Contents

Letter from the JAOCD Editors.................................................................4
Letter from the President........................................................................5
Dissecting Cellulitis of the Scalp Treated Successfully with Adalimumab .................................................................6
   Kristen Marie Aloupis, DO, MPH, Stanley Skopit, DO, FAOCD, Francisco Kerdel, BSc, MBBS
Acrodermitis Contiuua Following Surgical Trauma: A Case Report ...............................................................9
   Heather Higgins, DO, Steven Grekin, DO, FAOCD, Michael W. Whitworth, DO, FAOCD
Eruption of Lymphocyte Recovery: A Case Presentation and Review of the Literature ........................................11
   Lisa A. Zaleski, DO, LT, MC, USN, Peter R. Shumaker, MD, LCOR, MC, USN
Oral Lichen Planus: A Case Report and Review of Literature ........................................................................15
   Julie Malchiodi, DO, Michelle Bruner, DO, Melissa Hintz, Jean Holland, MD
Giant-cell Tumor of the Tendon Sheath: A Case Presentation and Review of the Literature ...............................18
   Chris Buckley, DO, Stanley Skopit, DO, FAOCD
Recurrent Abscesses: Underlying Immunodeficiency? .....................................................................................20
   Brian S. Walton, DO, and Stephen M. Purcell, DO
Idiopathic Thrombocytopenic Purpura: A case report and discussion .................................................................22
   Kevin DeHart, DO, Kristin Witfill, DO, Richard Miller, DO
MRSA—Case and Review ......................................................................24
   Robert A. Norman, DO, MPH, Steven Nodine, OMS III
Porphyria Cutanea Tarda: Case Presentation and Literature Review ......................................................................27
   Tracy Favreau, DO, Stanley Skopit, DO, FAOCD
A Case of Curious Axillary “Freckling” ................................................29
   Kevin Spohr, DO, Robert Berg, MD, Brad Glick, DO, MPH, FAOCD, Les Rosen, MD
A Woman With Gradually Spreading Telangiectasias ...................................................31
   Daniel Hansen, DO, MBA, Steven Grekin, DO, FAOCD, Don Collier, DO, FAOCD, Jonathan D. Richey, OMS IV
Griseofulvin-induced Photoallergic Reaction: A Case Report in a 10-year-old Hispanic Male ..............................33
   David R. Bonney, DO, Stanley Skopit, DO, FAOCD
Accessory Tragus ....................................................................................35
   Robert A. Norman, DO, MPH, Veronica Cabigas Davis, OMS IV
Treatment of Psoriasis with a Vascular Endothelial Growth Factor Inhibitor .........................................................36
   Stephen C. Verral, DO, MPH, Steven K. Grekin, DO, FAOCD
Mastocytosis: Mast Cell Burden and Symptomatology .................................................................................41
   Aaron Bruce, DO, David Esguerra, DO
Linear focal elastosis in a young Hispanic male: a new presentation ..............................................................43
   Brian Feinstein, DO, Stanley Skopit, DO, FAOCD
Amyopathic Dermatomyositis Associated with Myelodysplastic Syndrome ...................................................46
   David B. Roy DO, Don A. Anderson DO, FAOCD, F.A.S.M.S
Perianal Basal Cell Carcinoma: A Case Report .................................................................................................51
   Andrea Passalacqua, DO, Ronald Liskanich, DO, Gloria Stevens, M.D., David Horowitz, DO
Dermoscopy for Non-melanocytic Lesions .................................................................................................53
   Lynora Curtis Basset, DO, Brad P. Glick, DO, MPH, FAOCD
Sentinel Lymph Node Biopsy for Cutaneous Malignant Melanoma: A Review of the Rationale, Criteria, Procedure, and Controversies ...................................................................................56
   Raymond Ramirez, DO, Cindy Hoffman, DO, FAOCD, Charles Gropper, MD
Making Sense of the Perforating Disorders: A Review................................................................................62
   Brett B. Bender, DO, Michael J. Mahon, DO, FAOCD
Treatment of Lymphangioma Circumspectrum with Imiquimod 5% Cream ......................................................66
   Shaheen Oshtry, DO, Charles Gropper, MD, Cindy Hoffman, DO, FAOCD
Cutaneous Metastasis of Adenocarcinoma .................................................................................................68
   Adam D. Wray, DO, Lloyd J. Cleaver, DO, FAOCD, Jonathan Cleaver, MSIV
There was a woman cooking a pot roast. Her husband noticed that before she put the roast in the oven, she cut both ends off of the roast. He asked her why she cut off the ends, and she replied that it was the way her mother always cooked pot roast. So, the husband told his mother-in-law the story about the roast and she responded that she did, in fact, cut both ends off of the pot roast before placing it in the oven. When he inquired why she cut the ends off the roast, she said she did it because her mother always cooked a pot roast that way. Now the husband’s curiosity got the best of him, so he spoke to his wife’s grandmother and she admitted that she did always cut off the ends of the pot roast. When he asked her why she cut the ends off the roast, she said it was because that was the only way she could get it to fit into her baking pan.

Although this is a fairly long story, it does point out that we tend to do things the way we were taught, without ever questioning the reasons. This is true in all walks of life, including the medical profession. What makes life interesting and keeps medicine fun is that we have to constantly look for the reasons that justify what we are doing.

The AOCD is vibrant and growing. Our residents, interns and students are the spark that keeps those questions coming. They are the lifeblood of our profession. They keep us on our toes. They are our future leaders. They are going to be our legacy. We need to constantly help to improve their training and give them the confidence that is needed to be all of these things.

The JAOCSD is an excellent way to allow our residents to share their learning experience. Their manuscripts continue to improve as the years go by. The program directors are more involved in the publications of their residents than they have been in the past. We encourage this to continue. We need to do anything and everything to continually improve the quality of our AOCD residents.

We are thankful to have Global Pathology Laboratory, Medicis-The Dermatology Company, Stiefel Laboratory and our most recent sponsor, CollaGenex, as sponsors of the JAOCSD. They continue their commitment to the dermatology profession and support the AOCD in all of its endeavors.

Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)
James Q. DelRosso, D.O., F.A.O.C.D. (Associate Editor)
Dear Fellow & Resident AOCD members,

The holidays are now behind us and the New Year is in full swing. In the first 3 months as your president, I have been busy working with Drs. Lloyd Cleaver, Jim Towry and John Hibler and the residency program directors to ensure that the resident-in-training examination goes smoothly this year and in the years to come. Dr. Cleaver developed and implemented a Web site where the program directors can easily submit their questions each month. Dr. Hibler created a simple matrix for the program directors to utilize to ensure that the questions submitted cover all of the topics that need to be addressed in the examination. We will create a bank of questions that can simply be updated and then used for future in-training examinations.

Dr. Leslie Kramer has been working on putting together a very exciting and informational mid-year meeting in Monterey, California. Monterey is a very vibrant and exciting venue in which to be having our mid-year meeting. I hope to see each and every member and resident member in Monterey. It is going to be great.

Maintaining and growing corporate sponsorship for the AOCD seems to be more of a challenge each year. Federal requirements and restrictions make obtaining funding and grant money more and more time consuming. I encourage every AOCD member to assist our Director of Corporate Development by giving her leads that she can then develop.

Becky, Rick and Marsha continue to run our college’s office in Kirksville. More and more requirements are placed upon them as our college continues to grow. They also have more paperwork to complete each year as regulations and requirements mount. The logistics of keeping the residency programs on track is a daunting task in itself. I encourage the AOCD membership to give me both positive and negative feedback on your experiences with our AOCD office. Each comment is confidential and considered important by your Board of Trustees.

Being the editor of the JAOCSD is also very exciting. The manuscripts continue to improve in quality and quantity. Our sponsors continue to keep the JAOCSD a reality. Global Pathology Laboratory, Stiefel Laboratories, Medicis and CollaGenex have been providing the support that we need to keep a quality product in the pipeline.

I am enjoying my year as president of the AOCD. It is a learning experience and quite exciting. I wish you all a great year, and I will see you in Monterey!

Fraternally Yours,

Jay

Jay Gottlieb, DO, FAOCD, FOCOO
DISSECTING CELLULITIS OF THE SCALP TREATED SUCCESSFULLY WITH ADALIMUMAB

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ABSTRACT

Dissecting cellulitis of the scalp is an uncommon, chronic, progressive, suppurative and inflammatory scalp disease. Its pathogenesis and etiology are not completely understood. The disease is characterized by painful, fluctuant scalp nodules, abscesses and interconnecting sinus tracts, and it can lead to a scarring alopecia. Treatment of this condition is often difficult and includes medical as well as destructive therapies. We report the successful treatment of one patient with dissecting cellulitis of the scalp using adalimumab.

Case Report

A 24-year-old male presented with a several-month history of tender, fluctuant nodules on his scalp associated with a patchy alopecia. In general, the patient was in good health with a past medical history of guttate psoriasis. He had no known drug allergies and no family history of similar disorders. He had previously been treated with oral antibiotics and topical corticosteroids with minimal improvement. At initial consultation, physical exam revealed a well-developed, well-nourished young man with multiple erythematous, tender, boggy nodules and abscesses of the occipital and parietal scalp (Figures 1 and 2). No other skin lesions were noted, and there was no cervical or occipital lymphadenopathy. Most recent treatment included oral levofloxacin and clobetasol foam. Wound cultures were found to be negative, and a punch biopsy of the scalp was obtained. The skin biopsy specimen from the posterior scalp showed histopathological features consistent with dissecting cellulitis (Figures 3 and 4). Pathologically, there was a significant decrease of folliculo-sebaceous units with a dense cicatricial fibrosis and a chronic mononuclear perivascular interstitial and perifollicular infiltrate. One week later, the patient flared with increased pain, fever, and malaise, and required hospitalization. During his stay, the patient was treated with IV vancomycin, levofloxacin, and methylprednisone. He improved clinically over the next few days. A PPD and chest X-ray were negative, and the patient was discharged with the instruction to initiate adalimumab injections the following day.

After one month of treatment with adalimumab 40 mg given every other week, the patient reported to be greatly improved. At follow-up, approximately six weeks after initiation of treatment, there was a marked reduction in the inflammatory component of his disease, with resolution of the abscesses (Figures 5 and 6). Also, the patient’s psoriasis was notably improved.

Discussion

Dissecting cellulitis (DC) of the scalp, also known as perifolliculitis capitis abscedens et suffodiens, is an uncommon, chronic, inflammatory disease of the scalp characterized by painful fluctuant abscesses, sinus tract formation, and a resultant scarring alopecia. The vertex and occipital scalp are sites of predilection. The etiology of this disease remains unclear. It has been associated with acne conglobata, hidradenitis suppurativa, and a pilonidal cyst in the follicular occlusion tetrad. The disease is most commonly found in adult black men; it is rarely seen in white males as presented in our case. The course of this disease does not differ between races. DC follows a relapsing course and is usually considered progressive. Moreover, metastasizing squamous cell carcinoma arising in a chronically inflamed lesion has been reported by Curry et al.

Diagnosis is based on the presence of fluctuant nodules and abscesses on the scalp, sometimes with sinus tract formation and seropurulent discharge. The course is often protracted, and marked scarring alopecia may ensue. The histopathology of DC is well described, although the features are not diagnostic and depend on the stage of the disease. There is an acniform dilation of the follicular infundibulum with intrafollicular and perifollicular accumulation of neutrophils and subsequent follicular perforation in the acute suppurative phase. Later, keratogenous debris incites a granulomatous response with sinus tracts surrounded by a dermal fibrosis.

The treatment is often difficult and disappointing. Acute flares are best treated with antibiotics, and oral zinc has occasionally produced improvement. Systemic or intraslesional steroids offer partial relief. Oral isotretinoin is effective, although it needs to be continued for four months after clinical improvement to prevent relapse. Surgical approaches have also been employed. Intercommunicating sinuses can be marsupialized, and cautery-
ization is utilized to destroy the epithelium lining the sinuses.\(^\text{13}\)

Our patient had severe DC of the scalp, for which several treatments had failed. Given the recently reported cases of patients with hidradenitis suppurativa successfully responding to anti-TNF-α therapies,\(^\text{14-20}\) we attempted a trial of adalimumab, a fully human monoclonal antibody directed against TNF-α. He had a prompt and dramatic response to his initial injection and continues to show improvement on his current every-other-week treatment regimen.

Though the pathogenesis of DC is not well understood, case reports of hidradenitis suppurativa successfully responding to anti-TNF-α therapies,\(^\text{14-20}\) we attempted a trial of adalimumab, a fully human monoclonal antibody directed against TNF-α. He had a prompt and dramatic response to his initial injection and continues to show improvement on his current every-other-week treatment regimen.

Figure 4

Figure 5

Figure 6

Adalimumab is not without associated risk. Its safety profile is based on trials for its approved indications, namely rheumatoid arthritis, psoriatic arthritis, and, more recently, Crohn’s disease. Serious infections have occurred in patients receiving adalimumab therapy.\(^\text{21}\) It additionally has a black box warning recommending evaluation and treatment for latent tuberculosis.\(^\text{22}\) There is a lack of long-term data regarding potential increased malignancy risk due to TNF-α inhibition with the use of adalimumab. Since there is a lack of long-term data and the potential increased risk of malignancy, the Food and Drug Administration has recommended continued safety monitoring in patients being treated with anti-TNF agents. Other possible adverse effects of anti-TNF agents such as adalimumab include demyelinating disorders, congestive heart failure, and autoimmunity.\(^\text{22}\) Practitioners must discern appropriate candidates for anti-TNF treatment on a case-by-case basis.

To the best of our knowledge, this is the first English-language case report of dissecting cellulitis treated successfully with adalimumab. Given its convenient subcutaneous dosing regimen, along with its strong anti-inflammatory properties, adalimumab may represent a therapeutic option for this often frustrating disease. Additional research is needed before adalimumab’s true therapeutic benefit for treatment of dissecting cellulitis of the scalp can be elucidated.

**References:**

Members of the AOCD may advertise "position available"

This is a free service for all active members of the AOCD. A 3" column black and white ad will be provided in the journal as a free service. If members wish to use a larger space, they may do so. The cost for this advertising is:

- Black and White - 1/4 page-$125, 1/2 page-$200, full page-$350
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Resident members may run a 3" column black and white ad stating their desired professional position.

These ads must be submitted as an e-mail attachment and sent to jaocd@aol.com. Any photos to be included in an active member's ad, must be in a .pdf format.
Clinical Presentation

A 50-year-old male presented with bilateral thickened toenails and painful, hyperkeratotic erythematous plaques on his distal toes. The patient reported that the lesions initially developed within one month following laser matrixectomy of his bilateral great toes, performed by podiatry to treat his chronic onychocryptosis. Following the surgery, his distal great toes developed pustules with foul-smelling drainage and nail thickening. The pustular areas progressed to hyperkeratotic, tender scaly plaques, and subsequently most of his toes and several fingers were affected. In addition, he later developed two erythematous plaques with white scale on his dorsal penis and a scaly lesion on his left heel.

The patient denied any pruritus, eye irritation, oral lesions, or genitourinary symptoms. His medical history was unremarkable except for squamous-cell carcinoma of the scalp. The patient denied any family or personal history of psoriasis. He was self-employed as a long-haul truck driver, and his social history included frequent alcohol consumption.

Physical examination revealed markedly hyperkeratotic toenails. The periungual area and distal toes were edematous, tender, and covered in a thick scale on an erythematous base. Several of the patient’s fingernails were similarly affected. The patient was also noted to have two small non-healing erythematous plaques on the dorsum of his glans penis and an erythematous scaly plaque on his left heel.

Laboratory studies revealed elevated liver-function tests and triglyceride levels. All other tests were unremarkable. Culture of the toe lesions was positive for streptococcus and staphylococcus species. Fungal cultures were negative. Radiographic studies revealed periarticular edema and arthritic changes in his distal interphalangeal joints. A shave biopsy of the dorsal glans penis showed a psoriasiform hyperplasia consistent with psoriasis. A PAS stain was negative for fungal hyphae.

The patient was initially treated by podiatry with gentamicin cream and ketoconazole (Nizoral®) cream, followed by courses of oral cephalixin (Keflex®) and levofloxacin (Levaquin®). He failed to improve and was then treated with terbinafine (Lamisil®). On presentation to dermatology, the patient was treated with oral cephalxin 500 mg tid and topical silver sulfadiazine (Silvadene®) compounded with gentamicin for two weeks. Following a month-long course of sulfamethoxazole/trimethoprim (Bactrim DS®) po bid, the pustular lesions resolved, but the painful hyperkeratotic plaques persisted. He was then treated with a prednisone 60 mg taper and fluconazole (Diflucan®) 100 mg qd for two weeks. The patient subsequently developed tenderness and edema over his bilateral distal interphalangeal joints and was found to have new-onset arthritis. He completed a three-month course of acitretin (Soriatane®) 50 mg daily and showed improvement but not clearance. The patient is currently being treated with acitretin 25 mg daily and topical betamethasone/calcipotriene (Taclonex®). The penile lesions have resolved, but the toe and finger lesions remain refractory to treatment. The patient’s treatment options are complicated by his continued regular alcohol consumption despite repeated recommendations to abstain. In addition, his occupation as a self-employed long-haul truck driver requires almost constant travel, which precludes him from regularly scheduled in-office light therapy.

Discussion

Acrodermatitis continua, also known as dermatitis repens, was first described by Crocker in 1888 and further elucidated by Hallopeau in 1890. It is a rare, chronic, extremely painful form of palmoplantar pustular psoriasis. The exact etiology of the condition remains unknown. The condition typically begins following minor, incidental trauma and presents as either a sterile pustular eruption of the toes or fingers or as a paronychia. Pustules typically progress and coalesce to form lakes of pus. Erythema, keratotic changes and fissures are usually present. Eventually the pustular lesions are replaced by markedly hyperkeratotic plaques with erythematous bases.

Nail destruction is characteristic, and involvement of the nail bed and matrix leads to loss of the nail-plate or severe onychodystrophy. The process begins at the tips of fingers or toes and slowly extends proximally as well as to the dorsum of the hands or feet. Over time, some patients develop arthritic changes that may lead to osteolysis of the distal phalanx that lies beneath the lesion. In 2005, Kirkup and Lovell reported a case of acrodermatitis continua of more than 20 years’ duration that led to syndactyly.

Histologic features of pustular lesions include subcorneal neutrophilic pustules with psoriasiform hyperplasia. Neutrophils accumulate between the stratum corneum...
and stratum spinosum, between degenerated and thinned keratinocytes, to form the “spongiform pustules of Kogoj.” These lesions are later replaced by scale crust with collections of neutrophils trapped between parakeratotic layers.³

Acrodermatitis continua is often resistant to treatment, and no straightforward treatment guidelines exist. Topical treatments include corticosteroids,⁶ calcipotriene⁷ and 5-fluorouracil.⁸ In 2004, Wilsmann-Theis et al. reported two cases of acrodermatitis continua treated with tacrolimus 0.1% ointment under occlusion that produced marked improvement in the lesions.⁹

Systemic treatments include retinoids,¹⁰,¹¹ cyclosporine,¹² methotrexate¹¹ and PUVA.¹³ Recently, Nikkels et al. reported a case of acrodermatitis continua of four years’ duration that cleared when treated for three months with dapsone (4-4’-diaminodiphenyl sulfone, DDS).¹⁴ Several recent reports of acrodermatitis continua treated with etanercept also show promising results.¹⁵,¹⁶ Despite these reports of moderate success using biologic and novel systemic treatments, all treatment modalities show variable efficacy. There is no clear consensus on treatment protocol for acrodermatitis continua. Therapeutic results last as long as treatment is continued, with relapses common after treatment withdrawal.

**Conclusion**

There have been very few cases reported of acrodermatitis continua following a surgical procedure. Sahin et al. reported a case of a man who developed acrodermatitis continua after undergoing a nail avulsion procedure.¹⁷ Thomachot et al. also reported a case of acrodermatitis continua following an open reduction with internal fixation (ORIF) orthopedic procedure to repair a fractured calcaneus.¹⁸

This case illustrates an unusual example of acrodermatitis continua secondary to surgical trauma. The treatment of acrodermatitis continua is notoriously difficult, and the disease is a source of significant morbidity with adverse effects on quality of life. It is important to consider this rare but potentially devastating complication of surgical procedures.

**References**

ERUPTION OF LYMPHOCYTE RECOVERY: A CASE PRESENTATION AND REVIEW OF THE LITERATURE

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ABSTRACT
Eruption of Lymphocyte Recovery (ELR) is an uncommon eruption that develops 14 to 21 days after a period of bone-marrow aplasia, when immunocompetent lymphocytes return to the skin and peripheral circulation. The differential diagnosis for ELR is extensive, making history, physical examination, and laboratory data essential in differentiating these entities. Presented here is a case of eruption of lymphocyte recovery involving sun-exposed areas mimicking actinic keratoses, a finding not previously reported to our knowledge. The differential diagnosis for the eruption of lymphocyte recovery is discussed, along with why this case is believed to be unique.

