 chorionic carcinoma (1,3).

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) (5,6). Herpes Gestationis appears to be mediated by an IgG 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 (6). This is theorized to be secondary to the low incidence of HLA-DR4 in African Americans (6). There is also an increased risk of developing Graves Disease in patients with a history of Herpes Gestationis (7). 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 (8). 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 subpidermal edema and inflammatory dermal infiltrate with eosinophils and spongiosis (9). 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 (2,5,6). 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 (10). Case studies have indicated some benefit from tetracyclines in postpartum Herpes Gestationis, but their effectiveness requires further investigation (11).

References
Introduction

Melanoderma associated with mechanical factors have been reported frequently in the Japanese literature. It is caused by prolonged mechanical friction, pressure, heat, rubbing 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 vascular 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 cong red stains were negative excluding the presence of amyloid.

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. It was thought to be precipitated by physical stress such as exposure to prolonged mechanical friction, pressure, heat, rubbing and chronic irritation. In fact some authors considered friction melanosis as a distinct pigmentary disorder. 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. Hyperpigmentation due to performance of a precise rituals within a religious context were also reported in muslim men called prayer nod-
ules and in Talmudic male students in Jewish. 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. While others found epidermal hyperplasia and diffuse hyperpigmentation at the base of the epidermis with no melanophage or interface dermatitis or inflammatory infiltrate. Macular amyloidosis was also found in other reports which was not documented in our case. It is believed that the histopathologic changes are variable because this is a dynamic process with the late stage characterized by postinflammatory hyperpigmentation. 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 Davenor's dermatosis but with no clear history of regular body scrubbing 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 exaggerated 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. Further studies are needed to determine factors related to this disease and individuals who are susceptible to such pigmentary changes.

References:
PHOTODYNAMIC THERAPY FOR INTRA-EPIDERMAL SQUAMOUS CELL CARCINOMA: PRELIMINARY RESULTS WITH HISTOPATHOLOGIC CORRELATION

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AZ Desert Dermatology/Midwestern University/Kingman Regional Medical Center

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 morbidity.2 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 than 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

Pre-PDT: 4X, 10X, 40X
Post-PDT: 4X, 10X, 40X
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. 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.

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.

References:

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 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 Symmetrical 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. 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.

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. The incidence is highest in the Mediterranean area. 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. Associated disorders described in MSL include hyperuricemia, diabetes mellitus, hypothyroidism, liver disease, polynuropathy, abnormal glucose tolerance, hyperlipidemia, and malignant tumors.

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. Because of the symmetry, physical exam may not identify the

Table 1. Differences between lipomatosis and lipomas

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<th>Lipomatosis</th>
<th>Lipomas</th>
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<tr>
<td>Clinical lesions</td>
<td>Diffuse and symmetric</td>
<td>Single or multiple tumors</td>
</tr>
<tr>
<td>Infiltration of adjacent tissues</td>
<td>Present</td>
<td>Generally absent</td>
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<td>Connective tissue capsule</td>
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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. 3, 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. 4, 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. 4 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. 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**

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.

**References:**

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, butyrate, alpha lipoic acid, N-acetylcyesteine, vitamins K, A, and C, selenium, taurine, glyicine, L-carnitine, honey and astragals. 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. 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. 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.

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.

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. It also inhibits solid tumor development, invasion and growth of pulmonary metastases induced by melanoma cells as well as high-grade tissue sarcoma. 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.

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.

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 pro-matrix metalloproteinase-9 (pro-MMP-9) via the PKC pathway, causing cell cycle arrest. 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.

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

Isoflavonoids 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. Melanoma cells with the mutant P53 gene are strongly resistant to conventional chemotherapy, curcumin may overcome this chemo-resistance. 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 nodules formation were rutin, epicatechin (from green tea), naringin and naringenin (from grapefruit). Curcumin increased the life span of the test animals 143.85%.

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 anti-neoplastic agent, etoposide has this action. Curcumin also is a topoisomerase II poison that can only add to its effectiveness. And it is safe.

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.

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, oncoidal action and killed melanoa cells. 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.

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.

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. 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.

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

Heat shock protein (HSP) is over-expressed 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.

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, butyrate, silibinin (from milk thistle) 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. 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.

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
**RAW TEXT END**

**A WORD ABOUT MALIGNANT MELANOMA**

**Butyrate**, a short chain fatty acid, is also a histone deacetylase (HDAC) inhibitor. Nucleohistones are combinations of DNA and histones. 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. **Butyrate** also causes cell differentiation and apoptosis and an increase in tumor necrosis factor alpha (TNFalpha). **NAC** is an important source of intracellular reactive oxygen intermediates. It also down-regulates VEGF and associated with growth and metastases of solid tumors including 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.