Clinical Presentation
A 64-year-old Caucasian female presented with a five-day history of a mildly pruritic eruption primarily on the upper chest, upper back, dorsal hands, and central face that began approximately 14 days after her first session of chemotherapy for stage III large-cell non-Hodgkin’s lymphoma. Other past medical history included hypothyroidism, Sjogren’s syndrome, and hypertension. Chemotherapy with etoposide, prednisone, oncovin, cyclophosphamide, hydroxydoxorubicin, and rituximab began on day one and continued over a five-day period. Her initial eruption began approximately two weeks later and resolved abruptly at the beginning of her second cycle on day 24. A similar but more intense eruption appeared approximately 15 days after the conclusion of her second chemotherapy cycle, and she presented to the dermatology clinic for evaluation. She denied fever, malaise, diarrhea, joint pain, or other symptoms.

Physical examination revealed a fatigued Caucasian female with an eruption of coalescing, erythematous papules and plaques with scant scale and focal erosions. The lesions were primarily in sun-exposed areas including the face, neck, chest, upper back, and arms (Figures 1 and 2). The differential diagnosis included a drug reaction, eruption of lymphocyte recovery, Graft versus Host Disease (GvHD), subacute lupus erythematosus, viral exanthem, and bacterial or fungal sepsis.

Laboratory examination revealed no liver enzyme abnormalities, negative blood and urine cultures, and a close correlation between the onset of her rash and the return of her peripheral white-blood-cell (WBC) and lymphocyte counts to normal levels. Histopathology from a punch biopsy specimen revealed a lymphocytic infiltrate in the upper dermis with exocytosis, basal vacuolization, spongiosis, and dyskeratotic keratinocytes. A diagnosis of eruption of lymphocyte recovery was made based on the history, clinical appearance, and laboratory data. In light of her need for additional cycles of chemotherapy, the increasing nature of the symptoms, and the patient’s distress, anticipatory treatment with prednisone was coordinated with her oncologist to coincide with the peak in her WBC counts. The patient was treated with oral prednisone 40mg daily for three to four days, with a marked reduction in symptoms.

Discussion:
ELR was first reported in the literature in 1989 by Horn et al. and may be more common than once believed. Classically, ELR has been associated with chemotherapy in leukemia patients and can be easily distinguished from a leukemia-induced eruption due to the differences in the morphologic features of the rash. ELR tends to be a diagnosis of exclusion with history, physical examination, and lesion histology, all essential in establishing the correct diagnosis.

The typical clinical appearance of ELR is mildly symptomatic, erythematous papules and plaques that can be variably confluent and focal or more widespread. Typically, the eruption develops 14 to 21 days after a period of bone-marrow aplasia upon the recovery of peripheral lymphocytes, indicating bone-marrow recovery. There are no common medications or combination of medications that have been identified. ELR is associated with a transient increase in temperature with negative urine and blood cultures. Transfusion of blood products has not been correlated with ELR.

Although it is not well understood, the impetus for the cutaneous infiltration of lymphocytes is believed to be either a defect in the suppression of returning lymphocytes and/or the specific cytokine- and ligand-mediated recruitment of lymphocytes. More recently, it has been postulated that ELR could reflect a common clinical pathway in the manifestation of acute allogenic GvHD, acute autologous (spontaneous) GvHD, eruptions associated with the administration of cyclosporin A, and human recombinant cytokines in pharmacologic doses. All of these erythematous eruptions are thought to be caused either by an increase in the release of cytokines by infiltrating lymphocytes or to the administration of cytokines in pharmacologic doses.

Histopathology of ELR is almost identical to GvHD, revealing a T-cell infiltrate in the upper dermis with exocytosis, basal vacuolization, spongiosis, and dyskeratotic keratinocytes. Satellite cell necrosis can also be seen on rare occasions in both ELR and GvHD. However, there may be a subtle increase in the number of upper dermal lymphocytes in ELR compared to GvHD. The rash associated with GvHD involves
the introduction of autologous or syngeneic bone-marrow elements. Similarly, the rash of lymphocyte recovery involves the reappearance of lymphocytes to the peripheral blood and tissues after a period of immunosuppression. ELR occurs earlier than GvHD and does not develop diarrhea or liver abnormalities. Clinical information is essential to distinguish between these two entities.

Infectious complications or manifestations of the underlying cause of bone-marrow aplasia must be ruled out through examination and laboratory investigations. Certain viruses have been known to cause a transient eruption, such as the maculopapular rash that can develop 14 days after exposure to measles. This rash is related to the recovery from the immunosuppression caused by the measles virus. Exacerbation of pre-existing dermatologic conditions can result in a similar presentation. Hossein et al. reported an inflammatory effect on actinic keratosis with the use of systemic fluorouracil. The inflammation occurred one to two weeks after each chemotherapy cycle, producing a mildly pruritic rash on the midface and dorsal aspect of both forearms. Information involving the form of chemotherapy, the type of malignancy, white-blood-cell count, preparation regimen, and timing of rash relative to chemotherapy or bone-marrow transplant are significant facts to obtain when attempting to differentiate ELR from other causes of similar eruptions. ELR most often resolves spontaneously, and generally no treatment is required.

The lesions of the patient described in this case study were primarily in sun-exposed areas including the face, neck, chest, upper back, and forearms. The morphology of the lesions was not the distinctive scaling, erythematous papules of actinic keratoses, making ELR a more likely diagnosis. In addition, the timing of lesion onset with lymphocyte recovery, the rapid resolution with chemotherapy-induced cytopenia, and the lack of prior history of similar eruptions all were consistent with ELR. Though treatment is often not required, in this case brief courses of moderate doses of oral prednisone were used successfully to attenuate the patient’s symptoms prior to subsequent chemotherapy cycles, as they were a source of great distress to this patient.

**Conclusion:**

The presenting lesions and laboratory evidence support the diagnosis of ELR in this case. This transient, self-healing erythematous eruption occurs after chemotherapy cessation in concert with the return of lymphocytes to the peripheral circulation in predisposed individuals. The patient presented differs from the classic presentation of ELR in that the eruption occurred in sun-exposed areas, mimicking actinic keratoses. In addition, our experience in this case suggests that certain patients may benefit from anticipatory treatment with steroids in coordination with oncology.

**References:**

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Teratogenic effects: 1) Doxycycline, like other tetracycline-class antibiotics, can cause fetal harm when administered to a pregnant woman. If any tetracycline is used during pregnancy or if the mother is on a tetracycline during labor, neonatal candidiasis has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction has not been shown to occur when the drug was discontinued. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy (see PRECAUTIONS: Pregnancy section).

Gastrointestinal effects: pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is the primary cause of antibiotic-associated colitis. If diarrhea occurs, ATTENTION is directed to the fact that this drug may obscure the diagnosis of a potentially fatal colitis.

Microbiology

The plasma concentrations of doxycycline achieved with ORACEA during administration (see DOSAGE AND ADMINISTRATION) are less than the concentration required to treat bacterial diseases. In in vitro biological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.

Cardiovascular: Mutagenesis, Impairment of Fertility: Doxycycline was assessed for potential to induce carcinogenicity in a study in which the compound was administered to Sprague-Dawley rats by gavage at dosages of 20, 75, and 250 mg/kg/day for two years. An increased incidence of uterine polyps was observed in treated females that received 250 mg/kg/day. In terms of reproductive toxicity, no influence on pregnancy at the intravenous dose of 10 mg/kg/day could be observed in studies in animals with related compounds, i.e., oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Doxycycline demonstrated no potential to cause genetic toxicity in an in vitro mutation study with mammalian cells (CHL/GHNPW® forward mutation assay) or in an in vivo micronucleus assay conducted in CD-1 mice. However, data from an in vivo assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline is a weak clastogen.

Oral administration of doxycycline to male and female Sprague-Dawley rats adversely affected fertility and reproduction as evidenced by decreased body weight of the dams and litter, decreased corpora lutea on the day of mating, decreased sperm numbers in the epididymis, decreased embryo survival and reduced fetal weight. Administration of doxycycline to male and female Sprague-Dawley rats resulted in a decrease in body weight gain and increased the incidence of atypical seminiferous tubule hypoplasia. These effects were dose-related and could not be clearly related to any of the observations reported in the human studies. However, these effects were not evident at lower doses, and at the highest dose, it is possible that confounding factors were responsible for these observations.

In animals treated early in pregnancy (see PRECAUTIONS: Pregnancy section), ORACEA should be used with caution in patients with a history of or predisposition to candidiasis overgrowth.

Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in patients who were taking tetracycline-class antibiotics. Patients who are exposed to sunlight or UVA/B treatment while using ORACEA should avoid excessive exposure to sun or ultraviolet light. If patients need to be outdoors while using ORACEA, they should wear protective clothing and sunscreen with a high SPF, and use a hat to protect the face. The onset of photosensitivity reactions during tetracycline therapy is usually within 1 to 2 months of beginning treatment, but they can occur at any time. If a photosensitivity reaction occurs, ORACEA should be discontinued.

ADVERSE REACTIONS

In controlled clinical trials of ORACEA in adult patients with mild to moderate rosacea, 537 patients received ORACEA or placebo over a 16-week period. The most frequent adverse reactions occurring in these studies are listed in the table below.

<table>
<thead>
<tr>
<th>Incidence (%) of Selected Adverse Reactions in Clinical Trials of ORACEA (n=526) vs. Placebo (n=268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Pruritus/neuralgic Pain</td>
</tr>
<tr>
<td>Sinusitis</td>
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<tr>
<td>Nasal Congestion</td>
</tr>
<tr>
<td>Fungal Infection</td>
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<tr>
<td>Influenza</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
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<tr>
<td>Abdominal Distension</td>
</tr>
<tr>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Stomach Discomfort</td>
</tr>
</tbody>
</table>

Note: Percentages based on total number of study participants in each treatment group.

ADVERSE REACTIONS

Tetracyclines: The following adverse reactions have been observed in patients receiving tetracyclines at higher, antimicrobial doses:

- Gastrointestinal: diarrhea, anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with candidiasis) of the anogenital region. Hepatotoxicity has been reported rarely. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving the capsule forms of the drugs in the tetracycline class. Most of the patients experiencing esophagitis and/or esophageal ulceration took the medication immediately before lying down (see DOSAGE AND ADMINISTRATION section). Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (see WARNINGS section).

OVERDOSE

In case of overdose, discontinue medication, treat symptomatically, and institute supportive measures. There is no evidence that induced emesis or activated charcoal is of value after oral tetracycline ingestion. In case of suspected overdose, standard methods are appropriate for the patient's clinical condition. There is no specific antidote for tetracyclines. There are no data to suggest that dialysis is effective for depleting tetracyclines from the body. In the treatment of cephalic poisoning, the symptomatic and supportive therapy is the only one that should be considered.

HYPERSENSITIVITY REACTIONS

Anaphylaxis and angioneurotic edema, urticaria, angioedema, anaphylaxis, anaphylactoid purpura, serum sickness, and urticarial reactions have been reported rarely. Rare instances of thrombocytopenia and neutropenia have been reported in patients receiving parenteral tetracyclines. Rare instances of epistaxis, bronchospasm, bronchial asthma, and urticaria have been observed. Photosensitivity reactions have been reported rarely. These reactions are more frequent in children, especially those who are taking concomitant derivations of resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, ORACEA should be used only as indicated.

STORAGE

Storage: All products are to be stored at controlled room temperatures of 15°C-30°C (59°F-86°F) and dispensed in tight, light-resistant containers (USP). Keep out of reach of children.

PATIENT INFORMATION: U.S. Patents 5,789,395; 5,919,775; 7,232,572; 7,211,267 and patents pending. ORACEA is a registered trademark of CollaGenex Pharmaceuticals, Inc., Newtown, PA, 18940

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Phone: 7961-01 BPI 06/07
Case Report

A 62 year old white female presented with a 3 month history of painful mouth sores on her buccal mucosa. She reported having recent dental work with crowns placed and the oral symptoms began about one month later. She initially experienced ulcerations on the lower gingiva in proximity to the dental crowns, which subsequently developed on the bilateral buccal mucosa and tongue. Since the lesions were very painful she was only able to tolerate ice cream. She denied having any vulvar symptoms, skin rashes or pruritis and she had no history of skin conditions. Medical history included asthma and hypothyroidism and no allergies to medications were reported.

A physical exam of the oral mucosa revealed multiple scattered erosions and hyperkeratotic papules with surrounding erythema on the bilateral buccal mucosa (Figure 1). The erosions were not directly associated with the dental crowns and there were no erosions on the gingivae. Upon examination of the skin there was only diffuse xerosis, without evidence of plaques or papules.

A punch biopsy obtained from buccal mucosa showed squamous mucosa with focal erosion and fibrin deposition. Within the submucosa, there was a lichenoid infiltrate of lymphocytes with some plasma cells. Neutrophils were present at the base of the erosion as well as within the adjacent squamous epithelium. A PAS stain was negative for fungal hyphae (Figure 2). These findings are consistent with erosive oral lichen planus.

Complete blood count, blood urea nitrogen, creatinine, AST, ALT were all within normal range. Her cholesterol and triglycerides were elevated, which were attributed to her diet of mostly ice cream. Due to the timing of gold-containing dental crown placement and the appearance of her oral lesions, a gold patch test was performed to rule out a contact allergy. It was found to be negative.

The patient was seen for a follow-up visit approximately three weeks later and reported some improvement with the treatment given. However, she had an emergency root canal about three days prior to the visit and complained that her mouth had become very sore again with the development of more erosive lesions on her buccal mucosa.

Various therapies were tried over several months with little improvement in the patient’s symptoms. These included prednisone, acitretin, isotretinoin, retin-A mixed with fluocinonide gel, a mixture of tetracycline, celestone, benadryl swish and spit, triamcinolone ointment, and steroid injections. The patient was also treated for oral candidiasis with diflucan and mycelex troches. The patient was recently started on a trial of methotrexate and will continue to be followed periodically.

Discussion

Oral lichen planus (OLP) is a relatively common, often asymptomatic chronic inflammatory condition of the oral mucosa. The three main types of OLP include reticular, erosive and atrophic. OLP shares a differential diagnosis with several conditions that are difficult to distinguish clinically and histologically. Diseases that resemble OLP are referred to as lichenoid reactions and include allergic contact reactions to dental materials, lichenoid drug reactions, graft vs. host disease, erythema multiforme and lupus erythematosus. Controversy surrounds the possibility that OLP is a premalignant lesion. Because OLP has no cure, treatment is mostly palliative, focusing on decreasing lesion size, alleviating symptoms and decreasing the risk of possible malignant transformation. We present a patient with oral lichen planus of the erosive type and a review of literature.
it is postulated that the immune response is triggered by numerous factors in individuals with a genetic susceptibility or predisposition. The immune response takes place when basal keratinocytes are recognized by the immune system as foreign due to changes in the antigenicity of the cell surface. An intense hypersensitivity-like T cell mediated response occurs at the interface between the epithelium and the connective tissue. The release of cytokines and other inflammatory mediators results in injury to the basal keratinocytes.

This autoimmune process manifests itself clinically as bilateral, symmetrical lesions of the oral cavity. They are most commonly located on the posterior buccal mucosa but may be found anywhere, including the gingivae, tongue, palate and lips. They begin as small papules that eventually migrate together and fuse into a larger area with patterns specific to a particular type of OLP. The three main clinical types described are reticular (the most common), erosive and atrophic. Patients may display more than one type of lesion at a time. Reticular OLP may demonstrate a variety of presentations and morphologies, however its identifying characteristic is keratotic formations. These formations display thin, white and lacy keratotic lines, which appear reticular or annular, referred to as Wickham’s stria. Reticular OLP has a plaque-like variant that can resemble and be misdiagnosed as leukoplakia. Erosive OLP is the second most frequent type of OLP. Erosive OLP presents as a combination of shallow ulcerations and erythema surrounded by radiating keratotic lines. The erosions are typically well demarcated and ulcers may be covered with a pseudomembrane. Lesions can migrate and evolve into a multifocal distribution. This is the most symptomatic type of OLP and the severity of symptoms can range greatly from one person to the next. Some patients suffer mild episodic pain, while others may experience symptoms so severe that daily activities such as mastication and oral hygiene are compromised. Atrophic OLP presents as large areas of erythema among keratotic or thin, fine white lines or striae. Atrophic OLP is found most commonly on the gingiva. This form of OLP can be extremely sensitive to environmental irritants such as ingestion of spicy food. Irritation may lead to avoidance of tooth brushing and an eventual decline in oral hygiene, adding a variable of periodontal disease to the existing problem. In contrast to the other forms of OLP, literature has documented that atrophic lesions are more likely to undergo spontaneous resolution, with some studies reporting resolution rates as high as 12%.

Although the different types of OLP have variations in histological presentation, several specific features have been identified as shared by the three types and fundamental in their diagnosis. The shared features include a hyperparakeratosis, often with acanthosis or a widening of the spinous cell layer, occasional areas of thin epithelium showing rete ridges with a short and pointed saw-tooth-like morphology and necrosis of the basal cell layer defined as liquefaction degeneration with apoptosis of the keratinocytes. Also, there is a broad infiltration of T lymphocytes at the junction of the epithelium and connective tissue. These inflammatory T-lymphocytes may extend beyond the basement membrane. The microscopically visible thickened areas of rete ridges results in the clinical appearance of Wickham’s striae in reticular OLP. Despite the established shared features, the different types of OLP also exhibit unique histological characteristics. The epithelium in erosive OLP is thin and ulcerated with a total loss of the rete ridges. There is a thick infiltration of T-cells that extends into middle and upper levels of epithelium. Basement membrane liquefaction and basal cell destruction is present throughout most affected areas and the epithelium may be completely obliterated revealing connective tissue.

OLP is difficult to diagnose due to its clinical and microscopic similarity to other diseases and its asymptomatic nature. A large spectrum of diseases resemble lichen planus both histologically and on physical exam and they are referred to as lichenoid reactions. In order to categorize a lesion as lichenoid it must meet specific histological criteria, including basal keratinocyte injury or apoptosis, an inflammatory cell response in the connective tissue, and keratosis or hyperkeratosis. Conditions that present with oral lichenoid lesions according to these criteria include OLP, contact allergies to dental restoration materials, drug reactions, graft versus host disease, erythema multiforme and lupus erythematosus. An oral lichenoid lesion can be the result of a contact allergy to dental restorative materials in amalgam fillings. Allergic type IV delayed hypersensitivity reactions to products from dental amalgam cause tissue injury. This injury is manifested locally as oral contact mucositis. Oral contact mucositis has been reported in response to mercury, nickel and chromium in dental material. Overwhelming data in the literature states that it is both clinically and histologically difficult to distinguish a lesion caused by contact hypersensitivity from OLP. Thornhill published a study confirming the difficulty in distinguishing OLP from lichenoid lesions caused by hypersensitivity to amalgam fillings based on histological examination alone. The study reported that based on microscopic evaluation, pathologists were only able to make a correct distinction between OLP and dental lichenoid reactions 33% of the time. In addition, the pathologists emphasized that they experience a fair degree of uncertainty in their ability to distinguish between the two. Although the differentiation is difficult, pathologists were able to agree on four features that are present in amalgam related contact lesions and absent in OLP. These features include an infiltration of inflammatory cells located deep in relation to a superficial infiltrate, perivascular infiltrates, and plasma cells and neutrophils in the connective tissue. Just as histological differences exist, certain clinical findings and elements of the patient history may provide clues to differentiate OLP from a contact reaction. Oral lichenoid contact reactions to dental amalgam occur on mucosal surfaces in direct contact with the dental material. Clinically lesions usually display erosions or fissures among thick white lines or plaques but the thin white striae characteristic of OLP are usually absent. Contrary to OLP, these lichenoid contact lesions do not migrate. Lichenoid contact lesions resolve when the amalgam restoration is removed.

There is no straightforward clinical or histological characteristic that distinguishes an oral lichenoid drug reaction from oral lichen planus or the other lichenoid lesions. It has been demonstrated that drug related lichenoid reactions sometimes display unique microscopic characteristics. These include a deep and superficial perivascular infiltration of lymphocytes and eosinophils, plasma cells and neutrophils. A careful drug history in a patient with a lichenoid lesion is helpful in obtaining a diagnosis. The list of drugs that cause lichenoid reactions is extensive, however, drugs most likely to be implicated include antibiotics, antihypertensives, gold diuretics, antimalarials and nonsteroidal antiinflammatories. Clinically, an established temporal relationship between the onset and resolution of a lesion that correlates with drug use may serve as a diagnostic tool. A temporal relationship is not always obvious since drugs may cause lichenoid reactions even years after their introduction. The resolution of a lesion when a drug is discontinued can also aid in the diagnosis of a drug reaction.

Although many studies have shown OLP should be classified as a precancerous lesion, this still remains controversial. Scientific literature claims a wide range of frequency of malignancy. Some studies report a rate of malignant transformation of 0.04% to 1.74% while other research reports a transformation rate as high as 10%. Many theories exist for the discrepancy of reported frequency in the literature concerning malignant transformation. Discrepancies in inclusion and diagnostic criteria may contribute to the seemingly elevated level of malignant transformation. Patients entered into studies diagnosed strictly in a clinical manner may be misdiagnosed with OLP and may actually...
have premalignant dysplastic mucosa with lichenoid characteristics. The transformation of OLP into squamous cell carcinoma seems to be dependent upon the type of OLP. Little to no data has reported the development of squamous cell carcinoma from reticular LP. Malignant transformation occurs more frequently in atrophic, erosive and ulcerative forms of OLP. The predisposition of malignant transformation in specific types of OLP has created theories about the etiology of the transformation of OLP to squamous cell carcinoma. Possible explanations describe the damaged mucosa in these types of OLP makes the tissue more susceptible to the affects of carcinogens in the oral cavity. Immunomodulating therapies have been considered in the etiology of malignant transformation due to their ability to suppress the local immune system and possibly allow malignancy to progress. Candida albicans has also been implicated by many studies in the malignant potential of OLP. The immunomodulatory agents and corticosteroids frequently administered to patients with OLP may predispose them to candidal infection. These individuals have a higher rate of candida colonization and infection than the general population. Candida can form the carcinogen N-nitrosobenzylmethylamine, which has been related to malignant transformation in leukoplakia. Even researchers who conclude that they do not consider OLP to be a premalignant condition acknowledge there is a small increase in the risk of oral squamous cell carcinoma in individuals who have OLP, when compared to individuals without OLP:

Oral lichen planus is an idiopathic chronic inflammatory condition for which there is no cure. Treatment is mostly palliative, aiming to decrease lesion size, eliminate atrophic and ulcerative lesions, alleviate symptoms and decrease the risk of malignant transformation. First line treatment of localized lesions includes the use of topical steroids and intralesional injections, while systemic corticosteroids are often used for severe flares of widespread lesions. Studies have shown corticosteroids provided complete remission in some patients. However, corticosteroids are known to induce various side effects including atrophy, fragility, and higher infection rates.

Other treatments include topical immunosuppressants, topical or systemic retinoids, thalidomide, methotrexate and PUVA. Topical tacrolimus treatment is safe and effective treatment for both erosive and reticulated forms of oral lichen planus. Byrd reported symptomatic response in 89% and lesion clearance in 84% of participants. Lesions responded to treatment within 6 months (mean 1 month). All participants with both oral and genital lesions had symptomatic improvement. Pimecrolimus 0.1% cream can be used for erosive lichen planus with few side effects. According to Passeron, all but one patient treated with pimecrolimus had at least a moderate improvement in their condition. However, one study showed the benefits were not long-lasting, as those who improved subsequently relapsed when assessed 1 month after treatment. Methotrexate has been shown to provide excellent control of OLP in patients with the most refractory and aggressive disease. Trehan reports improvement of symptomatic lesions, especially erosive lesions, with low-dose 308-nm excimer laser radiation. Remission times for patients who demonstrated a significant response to treatment ranged from 2-17 months.

Patients with oral lichen planus, found to have an allergy to mercury compounds, may have significant improvement with partial or complete replacement of amalgam dental fillings. Whether patients without mercury allergies should have fillings replaced remains controversial. Some authors suggest the removal of amalgam fillings should only be performed in patients with known sensitivities.

Due to the risk of malignant transformation to squamous cell carcinoma, patients with oral lichen planus should have periodic follow-up. Promoting good oral hygiene in patients with OLP is also very important.

In summary, we reported a case of oral erosive lichen planus. OLP may be difficult to distinguish from other lichenoid reactions that may resemble it both clinically and microscopically. Although the criteria used to diagnose OLP are still debated, a biopsy is often helpful. Treatment is mostly palliative, focused on decreasing the length of episodes and severity of symptoms. In addition, since OLP may represent a premalignant lesion, patients should be followed regularly.

References
Introduction

Giant-cell tumor of the tendon sheath is a relatively rare, benign tumor that occurs most often on the hands. This is a case presentation of a 14-year-old female who developed a progressively enlarging, solitary, non-tender nodule on the extensor surface of her right thumb. Additionally, a review of the literature and discussion of the common causes, cutaneous and histologic findings, differential diagnoses, diagnostic techniques, and various treatment options for this disease will be presented.

Case Report

An otherwise healthy 14-year-old Caucasian female presented to the dermatology clinic with her mother for evaluation of a growth on her right thumb. The patient recalled that the growth was first noticed approximately three months prior to presentation as a large bump on her thumb, and it had grown slightly in size since that time. Neither she nor her family could recall any history of similar problems and denied any known trauma to the area or occupation that involved repetitive motion. Furthermore, the patient denied any pain, tenderness, difficulty with joint mobility or range-of-motion limitations. Upon further questioning of the patient, she denied painful joints, fever, or any other systemic symptoms. Although the patient appeared relatively asymptomatic, her mother was concerned about the appearance of the lesion and the possibility of malignancy or infection.

On physical examination, the patient was found to have an approximately 1.0 cm x 0.9 cm solitary, well-circumscribed nodule on the extensor aspect of the first digit of the right hand, just distal to the interphalangeal joint. The nodule was non-tender, firm, non-fluctuant, fixed, and did not appear to migrate with digit flexion or extension. No cutaneous erythema or edema was appreciated, and the overlying skin of the nodule was freely mobile (Figures 1 and 2).

Two separate 2mm punch biopsies were performed on the lesion for diagnostic purposes. The histological findings of the biopsies were characterized as a proliferation of mononuclear epithelioid cells with scattered xanthomatized cells, rare multinucleated giant cells, and a small amount of focal hemosiderin. The lesion was positive for the immunohistochemical markers CD68 and factor XIIIa, but negative for cytokeratins 5/6 and AE1/AE3 as well as melanocytic markers S-100 and Melan-A. These findings confirmed the diagnosis of giant-cell tumor of the tendon sheath. After evaluation and consideration of the parent’s concerns, the patient was referred to a hand surgeon for surgical excision of the lesion.

Comment

Giant-cell tumor of the tendon sheath, also known as localized nodular tenosynovitis, is a relatively rare, benign growth, but is the most common primary tumor of the hand. In spite of this, it appears to be rarely mentioned in dermatological literature. It was first described in 1852 by Chassaignac, who referred to these lesions as cancers of the tendon sheath; but malignant potential in these lesions has since been disproven. There is growing consensus that these tumors actually represent a localized form of pigmented villonodular synovitis.

Giant-cell tumors of the tendon sheath are typically painless, asymptomatic masses. They occur most commonly on the hand (80% of cases), with the next most common predilection being for the foot-ankle complex. Most cases arise along the volar aspect of the long fingers, typically adjacent to the DIP joint. There is a 3:2 female-to-male sex predominance, with the lesions arising most commonly in the third to fifth decades of life, and more rarely in children.

The true etiology of giant-cell tumors of the tendon sheath is unknown. Although controversy exists as to whether these tumors are neoplastic or localized reactive responses, the most commonly accepted theory is that they arise as a reactive or regenerative hyperplasia secondary to an inflammatory process. An association with rheumatoid arthritis or antecedent trauma has been occasionally reported, but no evidence of this causal or pathogenic relationship has been proven.

Histologically, giant cell tumors of the tendon sheath have a lobular outline and are typically attached to the tendon sheath. They display a polymorphic population composed of mononuclear histiocytes with abundant pale foamy or vacuolated cytoplasm and hemosiderin deposits, and characteristic multinucleated giant cells scattered throughout the tumor in variable densities.

For accurate diagnosis, incisional biopsy with intraoperative frozen section and histological analysis is the gold-standard. Plain radiographs and MRI evaluations can be conducted preoperatively to evaluate clinically confusing lesions, and are recommended for soft-tissue tumors in children when giant-cell tumor of the tendon sheath is being considered. Plain radiographs display a benign-appearing, circumscribed soft-tissue swelling in approximately 50% of cases. Cortical erosion of the bone adjacent to the mass is found in 10%-20% of cases and can be differentiated from osseous lesions by MRI. True bone invasion is not typical and suggests an aggressive neoplasm. On MRI evaluation, giant-cell tumor of the tendon sheath presents as a solid mass with areas of hypointense signal on both T1- and T2-weighted images, with mild to moderate enhancement on gadolinium administration. Common differential diagnosis includes foreign-body granuloma, tenosynovial xanthoma, necrobiosis granuloma, ganglion cyst, rheumatoid nodule, lipoma, and epernoid cyst, among others.
Surgical excision is the treatment of choice for giant-cell tumors of the tendon sheath. Recurrence rates of 10%-44% are reported, and risk factors for recurrence include incomplete excision, the presence of adjacent degenerative joint disease, and radiographic evidence of osseous erosion. Therefore, meticulous surgical excision with adequate exposure and use of surgical magnifying loupes is recommended.

In conclusion, giant-cell tumor of the tendon sheath is a relatively rare entity and one not commonly encountered in the dermatological setting. It has a predilection for the hand and is the most common primary tumor of the hand. In spite of its benign nature, surgical excision is usually recommended to prevent progression as well as bony deterioration. Treatment is often curative, but local recurrence is common.

References:

Case Report

A 30-year-old Caucasian male presented with a 15-year history of mild hidradenitis suppurativa and acne conglobata, in addition to multiple painful, draining abscesses affecting his face, neck, back, axillae, buttocks, and feet. These abscesses tended to be recurrent and recalcitrant to many therapeutic regimens, and had required multiple incision and drainages to relieve his symptoms. Prior therapies have included prednisone, cephalixin, azithromycin, levofloxacin, clindamycin, amoxicillin/clavulanate, dapson, minocycline, tetracycline, trimethoprim-sulfamethoxazole, clindamycin lotion, benzoyl peroxide wash, sodium sulfacetamide wash, tretinoin cream, intralesional triamcinolone acetonide, finasteride, and isotretinoin. Patient denied any childhood history of atopy, recurrent lung infections, or musculoskeletal/dental difficulties, although he reported his father had similar abscesses at “an early age.” On physical examination, multiple cicatrices, open/closed comedones, and draining sinus tracts of his face, neck, chest and back were observed, with predominant scarring of his axillae bilaterally (Figures 1, 2).

Laboratory evaluation included a complete blood cell count, complete metabolic panel, quantitative immunoglobulin levels, nitroblue tetrazolium assay (NBT), and several wound cultures. Studies revealed slightly decreased hemoglobin at 12.8 g/dL (13.2-17.1), hematocrit 38.0% (38.5-50.0), and IgM 17 mg/dL (948-271), as well as elevated IgG at 2,363 mg/dL (694-1,618) and IgE 301 kU/L (13.2-17.1), hematocrit 38.0% (38.5-50.0), slightly decreased hemoglobin at 12.8 g/dL (13.2-17.1), hematocrit 38.0% (38.5-50.0), and several wound cultures. Studies revealed slightly decreased hemoglobin at 12.8 g/dL (13.2-17.1), hematocrit 38.0% (38.5-50.0), and IgM 17 mg/dL (948-271), as well as elevated IgG at 2,363 mg/dL (694-1,618) and IgE 301 kU/L (13.2-17.1). Results of the NBT assay were negative. Wound cultures taken from the patient’s chest and left dorsal foot grew coagulase-negative staphylococci and beta-hemolytic streptococci, respectively. In addition, a 4-mm punch biopsy taken from the left dorsal foot demonstrated suppuration, necrosis, and granulation tissue consistent with an abscess.

Discussion

Given the increasing prevalence of community-acquired methicillin-resistant Staphylococcus aureus (MRSA) and subclinical colonization, patients presenting with recurrent abscesses may reflect inadequate treatment or failure to eradicate their carriage status. On the other hand, when patients present with refractory abscesses despite appropriate antibiotics, and have a history of non-specific dermatitides and systemic abnormalities, careful consideration should be given to a primary immunodeficiency. A search of the Online Mendelian Inheritance in Man yielded several of these primary immunodeficiencies; however, as it is beyond the scope of this paper to review this exhaustive list, hyperimmunoglobulin E syndrome seems to be the most prevalent and well-represented in the literature.

According to the Book of Job, “So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown.” Davis, Schaller and Wedgewood paid homage to this biblical reference when they first described two young girls with red hair, chronic dermatitis, and recurrent staphylococcal abscesses and pneumonias in 1966.2 Although several eponyms have been given to this condition, including both Job’s and Buckley syndrome, they currently fall under the heading of hyperimmunoglobulin E Syndrome (HIES).

HIES represents a rare, multisystem disease with only 250 cases reported in the literature.3 Both AD and AR variants have been reported, each with its own unique, albeit variable phenotypic expressivity. Chromosome 4q has been suggested to be the defective locus in patients with HIES. The underlying pathophysiology of HIES involves abnormal neutrophil chemotaxis and altered immunoglobulin profiles. Analyses of cytokine profiles have shown that patients with HIES have functional and quantitative deficiencies in interferon (IFN) gamma, which is a major activator of neutrophils. Moreover, studies have elucidated an upstream signaling error in interleukin (IL) 12 production, whose function includes increasing IFN gamma production and suppressing IgE production.

HIES represents a constellation of clinical findings, both dermatologic and extracutaneous. Perhaps the most common is recurrent “cold” abscesses, typically associated with Staphylococcus aureus. The pathogenic lack of calor signifies the underlying abrogated neutrophil response. Moreover, patients may demonstrate chronic candidiasis of the oral mucosa and nails, as well as atopic-like dermatitides affecting the retroauricular and intertriginous spaces. Patients with HIES also have an increased morbidity secondary to recurrent pneumonia, usually due to S. aureus and Haemophilus influenzae, although rare cases of Pseudomonas aeruginosa and Aspergillus fumigatus have also been reported.4 Certain structural anomalies have also been characterized as being suggestive for HIES. Grimbacher et al. studied 30 patients with HIES and found that many shared similar facial features, including facial asymmetry, prominent forehead, deep-set eyes, broadened nasal ridge, increased canthal distance, and generalized “coarse” facies. In conjunc-
tion with characteristic facies, delayed primary tooth shedding is an additional feature seen in HIES. Furthermore, other skeletal anomalies, including osteopenia, scoliosis, joint hypermobility and history of frequent fractures have been described. It has been postulated that patients with HIES have mononuclear cells that produce increased levels of prostaglandin E2, which in animal studies has been shown to mitigate demineralization and cortical bone loss.6,7

Although there is no consensus on the diagnostic criteria for HIES, many rely on the laboratory evaluation for confirmation. As the name implies, patients with HIES have elevated IgE levels usually exceeding 2,000 IU, which is 10 times normal level. Also, 93% of affected individuals have evidence of peripheral eosinophilia up to two standard deviations from the mean. An important caveat is that disease activity is not proportionate to the extent of laboratory findings, and children younger than 6 months of age may have little or no elevation of their IgE levels despite clinical disease. Management of HIES often requires judicious use of antibiotics with antimRSA properties. Prophylactic antifungal therapy has also been suggested. Several clinicians advocate the use of cyclosporine, as it has been shown to decrease IgE levels and modulate neutrophil chemotactic activity.6,7 Anecdotal reports describe the successful use of ascorbic acid, cinetidine, intravenous immunoglobulin G (IVIG) and recombinant IFN gamma, all of which have been postulated that patients with HIES have mononuclear cells that produce increased levels of prostaglandin E2, which in animal studies has been shown to mitigate demineralization and cortical bone loss.6,7

Considering the severity of our patient's clinical findings, as well as his lack of therapeutic response, we suspected our patient may have an underlying immunodeficiency, specifically HIES. However, after an extensive workup, his clinical findings and laboratory evaluation failed to support this diagnosis. Given his history of acne conglobata and hidradenitis suppurativa, we speculated that a "follicular occlusion" diathesis could be blamed for this patient's severe clinical phenotype. Nonetheless, clinicians must be cognizant of hereditary immunodeficiencies when evaluating patients with unusual or recalcitrant infectious processes.

References
IDIOPATHIC THROMBOCYTOPENIC PURPURA: A CASE REPORT AND DISCUSSION

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ABSTRACT

Idiopathic thrombocytopenic purpura (ITP) is a common cause of thrombocytopenia and should be considered in the differential diagnosis of those patients with petechiae, purpura or clinically significant bleeding. Laboratory studies show only an isolated thrombocytopenia in most cases, and an extensive workup is usually not warranted. Treatments are numerous and not always satisfactory, and multiple modalities are often indicated for the treatment of ITP. We present a case of ITP and discuss its pathogenesis, clinical presentation, diagnostic tests and treatment options.

Case Presentation

A 43-year-old female presented to the outpatient dermatology clinic with a two-month history of asymptomatic, easy bruising that progressively involved her entire body surface area, including the oral mucosa. Her past medical and dermatologic history was unremarkable. There was no personal or family history of bleeding disorders. A review of systems was negative for weight loss, fatigue, fever, menorrhagia, hematemesis, epistaxis, and hematochezia.

Physical exam revealed a well-appearing female in no acute distress. Skin exam demonstrated diffuse, non-blanchable petechiae and purpura of the face, oral mucosa, trunk, and upper and lower extremities (Figure 1, 2). Workup was unremarkable except for a thrombocytopenia of approximately 1000/μL. Given the physical exam, clinical history and isolated thrombocytopenia, the patient was diagnosed with idiopathic thrombocytopenic purpura. She proceeded to a full recovery and avoided splenectomy.

Discussion

Idiopathic thrombocytopenic purpura (ITP) is a common condition affecting both children and adults. Prevalence is estimated at one to 13 cases per 100,000 persons,1 with most cases presenting in the third to fourth decades of life. Children often have an acute but benign, self-limited course requiring minimal intervention. However, adults with ITP tend to have persistent disease with frequent relapses and usually require some form of treatment.

ITP is a diagnosis of exclusion and is defined by an isolated thrombocytopenia. A normal complete blood count and peripheral smear are mandatory. Other conditions such as HIV, SLE, lymphoproliferative disorders, agammaglobulinemia, alloimmune thrombocytopenia, and congenital or hereditary thrombocytopenia may cause thrombocytopenia and must be excluded.1 Certain medications may also have a propensity to cause thrombocytopenia, and a detailed medication timeline is essential. Drug-induced thrombocytopenia can be caused by quinine, heparin, abciximab, eptifibatide, tirofiban, or vancomycin.2 The underlying pathophysiology of ITP is not fully understood, but it most likely involves premature destruction of autoantibody-covered platelets by the reticuloendothelial system.

Idiopathic thrombocytopenic purpura presents with a wide range of clinical manifestations, from isolated cutaneous petechiae or purpura to life-threatening hemorrhage. Morbidity and mortality are increased with both recalcitrant and recurrent ITP.3 Intracranial hemorrhage remains the leading cause of death from ITP, with advanced age being an important risk factor for serious complications. Interestingly, thrombocytopenia in females is most often seen with pregnancy and is rarely related to ITP. Infants born to ITP-affected mothers may be at an increased risk of thrombocytopenia and bleeding diatheses compared to infants born to mothers with gestational thrombocytopenia.4

A detailed history and physical examination are important in the diagnostic workup of idiopathic thrombocytopenic purpura. Extensive laboratory workup is still controversial, but a complete blood count with peripheral smear is mandatory to rule out other causes of thrombocytopenia. HIV, thyroid disorders, and systemic lupus erythematosus, to name a few, are often complicated by thrombocytopenia, and in the appropriate clinical setting they should be considered in the workup. Bone-marrow biopsy, imaging studies and tests for immunoglobulins, platelet antibodies and lupus anticoagulant are other considerations, but are usually not indicated for a routine ITP workup.5 Myelodysplasia is one important cause of thrombocytopenia in the elderly and must be excluded by bone-marrow biopsy in those older than sixty. Bone-marrow biopsy is also indicated in those individuals who are candidates for splenectomy.