**Ginseng** is a Chinese herb that has been used for centuries to treat various ailments. **Ginsenosides**, derived from *Panax ginseng* (Panax ginseng), induced differentiation in melanoma cells and teratocarcinoma cells, changing them to normal melanocyte-like cells or parietal endoderm-like cells**.** Modulation of PKC isoforms were involved in this process. **Ginseng** also acts as an immunostimulant taurolidine. This not only has an immediate effect that, at these times, every effort be made to stimulate the patient’s own immunity. 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 caffate (PEMC), and phenethyl dimethyl caffeate (PEDMC). All these three inhibitors are present in **honey**. Now isn’t that sweet.

**Butyrate** and alpha lipioic acid, both HDAC inhibitors, are also effective against squamous cell carcinoma. **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-acetylcyesteine** (NAC) inhibits production of VEGF in three human melanoma cell lines. **NAC** acts by inducing genetic changes that arrest cell division in the cancer cells. Specifically, “NAC induces p16(NK4a) 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.

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

**Genistein**, 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 and to increase P53 and decrease the content of c-Myc within the cancer cells. It also has the ability to increase the activities of cytotoxic T cells and natural killer (NK) cells. **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. 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 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 good news is, all three promoters are inhibited by phenylethyl caffeate, (PEK), phenylethyl-3-methyl caffate (PEMC), and phenethyl dimethyl caffeate (PEDMC). All these three inhibitors are present in **honey**. Now isn’t that sweet.

**Vitamin C** increases intracellular reactive oxygen intermediates. It also down-regulates VEGF, 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.

**Selenium**, in its active form as selenomethionine or combined with soy protein, has been shown to decrease growth and metastases of melanoma cells. **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. **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-F. **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. 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. Aside from its anti-inflammatory action, glycine also prevents the growth of melanoma cells in vivo. Choline is found in lecithin and as phosphatidylcholine 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.

The bad news is that many different malignancies are related to 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 caffate (PEMC), and phenethyl dimethyl caffeate (PEDMC). All these three inhibitors are present in **honey**. 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 taouridine.

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.

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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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.

**SURGICAL PEARLS**

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

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**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
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.

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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.
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Key West, Florida • Pier House Hotel

Jay Gottlieb, D.O. • Program Chairman
**Dermatosis Papulosa Nigra With Mucosal Involvement**

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**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 forehead. 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. It is seen frequently in the Negroid race. 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 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.

**Discussion:**

It was first observed by Aldo Castellani in 1925 while visiting Jamaica and Central America and he named this condition dermatosis papulosa nigra. It is frequently seen in the Negroid race. The incidence among blacks can reach up to 77% 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. Occasional cases among Mexicans, Filipinos, Vietnamese, and Europeans have been described in the literature. 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 acanthetic 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...
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. In fact, approximately one half of affected individuals report at least one family member with this problem with no associated medical conditions 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.

References
Dermatologic Manifestations of Dilantin Hypersensitivity Syndrome: Case Presentation and Review


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 – 45 _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 levofloxacain (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 erythoderma 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 nascant toxic epidermal necrolysis. The recommendation was made to discontinue the phenytoin immediately and to retain body heat by covering the body with moisturizers. Moisturizers 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. In vitro studies dating as far back as the 1970s suggest that phenytoin inhibits collagenase, an enzyme found at the basement membrane. 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. In addition, phenytoin has been used to treat lichen planus, rheumatoid arthritis, and neuropathic pain in diabetics. Along with carbamazepine, phenytoin was the first anticonvulsant to be shown in controlled clinical trials to relieve paroxysmal attacks in patients with trigeminal neuralgia.

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. 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. Hair growth occurs on the extensor aspect of the arms and on the trunk and face; this
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. Phenytoin has also been associated with lupus in children. Phenytoin-induced linear IgA bullous disease has also been reported in the literature.

Generalized nodular cutaneous pseudolymphoma has been described in association with phenytoin. 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. 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 including Stevens-Johnson syndrome and toxic epidermal necrolysis. Fixed drug reactions have also been reported following use of phenytoin.

**Hypersensitivity 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. 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 and exfoliative dermatitis was published in the New England Journal of Medicine. 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. It is also seen in patients who have been exposed to other aromatic anticonvulsants including carbamazepine, phenobarbital, and primidone (Mysoline). 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. 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 erythoderma or toxic epidermal necrolysis with extensive desquamation. 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. 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 DHS.

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 lymphadenopathy, and evidence of hepatocellular insult (i.e., elevated transaminases) in patients who have taken phenytoin, carbamazepine, or myolane (recall that phenobarbital is the active metabolite of myolane). 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. 

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. Challenge with phenytoin can be dangerous in a patient who has previously been sensitized to the drug but has since discontinued the agent. 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 dysregulation.

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. 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 dosages equivalents of 60 mg prednisone daily, only to relapse when the corticosteroid was discontinued abruptly or even tapered over two weeks. Corticosteroid administration has not proved efficacious in controlled studies and management with systemic corticosteroids remains empirical. One source states that systemic corticosteroids, starting at 1 mg/kg/day, should be used for at least one month. 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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**References:**

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 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 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 xanthomas occurring with type III hyperlipidemia: a case report and review of the literature.