Treatment protocols are not always satisfactory for patients with ITP. Splenectomy, intravenous anti-RhD, intravenous immunoglobulin and glucocorticoids and are a few of the well known, albeit not perfect, treatments. Oral prednisone remains the mainstay of initial treatment for those requiring intervention.6 Duration, dosage and length of taper are not well defined in the literature and therefore must be individualized. Patients are considered
non-responsive if there is no improvement within three weeks. Intravenous immunoglobulin is often second-line therapy and generally reserved for those patients with contraindications to corticosteroids or who have failed initial treatment. Anti-RhD immunoglobulin is only effective in RhD-positive, non-splenectomized patients and can be considered in children with acute ITP.4

Responses to treatment with splenectomy are good, but this is considered second-line therapy by most experts. Platelet counts often improve in just a few days after the procedure, and in some patients no further treatment is required. An accessory spleen is seen in approximately 11% of refractory, post-splenectomy cases, and further workup is required if thrombocytopenia persists.4 Sepsis is a possible life-threatening complication after splenectomy, and appropriate vaccines should be administered.

Conclusion

Generally, ITP is acute and self-limiting, and no treatment is required. Treatment is usually reserved for those patients with clinically significant bleeding, patients with the potential for life-threatening hemorrhage or for those requiring a procedure. Hospitalization may be necessary in symptomatic patients or those experiencing bleeding complications.

ITP is a common cause of thrombocytopenia and should be considered in the differential diagnosis of those patients with petechiae, purpura or clinically significant bleeding. Laboratory studies only show an isolated thrombocytopenia in most cases, and an extensive workup is usually not warranted. Treatments are numerous and not always satisfactory, and multiple modalities are often indicated for the treatment of ITP.

References

Report of a Case:

A 60-year-old Caucasian male presented to our office for a follow-up visit to discuss the results of abscess cultures from the left jaw line and left upper thigh. The patient arrived for the appointment stating that a week earlier, he’d gone to the urgent care center concerned about acutely tender abscesses that had developed on his left jaw line and left upper thigh. The pus-filled abscesses had been lanced, cleaned, and packed to prevent re-infection of the wound area. Cultures of the areas had then been sent to a reference lab for identification and sensitivity. The physician at the urgent care center had prescribed cephalixin.

The cultures of the abscesses revealed the presence of colonies of Methicillin-resistant Staphylococcus aureus (MRSA). The sensitivity demonstrated ≤0.5/9.5 sensitivity to Trimethoprim-sulfamethoxazole. The patient was instructed to return at a later date to determine the efficiency of the antibiotics and to monitor the healing process. An infection with MRSA is a very serious matter, and prompt treatment saved him potentially harsh physical discomfort and disfigurement.

Diagnosis:

Methicillin-resistant Staphylococcus aureus

Discussion:

Gram-positive bacteria are bacteria that stain purple under the microscope due to their thick outer cell walls, which is made of peptidoglycan. The thick peptidoglycan cell wall is constructed by the enzyme transpeptidase (penicillin-binding protein). Transpeptidase enzyme cross-links the peptidoglycan chains, forming the bacterial cell wall. This is the last step in the cell-wall synthesis. Staphylococcus aureus has this thick cell wall and thus is classified as gram positive. It has a round shape, forming cocci that grow in grape-like clusters. This is due to the bacterial cell dividing in more than one plane. S. aureus is the most virulent of all 33 staphylococcal species. It causes both toxin-mediated and non-toxin mediated disease.

S. aureus was first discovered in pus from surgical abscesses by the surgeon Sir Alexander Ogston in Aberdeen, Scotland, in 1880. Staphylococcus aureus literally translates to “Golden Cluster Seed.” When S. aureus is grown on blood agar, it takes on a yellow-gold appearance. It is catalase positive (the enzyme catalase causes H2O2 to break down into oxygen and water). S. aureus is also coagulase positive (coagulase converts fibrinogen to fibrin, forming a clot). These two enzymes, catalase and coagulase, are both used to identify the bacteria.

Antibiotics such as penicillin, which are used to kill gram-positive bacteria, bind to the enzyme transpeptidase to prevent the bacteria from synthesizing their cell walls. S. aureus produces an enzyme called penicillinase (a beta-lactamase), which is secreted from the bacterium. It also hydrolyzes the beta-lactam ring on the penicillin, thus inactivating penicillin.

Methicillin is used to treat bacteria that produce penicillinase. This drug is penicillinase-resistant. There are an increasing number of strains of S. aureus that are resistant to methicillin. These methicillin-resistant staphylococci (MRSA) synthesize an additional penicillin-binding protein that has a much lower affinity for beta-lactam antibiotics than the normal penicillin-binding proteins. This enables cell-wall synthesis when its other penicillin-binding proteins are inhibited. MRSA strains of S. aureus usually develop around hospitals, where there is extensive use of broad-spectrum antibiotics.

MRSA is resistant to many antibiotics, and intravenous vancomycin is one of the few antibiotics useful in treatment. Since this patient came to our clinical office and not to a hospital, intravenous medications would not be practical. Trimethoprim-sulfamethoxazole (TMP-SMX) was found to be effective against this particular patient’s MRSA strain. TMP-SMX is a two-drug combination that results in the sequential blockade of folate synthesis. Since TMP-SMX can be taken orally, it was a more practical antibiotic to prescribe. The patient returned in two weeks, and his healing reflected that the antibiotic had worked effectively with his immune system.

Differential Diagnosis:

Fungal infection; bacterial infection other than MRSA

Resources:

CLINDAMYCIN & TRETINOIN
COME TOGETHER TO CREATE...

ZIANA®
(clindamycin phosphate 1.2% and tretinoin 0.025%) Gel

See reverse side for brief summary of Full Prescribing Information.
ZIANA™ (clindamycin phosphate 1.2% and tretinoin 0.025%) Gel
Rx only
For topical use only
INDICATIONS AND USAGE
ZIANA Gel is indicated for the topical treatment of acne vulgaris in patients 12 years and older.

CONTRAINDICATIONS
ZIANA Gel contains clindamycin and tretinoin, which are contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.

WARNINGS AND PRECAUTIONS
Colitis
Systemic absorption of clindamycin has been demonstrated following topical use of the product. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. When significant diarrhea occurs, ZIANA Gel should be discontinued.

Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up to several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.

Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis. The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool assay for C. difficile toxin may be helpful diagnostically.

Ultraviolet Light and Environmental Exposure
Exposure to sunlight, including sunlamps, should be avoided during the use of ZIANA Gel, and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have considerable sun exposure due to occupation and those with inherent sensitivity to the sun should exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are recommended. Weather extremes, such as wind or cold, also may be irritating to patients under treatment with ZIANA Gel.

ADVERSE REACTIONS
Clinical Studies Experience
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trial may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be related to drug use for approximating rates.

The safety data presented in Table 1 (below) reflects exposure to ZIANA Gel in 1,853 patients with acne vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions that were reported in ≥1% of patients treated with ZIANA Gel were compared to adverse reactions in patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the vehicle gel alone.

Table 1: Adverse Reactions Reported in at Least 1% of Patients Treated with ZIANA Gel: 12-Week Studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ZIANA Gel N=1,853</th>
<th>Clindamycin N=1,428</th>
<th>Tretinoin N=846</th>
<th>Vehicle N=423</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS WITH AT LEAST ONE AE</td>
<td>497 (27)</td>
<td>342 (24)</td>
<td>225 (27)</td>
<td>91 (22)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>65 (4)</td>
<td>64 (5)</td>
<td>16 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Pharyngodyngueal pain</td>
<td>29 (2)</td>
<td>18 (1)</td>
<td>5 (1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>23 (1)</td>
<td>7 (1)</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cough</td>
<td>19 (1)</td>
<td>21 (2)</td>
<td>9 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>19 (1)</td>
<td>19 (1)</td>
<td>15 (2)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Note: Formulations used in all treatment arms were the ZIANA vehicle gel.

Cutaneous safety and tolerability evaluations were conducted at each study visit in all of the clinical trials by assessment of erythema, scaling, itching, burning, and stinging.

Table 2: ZIANA Gel-Treated Patients with Local Skin Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Baseline N=1,853</th>
<th>End of Treatment N=1,614</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>636 (35)</td>
<td>416 (26)</td>
</tr>
<tr>
<td>Scaling</td>
<td>237 (13)</td>
<td>280 (17)</td>
</tr>
<tr>
<td>Itching</td>
<td>189 (10)</td>
<td>70 (4)</td>
</tr>
<tr>
<td>Burning</td>
<td>38 (2)</td>
<td>56 (4)</td>
</tr>
<tr>
<td>Stinging</td>
<td>33 (2)</td>
<td>27 (2)</td>
</tr>
</tbody>
</table>

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and 2, 1,277 subjects enrolled with moderate to severe acne, 854 subjects treated with ZIANA Gel and 423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were slightly higher for the ZIANA-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA Gel showed a similar adverse reaction profile as seen in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS
Concomitant Topical Medication
Concomitant topical medicinal, medicated or abrasive soaps and cleansers, soaps and cosmetics that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA Gel, there may be increased skin irritation.

Erythromycin
ZIANA Gel should not be used in combination with erythromycin-containing products due to its clindamycin component. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vivo antagonism is not known.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. Therefore, ZIANA Gel should be used with caution in patients receiving such agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA Gel. ZIANA Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA Gel for two weeks prior to artificial insemination and continuing until gestation day 19, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA Gel applied daily to a 60 kg person.

Clindamycin Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin
In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation were observed at doses in excess of 2 mg/kg/day (~ 78 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally with the administration of the drug would be expected by chance alone. Thirty cases of temporally associated congenital malformations have been reported during two decades of clinical use of another formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association have been established from these cases, 5 of the reports describe the rare birth defect category, holoprosencephaly (defects associated with incomplete midline development of the forebrain). The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on a body surface area comparison.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of ZIANA Gel. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIANA Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of ZIANA Gel in pediatric patients under the age of 12 have not been established.

Clinical trials of ZIANA Gel included patients 12–17 years of age.

Geriatric Use
Clinical studies of ZIANA Gel did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85258
Revised: 11/2006
300-13A
030507
Porphyria Cutanea Tarda: Case Presentation and Literature Review

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Case Presentation:

A 56-year-old Caucasian male presented with the chief complaint of an outbreak of blisters on both hands. Onset was approximately one week prior to this visit. The patient stated that the blisters on his hands developed after a weekend fishing trip and binge drinking of alcohol. Subsequently, he noted that exposure to sunlight caused an exacerbation of blistering followed by a gradual rupturing in stages. This resulted in scarring as well as a darkening of the skin in involved areas. Occasionally, he noticed while urinating that the color of his urine appeared dark brown. The only significant past history obtained from the patient was a previous diagnosis of hepatitis C approximately 40 years ago. He was scheduled for a liver biopsy five years ago, but due to financial difficulty and a lack of health insurance, it was never scheduled. Review of all systems was positive for fatigue only. The patient denied nausea, vomiting or loss of weight. Social history was positive for alcohol and drug abuse. There were no allergies to medications.

On physical examination, the patient appeared well nourished and well developed. The patient’s bilateral hands, dorsal aspects, revealed multiple bullae with erythematous bases. The erupted bullae formed small erosions with a significant amount of erythema in the periphery. There were large amounts of post inflammatory hyperpigmentation, and atrophy was noted within older healed lesions.

In order to establish a diagnosis of porphyria cutanea tarda, biopsies and laboratory analyses were performed. The diagnosis was confirmed with positive tissue pathologic findings and specific laboratory results. The uroporphyrins were elevated to 1190.8 μg/24h, the heptacarboxylporphyrin was elevated to 735.5 μg/24h, the hexacarboxylporphyrin was elevated to 11.3 μg/24h, the pentacarboxylporphyrin was elevated to 91.5 μg/24/h, and the coproporphyrins were elevated to 237 μg24/h. Thus the total porphyrins was elevated to 2266.8 μg/24h.

The patient was subsequently sent to a hepatologist and started on interferon-alfa 2b/ribavirin for treatment of his hepatitis C. Current consideration is to start the patient on chloroquine 125mg twice weekly or a low dosage of hydroxychloroquine if approved by his hepatologist. Until approval, phlebotomy will be the treatment. The patient abstained from alcohol and was placed on topical steroid cream and sunblock.

Comments:

A review of the literature establishes that PCT is the most common of all the porphyrias, though it only occurs in about 1 in 25,000 people. This sporadic condition appears to be more frequent than the inherited type. In the sporadic type, the enzyme deficiency is noted in the liver.7 Recently, hereditary hemochromatosis (HH) has been noted as an underlying condition for PCT.8 Many authors have published articles showing the high incidence of PCT associated with hepatitis C.9 What has been very interesting is the discovery of geographic preponderance. Of note is its prevalence increasing from northern Europe (8%-10%) to southern Europe (71%-91%).6,7 At this time, no studies have been performed in the United States to demonstrate any geographical relationship. There are several studies that establish a definite relationship between hepatitis C and PCT in North America. In these studies, the prevalence is reported as being as high as 94%.7 A similar relationship with the familial PCT has not been established at this point in time.9 In addition to the high association between PCT and hepatitis C, there are many articles in the literature that show an association with hemochromatosis, Wilson disease, diabetes mellitus, renal failure, HIV, Sjogren’s syndrome, rheumatoid arthritis and systemic lupus erythematosus.10 Alcohol, estrogens and some tuberculostatic drugs have also triggered PCT.11 The literature also reports that renal dialysis for renal insufficiency may create the same triggering mechanism.12 The pathophysiological mechanism that creates the skin lesions in PCT is somewhat dependant on the etiology, although most theories attribute the problem to accumulation of water-soluble porphyrins within the skin, which are light sensitive. The light is the triggering mechanism, causing the blister secondary to the release of proteolytic enzymes into the cell cytoplasm.13 As this complement activation takes place, the complement can be found at the dermal-epidermal junction on microscopic

ABSTRACT

It has been well established that porphyrnia cutanea tarda (PCT) is a porphyria that has both acquired and familial types. The acquired form of PCT is caused by a heterozygous inheritance of a gene mutation encoding partial deficiency of the activity of the enzyme uroporphyrinogen decarboxylase. This disorder presents most often in adults. The familial type of PCT is more common in children. This results in an excess of porphyrins within the lamina lucida of the epidermis. This manifestation causes cutaneous photosensitivity when exposed to sunlight, leading to fragility of the skin, thus inducing a bulla. A higher prevalence of PCT in patients with hepatitis C has been recently correlated in the literature. The case presented in this paper is an example of this relationship. This paper focuses on the acquired type of PCT.
evaluation. Analysis of the bullous lesions shows complement-degradation products.\textsuperscript{12} Scarlett et al. demonstrated immunoglobulins G and M around the dermal vessels. This was established using immunofluorescence, showing their presence at the dermal-epidermal junction.\textsuperscript{13} The most frequent sites for blistering are usually the dorsum of the hands and the upper extremities, because they are precipitated by a combination of sunlight and trauma.\textsuperscript{1}

The current approach to therapy is three-prong. The basic aspect is to avoid the triggering mechanism, whether that is light, alcohol or systemic drugs. Iron deple- tion and porphyrin elimination are the other two aspects of therapy. This can be achieved through phlebotomy, to reduce iron, and low-dose chloroquine therapy.\textsuperscript{10} Interferon-alfa 2b/ribavirin is the current therapy for treatment of hepatitis C. This has been shown to be most effective after phlebotomy.\textsuperscript{14}

**Case Presentation:**

A 71-year-old white male seen in our office for total cutaneous exam presented with a complaint of curious bilateral axillary "freckling," which had been present asymptotically for more than 10 years. The patient’s past medical history was significant for hyperlipidemia, hypertension, gastric reflux, arthritis and environmental allergies. Surgical history revealed in-situ squamous-cell and basal-cell carcinomas of the skin that had been treated successfully. Family history was negative for any chronic cutaneous and genetic diseases, neurofibromatosis or other genodermatoses. The remainder of the pertinent review of systems further excluded any ocular disorders.

Physical exam revealed purple-to-brown, reticulated atrophic patches with telangiectasias in both axillae without scale (Fig. 1). There was no cervical, submandibular, parotid, supraclavicular or axillary lymphadenopathy. As well, there were no papules, nodules, hyper- or hypopigmented macules or patches appreciated (Fig. 2).

The differential diagnosis at time of examination included poikiloderma vasculare atrophicans associated with mycoses fungoides, poikiloderma congenitale of Rothmund-Thompson, Bloom’s syndrome and dyskeratosis congenita, as well as dermatomyositis and, less commonly, systemic lupus erythematosus (SLE). A good history and clinical suspicion are essential in making the correct diagnosis. This report will briefly review these etiologies and comment on the treatment of mycoses fungoides.

**Discussion**

True axillary freckling is typically associated with NF-1. Our patient’s “curious freckling” was clinically consistent with PVA. A review of the literature revealed no other disorders directly associated with this entity (PubMed search words “axillary freckling”).

Poikiloderma vasculare atrophicans (PVA) is a non-specific finding that clinically, in its early stage, presents with erythema, slight superficial scaling, telangiectases and mottled pigmentation. In the later stage, the erythema resolves and the lesions present with the "classic triad" of epidermal atrophy, telangiectases and mottled pigmentation, as in our patient.

Oncology was consulted for further work-up, which initially included blood chemistries -- CBC, electrolytes, ANA, alkaline phosphatase, albumin, BUN, creatinine, total protein, calcium, glucose, chloride, LDH and serum for quantitative immunoglobulins. These studies were all within normal limits. Further studies included CT of the chest, abdomen and pelvis, PET scan and bone-marrow examination. These studies, as well, proved to be normal.
derma on the face, forearms and hands. Dyskeratosis congenita presents with widely distributed, net-like pigmentation suggestive of PVA.4

PVA can also be seen in dermatomyositis (poikilodermatomyositis) and systemic lupus erythematosus, but this is usually in the late phase of these diseases.

Finally, PVA can be clinically confused with the so-called "Crowe's" sign seen in neurofibromatosis 1; however, a good history and physical exam will rule out this entity.5

Treatment of mycoses fungoides can be classified in three groups. First, there are the skin-targeted therapies, including topical Class 1 high-potency corticosteroids; cytotoxic agents such as topical mechlorethamine (nitrogen mustard); topical retinoids such as bexarotene (Targretin®); phototherapy (PUVA); and radiotherapy (total-skin electron-beam irradiation, or TSEB).6-9 Next, there is systemic chemotherapy such as CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin® [vincristine] and prednisone).10 The final treatment class is biological response modifiers -- interferon alpha (IFN α)11 and oral retinoids such as the above-mentioned bexarotene (Targretin®).12

**Conclusion**

Axillary freckling is a clinical sign that may be confused with presentations of other dermatologic disorders, as in our case. Hopefully this review has expanded the reader’s differential diagnostic considerations and stressed the continued significance of careful history and physical examination.

**References:**
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Generalized essential telangiectasia (GET) is a rare, progressive, vascular condition. The cause of the widespread telangiectasias that is characteristic of this disease, without hereditary or systemic explanation, is unknown. We present a case of a 48-year-old female patient who demonstrated widespread telangiectasias spreading from her legs to her trunk, arms, face, and conjunctiva over the period of 10 years with consistently positive ANA laboratory findings. In addition, we discuss GET and review the sparse literature on the subject.

Case Presentation:

A 48-year-old female presented with a complaint of the progressive development of small, superficial blood vessels beginning on the medial thighs 10 years ago. They have since spread to the lower legs, trunk, arms, and face, including the conjunctiva. Over the same time span, laboratory tests consistently demonstrated an elevated ANA titer with a centromere pattern. She denied pain, pruritus, or bleeding of the lesions. She reported frequent pain in both elbows and the posterior aspect of the knees. She gave a history of Raynaud’s phenomenon primarily in the right index finger. Over the last year, intermittent dysphagia with a sensation of globus had developed that did not improve using a proton pump inhibitor. Also significant was a long history of smoking, one pack per day, and frequent alcohol consumption, one to two beers per day. The family history was negative for similar lesions and for connective tissue disease. Her mother had varicose veins.

On examination, there was a reticulated pattern of dark blue, violaceous, and red telangiectasias over the upper and lower extremities, abdomen, lower back, chin, nose, and conjunctiva of the eyes (Figures 1 and 2). These areas blanched with diascopy. There was no periungual erythema or telangiectasias. The hair, nails, and mucous membranes appeared unaffected.

Laboratory analysis showed a borderline positive ANA screen, with an ANA titer of 1:1280. The anti-centromere antibodies were 1:1280 and had a centromere pattern. All other labs were within normal ranges (Table 1).