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.
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.

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. Apoproteins 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.

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 by LDL receptors in the liver and other tissues.

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. Acutely, inflammatory components such as erythema, pruritus, and pain may be associated findings. In areas of trauma, keoonerization frequently occurs. 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. Type I hyperlipidemia is caused by lipoprotein lipase deficiency. It is typically seen in children who develop eruptive xanthomas, lipemia retinaii, and pancreatitis. Triglycerides are frequently greater than 1000 mg/dl. Type V hyperlipidemia or familial chylomicronemia 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 are 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.

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 cholesterolosis, or cutaneous Langerhans cell histiocytosis. In a patient with a history of diabetes mellitus and hypertension, hyperuricemia, pancreatitis, triglycerides are frequently greater than 250 mg/dl, increasing their risk of premature atherosclerosis.

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.

References
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.
Patients like the results.

- **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.
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 fatal harm when administered by a pregnant woman.

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. 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 instillation of therapy should be considered. A negative result for pregnancy test having a sensitivity down to 25 mIU/mL should be obtained 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 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 25 mIU/mL 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.

Reticinoids 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 for 24 hours after sunburn is 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 subsides 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 AUC0-24h in acne patients treated with 2 mg/cm² 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 intermittent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.011% 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 0.25 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 (AUC0-24h) at the highest dose was 13 times the maximum AUC0-24h in acne patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

TAZORAC® Cream was found to be non-mutagenic in the Ames assays using Salmonella and E. coli and did not produce dominant chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic 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 AUC0-24h in acne patients treated with 2 mg/cm² 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 AUC0-24h that was 6.3 times the maximum AUC0-24h in acne patients treated with 2 mg/cm² of tazarotene cream 0.1% over 15% body surface area.

Pregnancy: Teratogenic Effects: 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 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 25 mIU/mL 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).

Nursing Mothers:

After single topical doses of 0.1% tazarotene gel to the skin of lactating rats, radioactivity was detected in 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 sensitisation, phototoxicity, or phototesting.

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 and body, 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

U.S. Patent Numbers 5,089,509

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9087X
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 1980 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 β-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 AGEP³. In this study, 11 patients were also found to have a history of psoriasis⁴, 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 coalescence 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).
thyroiditis, inflammatory bowel disease, and multiple sclerosis all have been found as underlying diseases in patients with AGEP. 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.

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. 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 10^3/L is present and mild-to-moderate eosinophilia is found in about one third of cases.

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. In conclusion, we propose that celecoxib be added to the list of medications causing AGEP and physicians be aware of its association.

References:

Nephrogenic fibrosing dermopathy: A case report

Introduction

Nephrogenic fibrosing dermopathy (NFD) is a recently defined idiopathic disorder characterized by fibrotic skin plaques in patients with renal disease1. The disorder, formerly called “scleromyxedema—like cutaneous disease”, was first described by investigators at the University of California in San Francisco in 19971. Three years later, Cowper S. et al, described 14 patients who had undergone either hemodialysis or renal transplant and then developed thickening of the skin3. 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 disorder2.

Numerous reported cases have demonstrated the variance in presentations. Although the disorder was first described in a cluster of patients who had either hemodialysis or renal transplant, the disorder has since been seen in many other patients with renal impairment1. The causes of renal insufficiency that are associated with the skin manifestations are vast4. 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 eruptions5. Spontaneous resolution of symptoms as well as skin change improvement with aggressive dialysis have been noted in some patients4-5.

Erythematous, confluent papules, patches or raised plaques are common with islands of sparing within the indurated plaques5. Mackay et al described four patients having plaques with irregular edges and irregular finger-like or amoeboïd projections5. Patients typically present with symmetric skin tightening of the limbs and/or trunk5. Unlike other fibrotic disorders, the face appears to be spared5. The skin becomes textured with a peau d’orange appearance5. Progressive hardening of the skin leads to skin contractures causing decreased ability to flex and extend the joints5. Debilitating outcomes and inability to ambulate without assistance often result5.

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 asymptomatic4-5. 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 aged5. The reported cases encompass great racial diversity and many ethnic backgrounds5.

Diagnosis can be made by histopathological examination of a skin biopsy specimen. Incisional or punch biopsy are acceptable4. 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 bundles6. In addition, the specimen may demonstrate an increase in the number of subcutaneous spindle cells that can extend into the fascia and muscle6. Fragmented elastic fibers have also been noted6.

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.
At the age of 26, this white male presented with symmetrical rash over 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 followed by prompt resolution of the lesions.

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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 (ICNFD) at Yale University can be reached at http://www.icnfdr.org.²

References:
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

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-flourouracil 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

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 porphyria 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
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

Table 1 - Treatment Data Summary

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

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.
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.

**References:**

8. Levulan® Kerastick™ (aminolevulinic acid HCL) for Topical Solution 20% Full Prescribing Information. DUSA Pharmaceuticals, Inc., Wilmington, MA, Sept. 11, 2000.
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