A punch biopsy (right upper thigh), performed in an outside office, was described as having a slight superficial perivascular lymphoid infiltrate with vascular ectasia and hyalinization of vascular basement membranes (Figure 3). The pathology report also included a comment stating that while the biopsy lacked the interface alteration typical of mixed connective-tissue disease, the vaso-lopatic alterations described in the report have been described in patients with mixed connective-tissue disease.¹

The patient has seen two rheumatologists, who both dismissed the diagnosis of connective-tissue disease and dismissed the laboratory results as incidental findings. Without an identifiable cause of the telangiectasias, she was given the diagnosis of generalized essential telangiectasia, and therapy was initiated. A five-month course of tetracycline was attempted unsuccessfully. The patient was then started on a course of acyclovir 200mg taken five times daily. To date, none of the attempted therapies have yielded meaningful results. Laser therapies have been discussed but not yet attempted.

Discussion

Generalized essential telangiectasia (GET) is a slowly progressing and persistent condition in which primary telangiectasias first appear on the legs and then spread to the trunk, arms, and face.²³⁴ It is a diagnosis of exclusion, as there are no associated causes. Conjunctival telangiectases have been described, but they are rare.⁵⁶⁷ In the largest study of GET to date, the average onset was 38 years, and 72% of those affected were women.⁸ GET has been reported more commonly in whites, perhaps because of the marked contrast of the vessels on light-complexioned skin. This type of telangiectatic disorder is not generally associated with bleeding or systemic disease. A similar condition seen in families with an autosomal-dominant inheritance pattern has been termed hereditary benign telangiectasia.¹ A factor identifying GET from hereditary hemorrhagic telangiectasia (HHT) is the rarity of systemic involvement. HHT often causes recurrent epistaxis, liver enlargement and cirrhosis, and aneurysm enlargement and cirrhosis, and aneurysm

ABSTRACT

A WOMAN WITH GRADUALLY SPREADING TELANGIECTASIAS

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of blood vessels.\textsuperscript{10,11} The literature does not support a direct association between GET and connective-tissue diseases. There is, however, growing evidence of an underlying autoimmune process.\textsuperscript{15}

The histopathology typically shows thin-walled vascular channels found in the upper dermis with minimal mononuclear inflammatory infiltrate. These channels are produced by dilatation of postcapillary venules of the upper horizontal plexus.\textsuperscript{13} Telangiectatic vessels in GET reportedly lack alkaline phosphatase activity in the endothelium of both the terminal arterial and the arterial portion of the capillary loops.\textsuperscript{13} This may be a method of differentiating GET from the telangiectasia associated with systemic disease, in which the walls of normal terminal arterioles and capillary loops and the telangiectases associated with dermatomyositis are all alkaline-phosphatase positive.

In individual reports, tetracycline, ketoconazole, and the treatment of chronic sinus infection have led to resolution by involution of the vessels.\textsuperscript{14} Successful treatment with acyclovir has been reported in an autoimmune setting.\textsuperscript{15} Laser ablation using a high-energy, high-frequency, long-pulse Nd:YAG laser or a 585 nm flashlamp-pumped pulsed dye laser have both produced good results.\textsuperscript{16,17}

With regard to this patient’s serology, ANA titers have been shown to be elevated as a consequence of aging and without any signs of disease.\textsuperscript{19} In fact, up to 15% of otherwise healthy individuals over the age of 55 can have a significantly elevated ANA titer of no clinical consequence.\textsuperscript{18} In addition, anti-centromere antibodies (ACA) do not always indicate the presence of connective-tissue disease and have been documented in such conditions as primary biliary cirrhosis, pulmonary hypertension, and primary Raynaud’s phenomenon.\textsuperscript{19} This patient had consistently elevated ANA and ACA. She also had arthralgias, intermittent dysphagia, Raynaud’s phenomenon, and a skin biopsy reported as connective-tissue disease. The significance of this patient’s elevated ANA and anti-centromere antibodies with regard to the generalized essential telangiectasia is yet to be determined.

**Conclusion**

The diagnosis of GET has a good prognosis, and those affected with the disorder have a normal lifespan; however, the lesions have a tremendous negative impact emotionally. Our patient is very self-conscious about her appearance to the point that it alters her normal daily activities. We plan to refer this patient for laser therapy, as reports have shown good results.

**Table 1**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA Screen</td>
<td>Borderline</td>
</tr>
<tr>
<td>ANA Titer</td>
<td>1:1280 (normal &lt;1:160)</td>
</tr>
<tr>
<td>ANA Pattern</td>
<td>Centromere</td>
</tr>
<tr>
<td>Centromere Ab</td>
<td>1:1280 (normal &lt;1:40)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-RNP Ab</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-Sm Ab</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-SSA</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-SSB</td>
<td>Normal</td>
</tr>
<tr>
<td>IgG</td>
<td>Normal</td>
</tr>
<tr>
<td>Rheumatoid Factor</td>
<td>Normal</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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10. Wells RS, Dowling GB. Hereditary benign telangiectasia.

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32 A WOMAN WITH GRADUALLY SPREADING TELANGIECTASIAS
GRISEOFULVIN-INDUCED PHOTOALLERGIC REACTION:  
A CASE REPORT IN A 10-YEAR-OLD HISPANIC MALE

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Introduction

Photosensitive reactions are unwanted adverse effects that are recognized following the administration of topical and systemic medications, and subsequent exposure to either artificial or natural UV rays. These drug-induced photodermatoses are commonly divided into photoallergic reactions and phototoxic reactions. Tissue damage is a direct result in phototoxic reactions, and most clinically resembles an exaggerated sunburn. Eruptions develop shortly after exposure to light, with intensity increasing in a dose-dependent manner. In photoallergic reactions, the damage is immunologically mediated. There can be an immediate (humoral-mediated) hypersensitivity, delayed (cell-mediated) hypersensitivity, or both, developing into a photoactivated compound that is transformed into an antigen during radiation. In contrast to phototoxic reactions, photoallergy is usually elicited by the longer UV A wavelengths, only occurs in sensitized persons, and are not dose dependent. Clinically, drug-induced photoallergic reactions can appear as solar urticaria or as eczematous dermatitis on predominantly light-exposed areas.  

Photosensitive reactions have been studied for a number of topical antibiotics, systemic antibiotics (especially sulfonamides, tetracyclines and quinolones), and antifungals such as griseofulvin. The precise mechanism of photosensitivity reactions caused by griseofulvin are not completely understood, but is commonly listed as a systemic photosensitizing drug. UVA radiation is known to be responsible for eliciting griseofulvin photoreactions. Griseofulvin has also been shown to exacerbate preexisting systemic lupus erythematosus and to induce subacute cutaneous lupus erythematosus in reported cases.  

Griseofulvin is fungistatic against Trichophyton, Microsporum and Epidermophyton. It is not active against Pityrosporum dimorphic fungi, Cryptococcus or the fungi that cause chromomycosis. The indications for systemic griseofulvin include tinea capitis, onychomycosis, and widespread superficial fungal infections. Dosages of griseofulvin are based on weight in the pediatric population and do require a long duration of therapy in most cases. Absorption of griseofulvin is significantly improved by dietary fat intake. The medication is considered very safe, with reported use for over 40 years. Its most common side effects include headache and gastrointestinal disturbances, but may also cause a fixed-drug eruption, photosensitivity, petechiae, pruritus, urticaria, and may exacerbate lupus or porphyria.  

Adverse reactions secondary to photosensitization induced by griseofulvin is well known and documented, but only a few cases have been reported with detailed information on clinical appearance, histological exam and outcomes. One such report details six Japanese patients on griseofulvin for variable lengths of time in treatment of tinea unguium. The following case report details the particulars of a 10-year-old Hispanic male growing up in south Florida with histological evidence of a photoallergic reaction secondary to griseofulvin. 

Determining the mechanism of a photosensitivity reaction can be important because the phototoxic and photoallergic types can be managed differently. Phototoxins can be manipulated and even tolerated by decreasing the dose of a medication or the amount of radiation exposure. In photoallergic reactions, however, altering these parameters does not significantly change the outcome. Drug-induced photoallergic reactions usually disappear spontaneously once the offending photosensitizer has been removed. Rarely, a persistent light reaction can occur, remain longer and relapse with minimal UV radiation.  

Case Report

A 10-year-old Hispanic male presented to the clinic along with his father for evaluation of a rash that developed two days prior to this visit. The patient’s father reported that his son was placed on griseofulvin solution based on his weight for a fungal infection on his scalp five days prior at an emergency room. Three days after initiating the medication, the patient developed an itchy rash on his face, neck, ears, forearms and legs. The father does report spending time outside with his son on a football field in bright sunlight without sunscreen the day before the rash began. There were no other reported issues, including no fevers, chills, sweats, abdominal pain, nausea, vomiting, or changes in urination. There were no known drug allergies or prior exposure to griseofulvin according to the father. Family history was noncontributory as well.

On physical examination, the 10-year-old male did not appear acutely ill and was afebrile. The patient’s scalp revealed three erthyematous, boggy nodules with matting of the scalp hair in these areas. Examination of his face and ears revealed erythematous, follicular lesions on the bilateral cheeks, nose, and pinnae. There was a similar eruption noted on the patient’s anterior and posterior neck, anterior chest, forearms and tibial regions of both legs. The abdomen, lower back, thighs, buttocks, palms and soles were spared. There was no periarticular or periocular erythema or edema noted. No targetoid lesions were observed. There was mild, palpable, slightly tender cervical adenopathy appreciated (Figures 1, 2).

After discussion with the patient’s father,
34 GRISEOFULVIN-INDUCED PHOTOALLERGIC REACTION: A CASE REPORT IN A 10-YEAR-OLD HISPANIC MALE

Figure 3

Figure 4

a 3mm punch biopsy was performed on the right posterior neck. The patient was instructed to stop the griseofulvin at that time and to continue with Claritin and Benadryl as needed for itching as prescribed by the pediatrician. Cutivate cream was prescribed for symptomatic relief, with directions to apply it twice daily to the trunk and extremities for no more than two weeks. Serology was ordered, including a CBC, IgE level, ASO titers, urinalysis and Epstein-Barr virus IgM and IgG antibodies.

The patient followed up in the office two days later with his parents, with mild improvement of symptoms. On examination, the scalp was clinically unchanged except for a new purulent discharge and some serosanguinous fluid noted in the area. Examination of the face, trunk and extremities revealed improvement of the follicular eruption, with drying and less erythema noted. No new lesions were identified. The biopsy revealed a spongiotic dermatitis with dermal eosinophils consistent with eczematoid drug eruption. Biopsy results were discussed with the patient’s parents in detail, and the patient was placed on Azithromycin suspension 200mg per 5cc based on weight.

Two weeks after initial presentation to the office, the patient returned with his father for other treatment considerations for scalp fungal infection. They reported tenderness of the scalp with hair loss, but no fevers, chills or sweats. The patient also reported that the rash on his face, ears, trunk and extremities had resolved significantly on sun-exposed areas of the body about 48 hours later. In a Japanese study by Kojima et al. of six reported cases of griseofulvin-induced photodermatitis, all showed acute to subacute dermatitis histologically. The authors also reported variable results in photocross-linking reactions to penicillin, positive photopatch tests in some patients, distant flare-up phenomena and persistent light reactions, suggesting that the pathogenesis is photoallergic in these patients. The term photoallergy for systemically administered drugs is confusing in the literature, however, and whether systemically administered drug photosensitization is caused by photoallergy has not been clearly proven.

This case study suggests that, based on histology, the mechanism of griseofulvin-induced photodermatitis is most likely photoallergic. However, due to the sample size of one and the lack of supporting evidence with photopatch testing and photocross reactions to penicillin, the exact mechanism remains unclear. Kojima et al. recommend checking for penicillin allergy before administering griseofulvin based on their data of a 33% overlap with a penicillin allergy. As with any known potential photosensitive medications, recommendations for diligent photoprotection must be conveyed to patients.

References:
Case Report

A 2-year-old African American female presented with her foster father to our office with a small growth in front of her left ear. She’d had it since birth. The foster father denied any associated symptoms such as erythema, tenderness, pruritus, infection, or drainage. It had not recently grown in size or changed in shape or color. Her past medical history was noncontributory, and her family history was mostly unknown as she was in the foster care system. Her birth mother was a known methamphetamine addict, and her foster father attributed the abnormal growth to be a birth defect related to drug use in utero.

The patient was otherwise healthy, was not currently taking any medications, and had no known drug allergies. She was to be placed in daycare soon, and her foster father feared she would get made fun of by other children and was here to discuss treatment options. On physical examination, the patient was a well-appearing 2-year-old who was in the appropriate growth percentile for her age. Upon inspection, her left ear was normal in appearance, except for the presence of a single, unilateral, raised, pedunculated nodule approximately 1.5 cm in length and 0.5 cm in width, which protruded from the preauricular area (Figure 1). It was soft, non-tender and skin-colored. There were no other craniofacial abnormalities, and the rest of the physical exam was unremarkable. The patient’s foster father was told the diagnosis and the treatment options, which included surgery. He was told to think about it and returned two weeks later to have the child’s growth surgically removed, which yielded excellent results.

Diagnosis:

Accessory Tragus

Discussion

The tragus is the part of the external ear projecting posteriorly over the external auditory meatus. An accessory tragus is one of the most common congenital defects of the external ear in the absence of any other abnormality. It is believed to arise from an embryological defect in the development of the first and second brachial arches as they move dorsally to form the auricle. These arches appear in the fourth and fifth weeks of development.

Each pharyngeal arch is covered on the outside by surface ectoderm and on the inside by endoderm. Neural crest cells migrate into the arches to comprise the skeletal components of the face. The mesoderm is important in the formation of blood vessels and in the formation of the musculature of the face and neck.

The first pharyngeal arch is made by the maxillary process and the mandibular process, which involves Meckel’s cartilage. This cartilage subsequently disappears except for portions that form the incus and malleus. The premaxilla, maxilla, zygomatic bone, and part of the temporal bone from the mesenchyme (a loose kind of connective tissue), all part of the maxillary process, undergo membranous ossification. The formation of the bones of the middle ear takes place here as well.

The second pharyngeal or hyoid arch (Reichert’s cartilage) gives rise to the stapes, the stylohyoid ligament and, ventrally, the lesser horn and upper part of the body of the hyoid bone. The facial nerve supplies the muscles of this arch. Those muscles are the stapedius, the stylohyoid, the posterior belly of the digastric, the auricular and the muscles of facial expression.

Early on in development, an accessory tragus may develop anywhere along the line of migration from the angle of the mouth to the anterior border of the sternocleidomastoid muscle. Five percent of patients with accessory tragi also have associated developmental abnormalities of the pharyngeal arch. Accessory tragus is a consistent feature seen in Goldenhar’s syndrome, also known as oculo-auricular-vertebral syndrome, and is less consistently seen in Townes-Brocks, Treacher-Collins, VACTERL, and Wolf-Hirschhorn syndromes.

Differential Diagnosis

Differential diagnosis includes fibroepithelial polyp, soft fibroma, chondroma and hamartoma.

Resources

Introduction

Psoriasis is a T-cell-mediated chronic inflammatory skin disorder affecting 2% of the population. Angiogenesis has been shown to be a necessary inflammatory response early in the pathogenesis of psoriasis. Vascular endothelial growth factor (VEGF) causes hyperpermeability of blood vessels as well as endothelial cell proliferation, and its production is increased in the epidermis of psoriatic lesions. The overproduction of VEGF plays an important role in the pathogenesis of psoriasis. Studies have shown the level of VEGF to be 50 times greater in psoriatic plaques when compared to normal stratum corneum. The plasma levels of VEGF in psoriatic patients have also been demonstrated to decrease with improvement of their psoriatic plaques.

Shark lipids and other shark products have been studied significantly since the 1990s for their anti-angiogenesis effects and possibility in treating cancer. Some of the compounds studied in shark products seem to demonstrate the ability to inhibit angiogenesis. We report successful treatment of a patient with large plaque psoriasis with a VEGF inhibitor extracted from shark lipids.

Case Report

A 28-year-old Caucasian male presented with a 10-year history of plaque psoriasis on his chest, back, groin, buttock and upper and lower extremities, covering approximately 70% of his body surface area. He had previously been treated with etanercept 50mg subcutaneously twice weekly as part of a clinical trial, with some success after 12 weeks of therapy; but he was unable to continue treatment at the end of the trial due to financial circumstances. He had last received etanercept six months prior to presenting at our office. He had previously tried topical corticosteroids, dovonex and narrow-band UVB without success, either due to lack of efficacy or lack of compli-
ance with treatment regimen. He was not taking any other medications and was otherwise healthy. His family history was unremarkable.

Physical examination revealed large, well-defined erythematous plaques with thickened white scale on his chest, back, arms, legs, groin and buttocks (Figure 1). Palms and soles were clear of any lesions. All laboratory findings were within normal range, including complete blood count, liver function and basic chemistries.

A diagnosis of psoriasis was made, and the patient was started on Supermaco™, a shark-liver mucolipin extract, taken by mouth three times a day. Due to financial constraints, the patient was unable to obtain any other prescription medication and was only taking the Supermaco pills. The patient was seen in the clinic monthly, and no adverse events occurred. At the end of three months of therapy, the patient was almost completely clear, with small plaques remaining on the elbows (Figure 2). The patient reported not only looking better but also feeling better than he had in years.

Discussion

The new biologic therapies for psoriasis offer more targeted treatment capabilities, but most also possess some potentially serious side effects, are cost prohibitive, and currently are only available as a subcutaneous injection or intravenous infusion. Supermaco is an all-natural product with potent anti-angiogenesis effects that comes in a pill form and is a fraction of the cost of the new biologic therapies. There are several mechanisms thought to be involved in the anti-angiogenesis effects of Supermaco. A study conducted at the Wellington School of Medicine in New Zealand was able to demonstrate that shark lipids have the ability to inhibit vascular endothelial growth factors (VEGF), fibroblast growth factor (FGF-2), and transforming growth factor beta (TGF-Beta). VEGF are proteins shown to promote the formation of new blood vessels; FGF-2 is a protein shown to promote proliferation of many different cell types; and TGF-beta demonstrates suppression of cytokine production and major histocompatibility complex (MHC) type II expression, suppressing the immune system.

The shark lipids also demonstrated minor inhibitory effects against interleukin 2 (IL-2) and platelet-derived growth factor (PDGF). In another study by Pedrono et al., the alkylglycerols present in shark lipids were demonstrated to have a direct inhibitory effect on tumor neovascularization and dissemination of Lewis lung carcinoma in mouse models. Additionally, the lipids demonstrated a decrease in plasmalogens and von Willebrand factor content in the tumors, affecting the ability to promote angiogenesis. Shark products have also been shown to interfere with matrix metalloproteases (MMPs), allowing the growth of new blood vessels. MMPs are secreted by some tumors and are thought to break down surrounding tissue.

In this case study, our patient experienced significant improvement in his psoriasis without any adverse events after three months of therapy; however, some adverse events have been reported in other patients taking shark supplements. Some shark products have been shown to contain heavy metal contaminants such as mercury and cadmium. In these cases, the levels of mercury and cadmium were not considered to be dangerous, although there is some concern about accumulation if taken in high doses for long periods of time. One case of hepatitis has been reported in a patient taking a shark-cartilage product; and in some clinical studies, some participants taking shark products by mouth developed signs of liver dysfunction such as dark urine, excessive fatigue, widespread pruritis, nausea, vomiting, pain or swelling in the right upper abdomen, and/or jaundice. Cases of hypercalcemia have also been reported in some cancer patients taking various dietary supplements including shark products. Other less severe side effects also reported while taking oral shark products include constipation, dizziness, nausea, indigestion, bad taste in the mouth, diarrhea, low blood pressure, and weakness.
This case report demonstrates the possibly potent effects that the anti-angiogenesis compound SupermacoTM can have on the treatment of psoriasis. We are currently undertaking a pilot study to investigate the use of Supermaco as a treatment for psoriasis. If this case report is any indication of the therapeutic effects of Supermaco, we believe it will be a safe, targeted, inexpensive treatment to add to the currently available regimens.

REFERENCES


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**MASTOCYTOSIS: MAST CELL BURDEN AND SYMPTOMATOLOGY**

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ABSTRACT

Mastocytosis refers to a spectrum of diseases related to an accumulation of mast cells. The range of diseases caused by mast-cell aggregation and degranulation vary from relatively benign cutaneous forms to myelodysplastic disorders. The most common childhood form of mastocytosis, urticaria pigmentosa (UP), represents 60%-90% of cases. Typically, UP resolves by puberty; however, rare cases have evolved into systemic disease in adulthood. We present a 25-year-old female with a history of adolescent-onset urticaria pigmentosa, who presented to us complaining of recurrent episodes of flushing, pruritus, palpitations, wheezing, crampy abdominal pain, vomiting, syncope, and headache within the last year. Her skin lesions become raised, erythematous, and pruritic with exacerbations that coincided with “asthma attacks.” Exercise makes her symptoms worse, and Naprosyn also reportedly induced an acute episode. Despite her severe symptoms, an extensive workup revealed no evidence of extracutaneous disease. This case demonstrates the unpredictable relationship between mast-cell burden and symptomatology. A review of the literature related to mast-cell burden and symptom severity is discussed.

Case Report

A 25-year-old female with a history of adolescent-onset urticaria pigmentosa presented as a new patient to establish care and have “moles” examined. Neurocardiogenic syncope was noted on medical history. Upon further questioning, she admitted to recurrent episodes of flushing, pruritus, palpitations, wheezing, crampy abdominal pain, vomiting, syncope, and headache within the last year. Her skin lesions become raised, erythematous, and pruritic with exacerbations that coincided with “asthma attacks.” Exercise worsened her symptoms, and Naprosyn induced an acute episode. Multiple therapies targeted at the skin lesions had been tried in the past, including laser, intralesional and topical corticosteroids. Medications upon presentation included fluticasone propionate/salmeterol discus (Advair), iratoprim bromide/albuterol sulfate inhaler (Combivent), levothyroxine (Synthroid), montelukast sodium (Singulair), and drospirenone/ethinyl estradiol (Yasmin).

Examination reveals a healthy-appearing, 25-year-old female with numerous reddish-brown, well-demarcated macules and papules less than 1 cm in diameter. These lesions are symmetrically distributed and most numerous on the trunk, buttocks and proximal extremities. The face is spared.

An initial work-up, including CBC, CMP, rheumatoid factor, ANA, and serum protein electrophoresis, was normal. Serum tryptase was found to be normal at 12 ng/ml. Karyotype and bone marrow biopsy with flow cytometry were also negative. Peripheral smear showed the Pelger-Huet anomaly (PHA), a benign, inherited defect of terminal neutrophil differentiation. Upon further questioning, her father also reportedly was diagnosed with PHA. An exhaustive literature review found no correlation between PHA and mastocytosis. We concluded that the PHA was a coincidental finding.

Biopsy report and slides from 2001 were obtained and confirmed with a dermatopathologist. Histology revealed superficial dermal perivascular cells with granular cytoplasm. The cells stained metachromatically with Giemsa. These findings are consistent with cutaneous mastocytosis.

Discussion:

Mastocytosis (MC) is a heterogeneous group of disorders characterized by abnormal proliferation and accumulation of mast cells in the skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes. The spectrum of mast cell disease has been classified based on type and extent of involvement as well as age of onset.

Cutaneous forms include solitary mastocytoma, urticaria pigmentosa, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans. Urticaria pigmentosa is the most common form of cutaneous MC. Urticaria pigmentosa usually presents in childhood, and may persist into adulthood. However, most cases spontaneously improve. Cases have been reported of UP progressing into aggressive neoplasms such as mast-cell leukemia or mast-cell sarcoma.

A variety of laboratory tests are available for evaluation of patients suspected to have or being followed for mastocytosis. Elevated serum tryptase levels and 24-hour urine histamine metabolites both support a mastocytosis diagnosis. Serum tryptase is a mast-cell-specific marker and correlates closely with cumulative mast-cell burden. High levels of soluble CD117 and CD25 receptors are strongly associated with severity of bone marrow involvement. Flow cytometric analysis of bone marrow mast cells is also a sensitive method of diagnosing systemic mast-cell disease. However, more than one bone marrow biopsy may be required, as patchy marrow involvement may be missed on a single specimen.
An extensive Medline search dating back to 1966 reveals only one article that addresses some of these issues. A few authors do make generalizations, likely based on clinical experience.

Brockow et al. assessed the extent of cutaneous disease as a predictor of systemic disease. They looked at both adults and children. In children, the extent of cutaneous disease did not predict systemic disease. In adults, it was found that the absence of skin lesions and very dense cutaneous involvement were more likely to predict extracutaneous disease and more severe symptoms. However, the only symptoms discussed were flushing, pruritus, nausea, fatigue and musculoskeletal pain. In light of this paper, our case becomes even more peculiar.

Which factors may influence symptom severity can only be speculated. Ratios of the mast cell mediators could vary person to person, or some individuals may be more sensitive to the various mediators. Mast cells may have great variability in their propensity to degranulate, or some individuals may release greater quantities of mediators than others. Further research in this area would help elucidate some of the influencing factors and perhaps open new possibilities for treatment. It is clear by the absence of literature on this topic that this spectrum of diseases remains poorly understood.

In conclusion, extensive workup has not revealed any evidence of systemic disease in our patient. Follow-up visits reveal flares of pruritus, dizziness, and palpitations despite aggressive medical management. Current medical regimen includes montelukast sodium every evening. Her medical regimen includes fexofenadine at lunch, and cetirizine, ranitidine and atenolol in the morning, loratadine and ranitidine in the morning, loratadine and montelukast sodium every evening. Her main triggers are reported to be heat, exercise, emotional stress, sun exposure and certain foods. She is followed closely by her primary care physician. Regular follow-up visits and blood work, including tryptase, will be checked. If any evidence of change occurs, repeat bone marrow biopsy will be considered. This case demonstrates that even a minimal increase in mast cell burden can cause an unpredictable degree of symptoms, and, as in our case, severely disrupt a patient’s quality of life. The literature reveals a poor understanding of this spectrum of disease and calls for increased efforts in expanding our basic understanding and treatment options.

References
LINEAR FOCAL ELASTOSIS IN A YOUNG HISPANIC MALE: A NEW PRESENTATION

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ABSTRACT

Linear focal elastosis is an uncommon dermal elastosis that occurs predominately on the back. It was first described by Burket, Zelickson, and Pandilla in 1989 in three elderly white men. To date, only 27 cases have been reported in the literature. Case reports of linear focal elastosis have included Asian, Caucasian, black, Indian, and Turkish persons who range from 7 to 89 years of age. Reports of occurrence in men are more common than those in women. This is the first reported case of linear focal elastosis in a Hispanic male.

Introduction:

Linear focal elastosis is an uncommon disorder characterized by yellow, palpable striae on the middle and lower back. It was originally reported in three patients by Burket et al. in 1989.1 In 1991, Hagari et al. was the second to report a case of linear focal elastosis, this one in an 86-year-old Japanese man. He concluded that it was characterized by an onset after 60 years of age.2 Since then, 23 additional cases have been reported, including onset beginning in early childhood with facial, axillae, and extremity involvement.3,4 The pathogenesis remains unclear. Some authors have suggested that linear focal elastosis may be an unusual form of striae distensae or that it may reflect a keloid repair of striae distensae.5 The location of the dermatosis in sun-protected areas and the lack of any sign of solar elastosis suggest that it is not an actinically derived condition. Histologically, the clinically palpable linear plaques correspond to an increase in abnormal elastic tissue in the subpapillary to lower reticular dermis.6

Case Report:

A 15-year-old Hispanic male presented for consultative evaluation of palpable, yellow linear plaques on the mid and lower back. The patient had noticed the slow progression of these lesions over the past six months. The striae-like lesions were asymptomatic and were localized to either side of the vertebral column (Photographs 1, 2). He had no significant past medical history, no history of systemic or topical medications, and no history of trauma to that region. The patient and his mother both stated no dramatic changes in height or weight in the past 12 months. Laboratory studies revealed normal complete blood count, complete metabolic profile, thyroid-stimulating hormone, adrenocorticotropic hormone, and serum cortisol.

The clinical diagnosis was confirmed with a 4mm punch biopsy taken from the patient’s right mid back and sent for microscopic examination. The tissue sections were stained with hematoxylin-eosin, revealing abnormal findings (Image 1). The epidermis was unremarkable. There was deposition of abundant pale staining material separating and fragmenting the larger, darker staining bundles. Elastic tissue stain showed the pale staining material to be wavy, fragmented elastic tissue (Images 2a-c).

Discussion:

Because the elastic changes found in these lesions were so localized, Burket et al. found it reasonable to use the term focal to distinguish it from other forms of elastotic change. Therefore, linear focal elastosis had been coined to describe this specific condition.7 The differential diagnosis of linear focal elastosis includes striae distensae, pseudoxanthoma elasticum, dermatofibrosis lenticularis disseminate, and linear xanthomas. Striae distensae are characterized by white, red, or violaceous bands of atrophic, wrinkled skin and are associated with topical and systemic steroid use, pregnancy, and weight gain. Lesions usually occur on the axillae, abdomen, thighs, arms, or breasts, and histopathologic examination shows a flattened epidermis, abnormal collagen fibers, and variable changes in elastic tissue. In contrast, linear focal elastosis is characterized by palpable yellow plaques that show characteristic changes in elastic tissue; the epidermis and collagen fibers are not affected.8

Pseudoxanthoma elasticum may be differentiated from linear focal elastosis by the presence of calcified elastic-tissue fibers. The presence of calcium can be ruled out with a negative Von Kossa stain. Clinically, pseudoxanthoma elasticum is characterized by soft yellow papules found on the neck, axillae, and groin. In these areas, it has been described as having a cobblestone or plucked-chicken skin appearance.9 Dermatofibrosis lenticularis disseminate is also inherited in an autosomal-dominant fashion with a relatively high penetrance, making the presence of similar symptoms likely in family members.10 The etiology of linear focal elastosis remains unknown. There may be a familial or genetic tendency for development of the condition. Moiin reported a case in a 29-year-old black man who stated that his father, who was deceased at time of presentation, had similar symptoms for most of his adult life.11 Others have inferred an ethnic or geographic origin to this condition, as some clinicians practicing in relatively remote areas have found multiple cases within a relatively short period of time.12 Yet, low physician awareness and an asymptomatic nature may lead to underreporting, leading one to believe that the condition may be much more common than currently thought. In fact, many patients with linear focal elastosis have reported having symp-
44 LINEAR FOCAL ELASTOSIS IN A YOUNG HISPANIC MALE: A NEW PRESENTATION

toms for as long as 40 years prior to seeking medical evaluation. To date, no reports of linear focal elastosis in a person of Spanish or Hispanic ethnicity have been documented (see Table 1). All 27 case reports in the literature have described patients of either Asian, Caucasian, black, Indian or Turkish ethnicity.

Conclusion:

The first known case of linear focal elastosis in a Hispanic is presented. The condition is relatively rare; however, certain ethnicities appear to be more prone to its development. Due to the asymptomatic nature of linear focal elastosis, many patients may not seek care and simply go undiagnosed. It is important to recognize this entity and distinguish if from other forms of dermal elastosis for both clinical and patient reassurance.

Citations
Case Report

A 73-year-old Caucasian male presented to the clinic with a four-month history of erythematous patches involving his face, hands, chest, back, elbows, and knees. The onset of these patches was slow and asymomatic. The patient denied any fatigue, muscle weakness, myalgias, arthralgias, fever, or other constitutional symptoms. He was an avid golfer and spent a great deal of time outdoors. He reported a worsening of the erythema with sun exposure.

Physical exam revealed a healthy male appearing younger than stated age. Of note were erythematous patches with subtle areas of atrophy involving his forehead, neck, chest, and upper back. Erythematous patches with fine overlying scale were noted on his elbows and knees. A heliotrope rash was noted, as were clinical Gottron's papules and periungual telangiectasias. Mild tenderness to palpation was noted in the region of the left deltoid; however, this was attributed to a recent golf injury. The remaining physical exam was noncontributory.

Laboratory evaluation revealed a mildly decreased hematocrit at 39.3%. The remainder of the CBC, as well as a CMP, sedimentation rate, CPK, and aldolase were all normal. His chest X-ray was unremarkable. ANA, SSA, SSB, anti-Jo-1, anti-dsDNA, anti-Smith, anti-scl70, and anti-RNP antibodies were all negative. A G6PD level was within normal limits. In addition, two 4-millimeter punch biopsies revealed epidermal atrophy, a thickened basement membrane with mild interface changes, and perivascular and perifollicular infiltrate. Direct immunofluorescence revealed linear IgG 1+ at the DE junction, linear IgA 1+ at the DE junction, and IgM 3+ colloidal bodies at the DE junction.

Based on the clinical, laboratory, and pathological findings, a diagnosis of amyopathic dermatomyositis was made. The patient was referred to internal medicine for an occult malignancy workup which included a colonoscopy, bronchoscopy, upper endoscopy, and CT scans of head, neck, chest, and abdomen. The colonoscopy revealed four hyperplastic polyps, all of which were removed at the time of the procedure. The remaining tests were unremarkable.

Due to the lack of symptoms, it was felt that systemic immunosuppressive therapy was not warranted, and the patient was educated on the importance of sun avoidance and regular follow-up visits. Topical corticosteroids were prescribed, and the patient was monitored closely. At his three-month follow-up visit, the patient complained of cosmetic concerns with regards to the rash involving his face and hands and stated that he desired more aggressive treatment. After obtaining a consult with ophthalmology, the patient was started on Plaquenil 200mg twice daily.

Minimal response was noted at three months, and at six months a mild pancytopenia was noted. The Plaquenil was discontinued. Three months later, the pancytopenia continued to worsen. Iron levels, TIBC, folate, and B-12 were all within normal limits. However, his TSH was elevated at 6.63 mU/L, and anti-thyroglobulin and anti-microsomal antibodies were positive at 287 IU/ml and 47 IU/ml, respectively. The patient was referred to endocrinology for evaluation. There, a diagnosis of subclinical autoimmune thyroiditis was made; however, this did not explain the worsening pancytopenia.

Upon referral to hematology, a bone-marrow biopsy was performed and was consistent with myelodysplastic syndrome (MDS). To our knowledge, this is the first reported case of ADM associated with MDS. It is important to note that the pancytopenia developed approximately one year after the onset of the cutaneous symptoms.

ABSTRACT

Amyopathic dermatomyositis (ADM) is a subset of dermatomyositis in which biopsy-proven cutaneous findings are demonstrated for six months or greater with no clinical or laboratory findings of muscle involvement. The association between classic dermatomyositis and myelodysplastic syndrome (MDS) is rare. We report a case of ADM associated with myelodysplastic syndrome. To our knowledge, this is the first reported case of ADM associated with MDS. The identification of any autoimmune phenomenon is crucial to the management of patients with MDS, as they generally will have a poorer prognosis than those without an autoimmune component.

Table 1

<table>
<thead>
<tr>
<th>Diagnostic criteria for ADM as proposed by Euwer and Sontheimer</th>
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<tbody>
<tr>
<td>1. Cutaneous changes pathognomonic of CDM</td>
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<tr>
<td>2. Histopathological changes consistent with CDM</td>
</tr>
<tr>
<td>3. No clinical findings suggestive of proximal muscle weakness within two years of skin disease</td>
</tr>
<tr>
<td>4. Normal skeletal enzyme levels for two years after development of skin disease</td>
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</table>

Discussion

Due to the dynamic nature of the disease, amyopathic dermatomyositis (ADM) is difficult to characterize. ADM, as defined by Sontheimer, is a subset of dermatomyositis in which biopsy-proven cutaneous-findings are demonstrated for six months or greater with no clinical or laboratory findings of muscle involvement. Exclusion criteria include the use of drugs that are known to cause skin changes resembling classical dermatomyositis (CDM) at the onset of skin findings, and the use of systemic immunosuppressives for two months or longer within the first six months after the onset of skin findings.1 Euwer and Sontheimer suggested four criteria for the diagnosis of ADM (Table 1).2 Stonecipher et al. offered three group descriptions to distinguish patients with ADM, as did Kovacs and Kovacs.3,4 For the purposes of this article, Sontheimer’s definition and Euwer and Sontheimer’s diagnostic criteria have been used.

Sontheimer also offered definitions for other dermatomyopathies. While most
are beyond the scope of this paper, three are of importance. Confirmed amyopathic dermatomyositis is defined as the presence of amyopathic dermatomyositis for 24 months or longer. Hypomyopathic dermatomyositis (HDM) is diagnosed in patients with the classical findings of DM with no clinical evidence of muscle involvement but with positive evidence of muscle involvement on laboratory, electrophysiological or radiologic evaluation. Finally, clinically amyopathic dermatomyositis (CADM) encompasses both AMD and HDM, with the essential element being that the predominant component of the disease is skin involvement.1

The most comprehensive review of ADM was reported by Gerami et al. in 2006. Two hundred and ninety-one patients were identified as having CAMD. The average age of these patients was 50, and there was a female-to-male predominance of 3:1. The average duration of skin involvement without clinical muscle involvement was 3.74 years. Seventy percent of the patients were Caucasian.3

With regard to laboratory evaluation of these patients, 63% were ANA positive. Only 3.5% of patients were anti-Jo-1 antibody positive, but overall reporting was low, and as a whole, myositis specific antibodies (Jo-1 and Mi-2) were typically negative. ESR was elevated in 25% of patients. Anti-double stranded DNA, anti-Smith, Ro and La antibodies were negative in the majority of patients.3

Targoff et al. reported that in 16 of 18 patients with amyopathic dermatomyositis, autoantibodies to the Scl 70 protein and the 155-kd protein were identified. None were found to be positive for Jo-1 or Mi-2.6

Gerami et al. reported that calcinosis is rare. Malignancy and lung disease associations were similar to CDM, but, in contrast, there was a low rate of positive anti-Jo-1 antibody in ADM associated with lung disease. Lung disease was reported in 13% of patients, and internal malignancy was reported in 14%.7 It is important to note that potentially fatal interstitial lung disease has been reported in association with ADM.7 Histopathological and immuno-fluorescent findings currently do not allow for a distinction between CDM and ADM. CPK is the best initial test for muscle involvement. EMG and MRI appear to have a higher sensitivity than muscle biopsy for identifying muscle involvement due to ADM. In terms of muscle involvement, it is recommended that if CK and physical exam are negative for evidence of muscle involvement, no further workup is warranted. However, it is important to repeat enzymes and exams regularly.7

Reports of the coexistence of dermatomyositis and myelodysplastic syndrome are limited. In 2003, Tsuji et al. described a patient presenting with CDM and MDS/myelofibrosis concurrently. The patient described had positive laboratory and clinical findings of muscle involvement. Laboratory evaluation revealed elevated AST, LDH, CK, aldolase, CRP, and ferritin, and a positive ANA. Anti-RNP, anti-Scl 70, and anti-Jo-1 antibodies were negative. Initially resistant to monotherapy with systemic corticosteroids, the patient responded well to the addition of methotrexate 3mg weekly.7

In 2006, Muslimani et al. reported a case of a 62-year-old female with CDM and myelofibrosis. CPK, LDH, aldolase, myoglobin, AST, and ALT were elevated, with evidence of anemia and thrombocytopenia. No comment was made on the patient’s ANA or other extractable nuclear antigens. An electroneuromyogram of the deltoid and tensor fascia lata revealed evidence of an inflammatory myopathy, polymyositis or CDM, and a muscle biopsy demonstrated perivascular lymphocytes consistent with CDM. Treatment consisted of 40mg of oral prednisone daily, to which the patient responded well.8

In 2006, Ito et al. reported a case of a 74-year-old female with CDM associated with chronic idiopathic myelofibrosis (CIMF). Her skin disease developed three years after her diagnosis of CIMF. Muscle involvement was apparent both clinically and serologically. CK was elevated at 1,757 IU/l, while ANA, RF, and anti-Jo-1 were all reported as negative. Initially failing to respond to systemic corticosteroids, the addition of azathioprine resulted in a reversal of her autoimmune symptoms.9

Approximately 10%-13% of patients with MDS will display some form of autoimmune phenomenon. Of these, systemic vasculitis appears to be the most common. Autoimmune manifestations associated with MDS have been classified into five groups: acute systemic vasculitis or autoimmune disorder, chronic or isolated autoimmune phenomena, classical connective tissue disorders, immune-mediated hematological abnormalities, and asymptomatic serological immunologic abnormalities. Several dermatologic manifestations have been associated with MDS. These are summarized in Table 2.11-15

Shimamoto et al. analyzed, specifically, autoantibodies and dermatologic manifestations in 22 patients with MDS. Five patients were found to be positive for autoantibodies and dermatoses. One demonstrated a positive ANA, while four had a positive rheumatoid factor. No other autoantibodies were found to be present.12 Other autoantibodies that have been reported in MDS include rheumatoid factor, ANA, alloantibodies, antiglobulins, ANCA, lupus anticoagulant, anti-mitochondrial antibody, anti-microsomal antibody, and anti-smooth-muscle antibody. Cryoglobulins, cold agglutinins, hypogammaglobulinemia, hypergammaglobulinemia (polyclonal and monoclonal), positive Coombs test, and decreased levels of C3 and C4 have also been reported.12-13

Conclusion

The identification of any autoimmune phenomenon in patients with MDS is crucial to their management, as these patients generally will have a poorer prognosis than those without an autoimmune component. The role of amyopathic dermatomyositis in MDS is unclear, and is rarely reported. At this time, the patient reported herein has had an unremarkable course; however, his prognosis remains guarded.

References


Table 2

<table>
<thead>
<tr>
<th>Dermatologic manifestations associated with MDS</th>
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<tbody>
<tr>
<td>Leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
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<tr>
<td>Bullous pemphigoid</td>
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<tr>
<td>Vitiligo</td>
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<tr>
<td>Lupus erythematosus</td>
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<tr>
<td>Sjogren’s syndrome</td>
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<tr>
<td>Raynaud’s phenomenon</td>
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<tr>
<td>Relapsing polychondritis</td>
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<tr>
<td>Dermatomyositis</td>
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<tr>
<td>Anaphylactoid purpura</td>
</tr>
<tr>
<td>Xerotic dermatitis</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
</tr>
<tr>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Sweet’s syndrome</td>
</tr>
<tr>
<td>Ichthyosis vulgaris</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
</tr>
<tr>
<td>Livedo reticularis</td>
</tr>
</tbody>
</table>

Dermatologic manifestations

Autoimmune manifestations associated with MDS include rheumatoid factor, ANA, alloantibodies, antiglobulins, ANCA, lupus anticoagulant, anti-mitochondrial antibody, anti-microsomal antibody, and anti-smooth-muscle antibody. Cryoglobulins, cold agglutinins, hypogammaglobulinemia, hypergammaglobulinemia (polyclonal and monoclonal), positive Coombs test, and decreased levels of C3 and C4 have also been reported.12-13

Conclusion

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Now you can treat acne wherever it pops up.

The first and only once-daily acne foam that offers easy body coverage and effective lesion reduction.1,2

EVOCLIN is a once-a-day topical clindamycin foam for the treatment of acne vulgaris.
EVOCLIN is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, or a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and pseudomembranous colitis have been reported with systemic and rarely with topical clindamycin. Discontinuation is recommended if diarrhea develops.
The most common adverse events in clinical trials were headache (3%) and application-site reactions including burning (6%), itching (1%), and dryness (1%).

Please see following page for full prescribing information.

For further details, visit www.evoclin.com
A 1% clindamycin phosphate gel similar to Evocin caused a statistically significant shortening of the median time to tumor onset in a strain of mice in which tumors were induced by exposure to dimethyl nitrosamine. Tumor incidence tests performed included a nitrosourea test and an Ames Salmonella mutagenicity test. Both tests were negative.

Reproduction studies in rats using oral doses of clindamycin phosphate, clindamycin hydrochloride, and clindamycin palmitate hydrochloride have revealed no evidence of impaired fertility.

Pharmacology: Teratogenic effects - Pregnancy Category B

Reproduction studies have been performed in rats and mice using subcutaneous and oral doses of clindamycin phosphate, clindamycin hydrochloride, and clindamycin palmitate hydrochloride. These studies revealed no evidence of fetal harm. The highest dose used in the rats and mice teratogenicity studies was equivalent to a clindamycin phosphate dose of 420 mg/kg. For a rat, this dose is 8.4 fold higher, and for a mouse 42 fold higher than the anticipated human dose of clindamycin phosphate from Evocin based on a 70 kg individual. There are, however, no adequate and well-controlled studies in pregnant women. Therefore, because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether clindamycin is excreted in human milk following use of Evocin. However, orally and parenterally administered clindamycin has been reported to appear in breast milk. Therefore, because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and effectiveness of Evocin in children under the age of 12 have not been studied.

Adverse Reactions:
The incidence of adverse events occurring in ≥1% of patients in clinical studies comparing Evocin and its vehicle is presented below:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number (% of Subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12% (115)</td>
</tr>
<tr>
<td>Application site burn</td>
<td>27% (14)</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>5% (1)</td>
</tr>
<tr>
<td>Application site dryness</td>
<td>4% (1)</td>
</tr>
<tr>
<td>Application site erythema</td>
<td>3% (1)</td>
</tr>
</tbody>
</table>

In a clinical study, none of the 256 subjects developed evidence of allergic contact sensitivity to Evocin. Daily and parenteral administered clindamycin has been associated with severe cutaneous reactions, which may result in patient death. Use of the topical formulation of clindamycin in the skin fold areas should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

Contraindications:
Evocin is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

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Warnings:
PERIANAL BASAL CELL CARCINOMA:
A CASE REPORT

Andrea Passalacqua, D.O.,* Ronald Liskanich, D.O.,** Gloria Stevens, M.D.,*** David Horowitz, D.O.****

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**Dermatology Residency Co-Program Director at Western University/Pacific Hospital of Long Beach, Long Beach, CA
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****Dermatology Residency Program Director at Western University/Pacific Hospital of Long Beach, Long Beach, CA

ABSTRACT

We report the case of an 80-year-old Caucasian male with a basal cell carcinoma (BCC) on the perianal region. BCC on the perianal region is extremely rare and is generally not an aggressive tumor. Clinical and histopathologic findings are described along with the differential diagnosis for such a lesion in the perianal region. The patient was treated with a trial of imiquimod, but ultimately required surgical excision to provide adequate treatment.

Case Report:

An 80-year-old Caucasian male presented with a rash located in the perianal area of approximate six-month duration. He initially complained of a pimple-like lesion with intermittent bleeding and tenderness. The patient was unsure if he had scratched the area at night while sleeping and admitted to excessive wiping after bowel movements. He denied any history of tanning-bed use or nude sunbathing. His primary-care physician treated the area with acouzyme (a debriding agent) and nystatin powder; however, there was no improvement. Past medical history included prostate cancer, neurodermatitis, psoriasis, and eczema. The prostate cancer was staged at T2N0M0 and treated with Lupron injections. No radiation therapy was administered. The patient had no significant family history of skin disease.

On physical examination, the patient was found to have a perianal, erythematous plaque measuring 5cm x 7cm, with whitish, serpiginous borders. Some nodularity was also noted (Figure 1).

Initial treatment included desonide cream and ketoconazole cream twice daily to the perianal area. A bacterial culture was performed, which showed E. coli and Klebsiella pneumoniae, and the appropriate oral and topical antibiotics were given. Since it was unclear if the erythematous lesion extended into the rectum, and with his history of prostate cancer, he was sent to a gastroenterologist for a colonoscopy. The colonoscopy demonstrated severe perianal dermatitis and internal hemorrhoids, and aggressive wound care was recommended. The area was treated with desoximetasone 0.25% cream and vusion ointment (miconazole nitrate, zinc oxide, and white petrolatum).

A punch biopsy was performed to rule out intertrigo (versus psoriasis). The biopsy showed interconnecting thin cords of basaloid cells contiguous with the epidermis, prominent palisading of the peripheral nuclei, and fibrotic stroma with mucin deposition (Figures 2 and 3). A PAS stain failed to demonstrate any fungal organisms. The patient was diagnosed with having a perianal basal cell carcinoma. Because of the location of the lesion, the slides were sent out for an additional dermatopathology consultation. That diagnosis was felt to be basal cell carcinoma with striking isthmic and superficial follicular differentiation, with possible concurrent squamous cell carcinoma in situ.

The topical medicines already prescribed were discontinued immediately given the histopathology. Options were discussed with the patient regarding surgical excision versus a trial with topical imiquimod. Based on his age and the extent of the surgical excision required to remove the lesion in its entirety, the patient opted for a trial of topical treatment first.

The patient was instructed to apply imiquimod three to five times per week at night to the lesion for approximately three months. Due to the expected irritation resulting from imiquimod, the medication was discontinued intermittently to minimize discomfort. The perianal lesion appeared to be slightly receding, and a decrease in the nodularity was noted (Figure 4). The area was re-biopsied and still showed perianal basal cell carcinoma, extending to the peripheral margins.

Since there seemed to be no resolution of the basal cell carcinoma, the patient was offered the option to undergo either Mohs micrographic surgery or radiation. He opted for Mohs surgery and is currently undergoing treatment.

Discussion

Basal cell carcinoma (BCC) is the most common cancer and accounts for more than 75% of all non-melanoma skin cancers diagnosed in the United States each year.1,2 The origin of the tumor is in the basal cell layer of the epidermis and appears to arise from immature pluripotent cells associated with the hair follicle. Risk factors in the development of basal cell carcinoma include ultraviolet radiation, radiation therapy, a positive family history of BCC, immunosuppression, skin types I and II, and a history of blistering sunburns in childhood. BCC is a slow-growing skin cancer that locally invades, extending over time, and eventually can become ulcerative. Patients typically do not feel any pain, but will often state that the lesion bleeds intermittently. As the BCC spreads, it may form serpiginous patches. Metastasis is extremely rare, but has been reported to occur.2

Basal cell carcinoma occurs most often in the elderly population on the sun-exposed...
areas, such as the head and neck. BCC occurring on non-sun-exposed areas is very rare. There have been fewer than 200 cases of BCC in the perianal and genital regions reported, accounting for less than 1% of all basal cell carcinomas. Perianal basal cell carcinoma accounts for only 0.2% of the anorectal tumors. Perianal BCC can often be misdiagnosed as an inflammatory or infectious skin condition and incorrectly treated. Patients affected by perianal BCC tend to be middle-aged to elderly. There may be a delay in seeking treatment because of the location of the lesion and the thought that it may be temporary irritation. Therefore, these lesions on average are large in size and ulcerated. It is recommended that a biopsy of the site be performed.

Histologic subtypes of basal cell carcinomas include nodular, superficial, micronodular, infiltrating, morphoeform, and fibroepithelioma of Pinkus. Nodular BCC is the most common subtype, comprising more than 60% of all tumors, with superficial BCC being the second most common type. Histologic features of basal cell carcinoma include the presence of necrosis en masse, dyskeratosis, prominent palisading of peripheral nuclei, predominance of basaloid lobules over stroma, and clefts between neoplastic aggregates and the stroma.

Since certain neoplasms, both premalignant and malignant, can clinically mimic chronic eczematous changes in the perianal region, it is important to differentiate them from benign processes. The differential diagnosis of chronic perianal dermatitis includes the following: anal intraepithelial neoplasia, verrucous carcinoma of the perianal region, extramammary Paget disease, Langerhans cell histiocytosis, and cutaneous T-cell lymphoma. In addition, basal cell carcinoma must be distinguished from basaloid carcinoma of the anus. Histologically, the two are similar; however, basaloid carcinoma of the anus is more aggressive, metastasizes early, can be fatal, and requires different therapy. The monoclonal antibody Ber-EP4 is a positive marker for perianal basal cell carcinoma and can be useful in differentiating it from basaloid carcinoma of the anus. BCC of the perianal region is approximately 15-fold less common than squamous cell carcinoma in the same area. Considering this differential diagnosis, biopsies and histopathologic examination are recommended in order to avoid delays in the diagnosis and treatment of such lesions.

Even though perianal basal cell carcinoma is a rare tumor, the diagnosis alone should prompt physicians to thoroughly examine the patient to ensure detection of other possible basal cell carcinomas on the body. Perianal BCC has not demonstrated to be an aggressive neoplasm compared to BCC on other areas of the body. Local excision of the lesion has proved to provide adequate therapy. Mohs micrographic surgery may be preferred for treatment of this area for tissue preservation and if the histology is more aggressive. Other therapy options are localized radiation and electron therapy. Perianal basal cell carcinoma has a good prognosis, but strict follow-up is recommended because of the possibility of local recurrence.

References:
**DERMOSCOPY FOR NON-MELANOCYTIC LESIONS**

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ABSTRACT

Dermoscopy is primarily used to evaluate pigmented skin lesions, to improve clinical differential diagnosis, and to aid in the early detection of melanoma in situ and malignant melanoma. Dermoscopy can also be used to evaluate non-melanocytic lesions and increase the accuracy of a clinical diagnosis. This paper will look at the history and principles of dermoscopy, describe the value of using a dermatoscope in daily patient care, and present the dermoscopic features of non-melanocytic lesions. The non-melanocytic lesions reviewed include: seborrheic keratosis, solar lentigo, basal-cell carcinoma, squamous-cell carcinoma, dermatofibroma, and vascular lesions.

Introduction

When assessing cutaneous lesions for removal/biopsy, evaluation with the naked eye is limited to characteristics such as size, shape, color, symmetry, elevation, and ulceration of the lesion. This limitation is due to the reflection, refraction, and deflection of light off the lesion's stratum corneum. The clinical evaluation and diagnosis of a lesion can be improved by using a tool called a dermatoscope. This tool uses polarized light to allow the observer to see additional features inside the lesion and beyond what is appreciated with the naked eye or simple magnification. Dermoscopy is primarily used for the evaluation of pigmented lesions to improve clinical differential diagnosis while looking for features of malignant melanoma or early melanoma in situ. Dermoscopy can be used for non-melanocytic lesions as well. Non-melanocytic lesions have characteristic features appreciated with the dermatoscope that help to differentiate benign from malignant. These features aid the clinician in setting up a framework to determine which lesions to biopsy, saving the patient from unnecessary biopsies and scars.

The History of Dermoscopy

The idea of looking “into” the skin surface has been around for a long time. Skin surface microscopy started with Peter Borrelus in 1655 and Johan Kolhaus in 1663 to investigate the small vessels in the nail bed and nail fold using a microscope. In 1893, Unna transferred the application of immersion oil in microscopy to skin-surface microscopy, recognizing that the oil made the upper layer of the epidermis more translucent. Over the next 25 years, monocular and binocular capillary microscopes were built that also allowed 10-172x magnification of the skin. In Germany, Johann Saphier used the term “dermoscopy” in 1920 for the first time. He applied a binocular microscope primarily to evaluate skin capillaries, tuberculosis, syphilis, morphological basis of skin color, and study melanocytic nevi. Saphier was the first to describe the globules that are still used in the modern classification. Dermoscopy was first applied in the United States in 1922 by Michael, a Houston dermatologist, and further developed by Goldman in the 1950s. In 1971, Rona MacKie differentiated for the first time between benign and malignant pigmented skin lesions. In 1990, Bahmer et al. described the features in pigmented lesions and correlated them with underlying histology. That paper was the first to standardize terminology used in dermoscopy. The work has continued over the years in Europe and in the United States. Dermoscopy, also known as epiluminescence microscopy (ELM), dermatoscopy, and amplified skin surface microscopy, is becoming more widely accepted. Although there have been many terms used for looking at the skin surface, currently “dermoscopy” is the favored term in the United States.

Principles of Dermoscopy

When a lesion is examined with the naked eye, visible light is reflected by the stratum corneum, and only certain features such as size, shape, color, symmetry, elevation, and ulceration can be appreciated. When an immersion liquid (mineral oil, alcohol, water, gel) is applied to the skin surface, it reduces the air pockets in the stratum corneum, which in turn reduces the reflection, refraction, and diffraction of light. The immersion liquid with magnification allows the observer to evaluate the structures and features of the lesion at the dermal-epidermal junction and papillary dermis. In addition, a flat surface can be examined when the glass of the dermatoscope is used to compress the skin surface. An alternative to direct-contact dermoscopy is to use a dermatoscope with polarized light. The cross-polarized lens absorbs all the scattered incident light that is reflected...
The Dermatoscope

The most popular type of dermatoscope is the hand-held one. It is light-weight, convenient, and easily fits into a clinician’s pocket. It is equipped with a transilluminating light source and standard magnifying optics. Light sources tend to be halogen or LED (light emitting diode). It is battery powered, and the magnification is usually 10-fold. Several of the handheld units have a cross-polarization lens that eliminates the need for a liquid interface or direct contact with the skin. Other types of dermoscopic equipment include binocular stereoscopes, as well as electronic dermoscopes with and without computer link and analytic algorithms. Further advancement in the field of “algorithmic dermoscopy” involves the use of multispectral dermoscopy imaging systems for computer analysis of dermoscopic images.

The Value of Dermoscopy

Dermoscopy is a tool that is noninvasive, quick, and convenient to use. A dermatoscope is useful to confirm a clinical diagnosis while examining a patient or to aid in the evaluation of a lesion that has clinical uncertainty. It can be looked at as the bridge between clinical inspection with the naked eye and histopathological interpretation with a microscope. After the reflection of visible light is removed from a lesion, the clinician is able to “look into the lesion.” The features within the lesion can help distinguish between benign lesions (seborrheic keratosis, lentigo, compound nevus, blue nevus, hemangioma) and malignant lesions (early melanoma in situ, malignant melanoma, basal-cell carcinoma, squamous-cell carcinoma). On the one hand, it may save a patient an unnecessary biopsy; and on the other hand it may save a patient’s life. It also has value in differentiating between melanocytic lesions, such as nevi, and non-melanocytic lesions such as solar lentigos, seborrheic keratoses, and even pigmented basal-cell carcinoma. Vascular lesions can be evaluated with the dermatoscope to confirm a clinical diagnosis. In addition, capillary microscopy can aid in early detection of systemic connective-tissue disease when inspecting the nail folds for vascular changes such as telangiectasias. Inflammatory lesions such as psoriasis can be seen more clearly. It has even aided in the location of a foreign body, such as a thorn, that can’t be visualized with the naked eye. The dermatoscope is a useful tool for the clinician to have at his disposal to quickly give additional information when examining a patient. The application of such a tool requires training, and with experience it becomes invaluable.

Non-melanocytic Lesions

The non-melanocytic lesions whose dermoscopic features will be discussed in detail include the following: seborrheic keratosis, solar lentigo, basal-cell carcinoma, pigmented basal-cell carcinoma, squamous-cell carcinoma, dermatofibroma, and vascular lesions including hemangioma.

Seborrheic keratoses. Seborrheic keratoses are benign lesions that tend to have a “stuck-on” appearance. They can vary in size, shape, and color. The borders tend to be sharply demarcated. Although the diagnosis of these lesions tends to be straightforward, clinical uncertainty can arise when the lesion is heavily pigmented, simulating a melanoma, or early in its evolution, mimicking a solar lentigo. Dermoscopy is valuable in confirming that the distinctive features are those of a seborrheic keratosis and not those of an atypical melanocytic lesion. Early seborrheic keratoses are sharply demarcated with moth-eaten borders and a fingerprinting or network-like pattern. Features include comedo-like openings (crypts) -- ovoid craters that have
black or brown comedo-like plugs. These plugs correlate histologically to keratin-filled invaginations of the skin surface. Fissures (a.k.a. "valleys" or "sulci"), linear depres-
sions within the lesion, correlate with deep, keratin-filled invaginations of the epidermis. These produce either a network or cribi-
form pattern. They may also be seen in congenital melanocytic lesions. Ridges ("mountains") on either side of a fissure and can be hyperpigmented. These ridges or "gyri" have also been called "fat fingers." Multiple sulci and gyri give a seborrheic keratosis a "cribiform" or "brain-like" appearance. Hairpin blood vessels tend to be clustered in seborrheic keratoses, with each one surrounded by a whitish halo, mainly at the periphery of the lesion. They correspond to long capillary loops commonly seen in keratinizing tumors. Although hairpin vessels may be associated with seborrheic keratoses, they can also be seen with some melanomas. Dermoscopy will aid in the important differentiation of uncertain seborrheic keratoses from melanoma, especially when a patient may have hundreds of seborrheic keratoses and performing numerous biopsies is unrealistic and unappealing.

Solar lentigines. Solar lentigines are benign lesions found predominantly on sun-exposed areas. They are induced by UV exposure and persist indefinitely. They are formed from increased melanin accumula-
tion in hyperplastic keratinocytes and can evolve into a seborrheic keratosis. The borders are sharply demarcated, curved, irregular, and "moth-eaten." There may be the appearance of a network that is faint, irregular, or "finger-print" like (Figure 2). Many of these lesions have structureless areas that are light brown and void of a network or structure. In addition to the previous features, lentigines on the face and scalp may also have a pseudonetwork. Ink spot lentigos have a black-pigmented, thick or thin network that ends abruptly at the edge of the lesion. They exhibit an absence of other structures and melanoma-specific criteria and tend to be located on the upper trunk and extremities.

Pigmented and non-pigmented basal-cell carcinoma. Dermoscopy can help differentiate pigmented basal-cell carcinoma from other pigmented lesions, and non-pigmented basal-cell carcinoma from nevi, sebaceous-gland hyperplasia, melanoma, fibrous papules, and seborrheic keratoses. In pigmented basal-cell carcinoma, the melanin pigmentation is irregularly deposited in dermal melanophages, tumor melanocytes, and tumor cells. Since the pigment is deep in the dermis and not located in the rete ridges of the epidermis, there is no pigment network. Viewed dermoscopically, dots in a pigmented basal-cell carcinoma are due to small deposits of pigment in the dermis. Globules and ovoid nests are due to large deposits of pigment in the dermis. Blue-gray globules are smaller than ovoid nests. Ulceration appears as congealed blood with dermoscopy, and there should be an inquiry about a history of trauma to the lesion. Arborizing telangiectasias are multiple branching blood vessels in a tree-like pattern resulting from the dilated arterial circulation that feeds the tumor. Arborizing vessels are 99% specific and are seen in both pigmented and non-pigmented basal-cell carcinomas. Structureless, pink-white to white shiny areas are another common feature in basal cell carcinomas (Figure 3). Other characteris-
tic findings of pigmented basal-cell carcinomas include the leaf-like pattern and spoke-wheel pattern. The leaf-like pattern is usually brown or blue-gray in color and has the appearance of a maple leaf due to discrete, bulbous extensions connected to a base. The spoke-wheel pattern has a central point of dark brown, blue, or black, with well defined tan, blue, or gray radial projections (Figure 4).

Squamous cell carcinoma. Squamous-cell carcinoma lacks all the features of melanocytic lesions. It has characteristic glomeruli vessels and erythema (Figure 5).

Dermatofibromas. Dermatofibromas are benign dermal nodules. Although the exact etiology is unknown, a dermatofibroma is thought to arise from trauma to the skin, such as an arthropod bite. It tends to be a firm solitary nodule on the lower extremity that "dimples" when squeezed laterally. Patients come to the office concerned about these benign lesions after noticing them. The dermoscopic features include a central depigmented area due to fibrosis in the lesion. In the surrounding periphery, there may be a tan-to-dark-brown delicate network of pigmentation resulting from hyperpigmentation (rather than from melanocytic proliferation) of the basal layer (Figure 6). Although usually structureless, brown globule-like structures or blood vessels may be found in the scar area. In melanocytic lesions, globules are due to nests of melanocytes, but in dermatofibromas the globules are due to flat, confluent, and hyperpigmented rete ridges.

Vascular Lesions. Vascular lesions, such as hemangiomas, have a characteristic dermoscopic pattern of multiple, well demarcated, red-to-blue-red or blue-black-to-maroon, round-to-oval lacunae (Figure 7). These lacunae are diagnostic when there is an absence of criteria for a melanocytic lesion such as a pigmented network, globules and/or branched streaks. When the vascular lesion with lacunae is accompanied by hyperkeratosis, the lesion is considered to be an angiokeratoma.

When hemangiomas or angiokeratomas become thrombosed, they can have a dark blue-black color and resemble a melanoma (Figure 14). Dermoscopy will differentiate these benign vascular lesions from nodular melanoma and save the patient an unnecessary biopsy.

Conclusion

In summary, the history, principles and tools of dermoscopy were presented here. The value of dermoscopy for non-melanocytic lesions was discussed, and the features of several non-melanocytic lesions that can be appreciated using a dermatoscope were reviewed. Dermoscopy adds valuable additional information to the clinical picture of a lesion and increases the accuracy of a clinical differential diagnosis in the ultimate distinction from, or determination of, a malignant melanoma. Although the dermoscopic features of melanocytic lesions including melanoma are outside the scope of this commentary, it must be said that there is great satisfaction in finding melanoma in situ or malignant melanoma lesions by simply assessing the lesion with the dermatoscope and having a firm belief or suspicion that a clinically benign lesion must be biopsied.

Acknowledgment

I wish to sincerely thank Dr. Harold Rabinovitz for his review of this manuscript, insight, and assistance with the dermoscopic images. I also sincerely thank Dr. David Alperstein for his review and support in the preparation of this manuscript.

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Cutaneous malignant melanoma remains a major public health threat worldwide. Nodal metastasis (Stage III disease) occurs in 15% to 20% of intermediate-thickness melanomas and, alongside tumor thickness and ulceration, has profound prognostic impact. Sentinel node biopsy has become the de facto standard of care, but it remains the topic of controversy and heated debate. The purpose of this article is to familiarize ourselves, as dermatologists, with the rationale, criteria, procedure, and controversies of the sentinel lymph node biopsy.

Introduction

Cutaneous malignant melanoma remains a major public health threat worldwide. According to CDC estimates, there will be an expected 59,940 new cases and 8,110 deaths due to melanoma in the United States in 2007. As dermatologists, we are on the frontline of efforts to contain this threat. Data has shown some positive effects of these efforts, with melanomas being detected earlier and thinner, and hence with greater rates of survival. The majority of cutaneous melanomas are curable with wide resection. Nodal metastasis (Stage III disease) occurs, however, in 15% to 20% of intermediate-thickness melanomas. The importance of nodal metastatic involvement cannot be overstated. Nodal metastatic involvement, in addition to tumor thickness and ulceration, has profound prognostic impact, with a significant difference in five-year survival between patients with occult, microscopic nodal metastatic involvement (one node with microscopic nodal metastasis (one node with clinical metastasis: 29%). To address the risk of nodal metastasis, melanomas of sufficient thickness or displaying other so-called high-risk features have been evaluated initially by elective lymph node dissection (ELND) and later by sentinel lymph node biopsy (SLNBx). In its most current form, the sentinel-node biopsy has become the de facto standard of care in the medical community. In spite of its widespread usage, the procedure remains the topic of controversy and heated debate. The purpose of this article is to familiarize ourselves, as dermatologists, with the rationale, criteria, procedure, and controversies of the sentinel lymph node biopsy.

Rationale

**Nodal metastasis and elective lymph node dissection**

The core concept behind both ELND and SLNBx is the detection and management of occult nodal metastatic (Stage III) disease (Figure 1). In 1892, Snow put forth the theory that melanoma spreads from its primary site in the skin via the lymphatic vasculature to a draining nodal basin. In 1874, Sappey published a detailed description of the lymphatic vascular anatomy. The expectation that metastatic melanoma cells will follow an orderly progression of spread via lymphatics, and that these lymphatic channels can be accurately predicted, led to the practice of prophylactic dissection of suspected nodal basins to detect occult disease. It was hoped that occult metastatic disease could not only be detected, but that a surgical cure might be achieved. In practice, this procedure is the elective lymph node dissection (ELND).

With elective lymph node dissection (ELND), primary cutaneous melanomas that are considered of sufficiently high enough risk are evaluated for occult nodal spread via prophylactic dissection of the suspected draining nodal basin. While intended to both detect and possibly cure occult metastatic disease, analyses of ELND demonstrate a survival benefit only in selected patient populations -- specifically, males aged 60 years or less with primary melanoma tumor thicknesses of 1.1mm to 2mm. The remainder of patients is subjected to significant morbidity, such as chronic lymph edema, without a demonstrable survival benefit. In addition, ELND...
is not suitable for the evaluation of melanomas that are located in areas of ambiguous or multiple draining patterns such as the head and neck, lymphatic drainage may be multi-directional.

'Sentinel node' and sentinel lymph node biopsy

The sentinel node is described as the first node to receive lymphatic drainage, and thus tumor emboli, from the primary tumor site. Studies have shown the presence or absence of metastatic tumor cells within this sentinel node to be indicative of the status of the remainder of the basin's nodes.

Early research in lymphatic mapping for solid tumors was carried out for penile carcinomas by Cabanas. Later studies, however, failed to show improved survival. The procedure of choice for malignant melanoma, meanwhile, remained ELND. Investigation of the sentinel lymph node in relation to malignant melanoma was introduced by Morton et al. in 1992. Initial studies by Morton et al. using vital blue dye demonstrated an accuracy rate of 82% in identifying the sentinel lymph node. With the later addition of radiocolloid and lymphoscintigraphy, nodal identification rates as high as 99% accuracy were obtained.

Sentinel node biopsy versus elective lymph node dissection

SLNBx provides a number of advantages over ELND. Since SLNBx allows for identification of specific draining (sentinel) nodes, much less-invasive surgery is required, with completion of dissection only occurring if metastases are found on histologic evaluation. SLNBx also has the advantage of identifying drainage patterns in ambiguous or so-called "watershed" areas of the body. Early descriptions of these areas of ambiguous drainage include Sappey's line and the midline (Figure 2). The limited predictability of lymphatic drainage leads to limitations regarding when and where the ELND is the appropriate procedure. Studies of lymphatic mapping, however, have demonstrated even more variability in lymphatic drainage than early lymphatic diagrams would suggest. The watershed areas of lymphatic drainage have been shown to be unpredictable to as far as 10 cm away from the traditional Sappey's and midline areas (Figure 3).

Through intraoperative lymphatic mapping, the lymphatic drainage pattern of melanomas can now be traced even within these ambiguous areas. There is improved accuracy in defining and evaluating the most likely involved lymph node(s) (i.e. the sentinel node). A completion of nodal dissection is only performed for the approximately 20% of cases where metastatic involvement is detected. The remaining ~80%, meanwhile, will have undergone a much less invasive procedure with minimal morbidity.

Criteria

Criteria for SLNBx vary among different institutions. In general, SLNBx is offered for patients with a melanoma primary tumor >1mm in Breslow thickness, or less than 1mm if there is involvement of Clark level IV or V (i.e. reticular dermal or subcutaneous involvement) or tumor ulceration. Some institutions will also include features such as high mitotic rate, vertical growth phase, and vascular involvement in their inclusion criteria. Tumors with undetermined Breslow thickness due to extensive regression or involvement of the deep tumor margin may also be considered for SLNBx.

The 2007 NCCN (National Comprehensive Cancer Network) recommends the discussion of lymphatic mapping and SLNBx in patients with melanomas >1mm Breslow thickness or in patients with lesions <1mm Breslow thickness but with other adverse histologic findings such as Clark level IV or V, ulceration, or high mitotic rate.

Procedure

Once the initial diagnosis of malignant melanoma is made, our role as dermatologists becomes more limited in scope. By the above criteria, our role for the treatment of melanoma would be limited to a wide re-excision of primary tumors that are less than 1mm Breslow thickness and lacking in adverse histologic features such as ulceration, Clark level IV or V, deep margin involvement, and extensive regression. Beyond this, the surgical treatment of the melanoma falls under the purview of surgeons and nuclear medicine physicians.

There are a number of in-depth articles detailing the technique(s) for SLNBx. This section will summarize the key steps of the procedure (Figure 4).

Lymphoscintigraphy

At present, there is no FDA-approved radiocolloid for use in SLNBx. In the United States, Technetium-sulfur colloid (Tc-sulfur colloid) is generally the radiocolloid of choice. It has a particle size that varies from 50nm to 2,000nm (mean: 300nm). Some authors advocate 0.2μm filtration prior to injection, which decreases particle size to below 200nm.

Injection of the radiocolloid is performed preoperatively. Injections are performed intradermally to ensure entry into the draining lymphatic channels. A 25- to 27-gauge needle is used to inject small volumes (0.05 to 0.2mL) in the immediate vicinity of melanoma tumor (if present) or narrow excision scar. Enough radiocolloid is injected to raise a small wheal at the site. The number and exact location of the injections depend on the location of the tumor.

Once the radiocolloid is injected, dynamic and static images are taken via a high-resolution gamma camera (Figures 5 and 6). Dynamic images are taken over 20 to 30 minutes to demonstrate path of lymphatic drainage and receiving nodal basin. This is very useful in areas of ambiguous drainage, as discussed earlier, in which the lymphatics may drain to totally unexpected sites. It is also useful for detecting
drainage to so-called in-transit or interval lymph nodes, nodes that exist outside of regional basins. Static images are also taken of all possible draining basins to detect possible radiotracer deposits. Once the draining nodal basins have been identified on lymphoscintigraphy, surface markings are made on the patient’s skin, tracing the lymphatic drainage route(s) to the receiving basin(s). These act as anatomic guides to help guide the surgeon.

As demonstrated earlier, nodal drainage may be ambiguous, with multiple or unusual sites of drainage. A number of studies have been performed, investigating the possible discrepancies between the expected sites of lymphatic drainage and sites of actual involvement. Discordant findings are most often observed in the head/neck region as well as on the trunk. Doris et al. noted that 43% of preoperative head/neck lymphoscintigraphy identified a sentinel node in a basin not clinically predicted. Leong et al. identified, though in some cases, two or more sentinel lymph nodes are revealed. The surgeon may also remove incidental lymph nodes that are encountered during the dissection of the sentinel node. These “non-sentinel” nodes are also examined for tumor involvement.

**Histopathologic examination**

Different sectioning techniques are used in different centers. In their multi-center trial, Morton et al. standardized the sectioning technique in the participating MSLT centers. Their technique advocates first bisecting the lymph node in the longest dimension. Following fixation, 10 serial sections are obtained. Sections 1, 3, 5, and possibly section 10 are stained with hematoxylin–eosin (H&E). Section 2 is stained with S-100 protein, and section 4 is stained with HMB-45 antigen. Sections 6 and 7 are used as negative controls for immunoperoxidase studies, while sections 8 and 9 are kept in reserve for possible additional staining.

Histopathologic evaluation of the resected lymph nodes is performed with routine H&E staining as well as immunohistochemical staining with HMB-45 antigen and S-100 protein. H&E staining has a detection sensitivity of one melanoma cell per 10,000 background cells, while S-100 protein has been shown to detect one melanoma cell per 100,000 background cells. Immunohistochemistry techniques improve detection over routine H&E staining, but they have also led to some controversy. In some cases, H&E staining will be negative, while immunohisto staining may be positive. This raises the question of what to do with a patient who is H&E negative and S-100 positive. Some centers consider this to be a positive SLNBx, while others do not.

Some centers also perform RT-PCR analysis for detection of so-called “submicroscopic” metastases. RT-PCR is not, however, widely in use.

**Further treatment decisions**

This section discusses the steps required following the SLNBx (Figure 7).

Once a patient is found to have microscopic nodal metastases, the next step is the complete dissection of the involved nodal basin. The intent of complete lymphadenectomy is to determine whether there may be further metastatic nodal involvement and to possibly affect a surgical cure (i.e. no evidence of further metastatic disease). In the majority of cases (~80%), no further nodal involvement is discovered, while the remaining 20% will have one or more additional nodes with metastatic foci.

The patient will also require evaluation for possible distant metastatic involvement (i.e. Stage IV disease). Different centers may have their own protocols for a metastatic work-up, but should include imaging studies such as CT scans of the chest, abdomen, and pelvis, an MRI scan of the brain, liver ultrasonography, and a whole body PET scan or the new CT-PET scan. Each modality has its advantages and idiosyncrasies, which are beyond the scope of this article. Laboratory evaluation includes liver function studies and LDH, as well as a complete blood count. Confirmed findings, indicating distant metastatic disease, changes the treatment options for the patient yet again.

If the metastatic work-up proves negative, however, the patient may be considered for stage III (nodal) disease protocols. The only FDA-approved treatment for stage III disease is interferon α2b therapy for one year. There are also experimental treatment protocols in multiple centers around the country. A list of nearly 200 experimental trials, their locations, and inclusion criteria are listed on the National Cancer Institute (NCI) Web site: http://www.cancer.gov/clinicaltrials.

Should the SLNBx findings demonstrate no microscopic metastatic involvement, the patient will be considered as having only local involvement (Stages I and II), with adequate treatment and requiring no
further surgery. These patients will require regular follow-up and observation to detect future recurrences of melanoma. In a review of 1,019 patients undergoing axillary or inguinal lymphadenectomy for melanoma, 80% of recurrences occur within two years of surgery. Late recurrences of disease, however, may occur years later. For this reason, most centers and physicians have observation protocols that start with frequent, regular follow-up examinations (every three to four months) and annual studies such as a chest X-ray and laboratory tests. Over the next several years, the follow-up visits are spaced farther apart (every six months to one year). All melanoma patients should, however, be seen on an annual basis for the rest of their lives. This is not only for the detection of recurrent and metastatic disease, but also to detect future additional primary melanomas.

### Questions and Controversies

SLNBx has become widely available and is the de facto modality of choice for the evaluation of possible microscopic nodal metastatic disease. Nevertheless, SLNBx remains a topic of intense controversy. Opponents to SLNBx have voiced objection to subjecting patients to a surgical procedure that has not, to date, demonstrated a benefit to overall patient survival. Likewise, the literature (as well as any large discussion among dermatologists) is replete with anecdotal accounts of patients who underwent SLNBx only to suffer melanoma recurrence and death. This controversy is, of course, more than a subject of statistical debate. As dermatologists, we are the physicians most likely to diagnose our patients’ melanoma and are likewise the ones who will have to break the news of their diagnosis. As the bearer of these tidings, we will be expected to explain the diagnosis and advise our patients on what they should do next. It is this advice that brings the controversy over SLNBx into sharp perspective.

This section will attempt to address the outstanding questions that both the patient and dermatologist may have:

**What is the likelihood of the SLNBx being positive?**

- A number of studies, both single and multi-institution, have been performed with varied database sizes and results. In the largest recent multi-institutional study (Multicenter Selective Lymphadenopathy Trial, or MSLT), sentinel node positivity was found to be 19.4% with the initial SLNBx for melanomas of 1.2mm to 3.5mm thickness. Other studies have noted similar percentages. Rousseau et al. stratified 1,375 SLNBx patients according to the 2002 AJCC staging system. They found that 16.9% of patients had positive SLNBx results. They further stratified these positive findings according to 2002 AJCC staging (Table 1).

**What are the risks or side effects (i.e. morbidity) associated with SLNBx?**

- The reported rate of sequelae from SLNBx is significantly lower than the older ELND procedure. Sequelae include reactions to vital blue dye (as previously mentioned), lymphedema, seroma, nerve injury, wound infection, and wound dehiscence. Morton et al. examined the rate operative morbidity with SLNBx versus SLNBx plus completion of lymph node dissection. The overall rate of morbidity in 937 SLNBx patients was 10.2%. A stratification of these complications is listed below (Table 2).

**What is the chance of the test being wrong and missing the melanoma?**

- False negative findings, as demonstrated by recurrence of metastases in the SLNBx-negative nodal basin, have been noted in various studies. The rate of false negative cases was also evaluated by Morton et al. in the MSLT-1 trial. They found 59 cases of regional nodal recurrence out of 944 SLNBx-negative patients, meaning a total rate of 6.3%. Eighty-one percent of these recurrences (48 patients) occurred in the sentinel node draining basin, while the remaining 11 patients had recurrences in nodal basins that had not been sampled.

- Explanations for this false-negative phenomenon are varied. One possible explanation is related to the injection process. When the radiocolloid (and possibly vital blue dye) is injected at the primary melanoma site, care must be taken to ensure that the injectant is placed in the correct area to be picked up by the
correct draining lymphatic channels. This procedure, obviously, is operator dependent, requiring the requisite experience. In the MSLT trial, Morton et al. noted a learning curve of 30 training cases before operators were considered proficient at performing SLNBx. As a practical matter for us, the referring dermatologists, we should be sure that the prospective surgeon has experience (>30 cases) with malignant melanoma.

- Proper placement of radiocolloid and vital blue dye is also affected by the condition of the primary site. If the tumor is still present, or if there has been only minimal surgical alterations of the site, the lymphatic vasculature is less likely to have been altered. If, however, a wide local excision with or without tissue transfer, such as a flap, has been performed, the lymphatics may be altered to the point that the dye may no longer be reliable for locating the “true” sentinel lymph node. As such, it behooves us, the dermatologists, to perform the minimal amount of surgery required to diagnose the melanoma without significant tissue alteration.

- Assuming the proper node(s) are dissected, there remains the possibility for metastases to be missed. In a perfect world, pathologists would serially section and review the entire sentinel node specimen. This is, however, impractical if not impossible. Sectioning and staining techniques have been discussed previously. Even with such dramatic sensitivities, it is still possible to simply “miss” the section of the node that has the few metastatic cells, thus leading to a falsely negative report.

- Finally, the question of “hematogenous spread” is often raised. If metastatic cells are able to penetrate lymphatic vasculature, then why might they not also be able to enter the capillary vasculature with direct access to distant sites? Early studies evaluating the spread of melanoma have consistently demonstrated a predilection for a stepwise spread from the primary cutaneous site to regional lymph nodes, and then to distant sites. Cases of distant spread without demonstrable nodal involvement certainly occur, but only rarely. In a study of 243 SLNBx-negative patients with recurrence of their melanomas, nine patients (3.7%) developed distant metastases as their first site of recurrence. One proposed explanation for this is that shielding forces related to entry and exit from the blood vasculature destroys metastatic cells before they have the chance to take hold.

What is the prognostic significance of SLNBx?

- This is perhaps the most contentious issue concerning SLNBx. A number of institutions have examined the impact of SLNBx on disease-free survival, disease-specific survival, and of course overall survival. Findings in some institutions have shown a positive prognostic impact, while others have not.

- Morton et al. recently published the third of five interim analyses for the MSLT. This multi-institution, international trial examined 1,269 patients with melanomas of 1.2mm to 3.5mm Breslow thickness. Patients were randomly assigned to either a wide excision and sentinel node biopsy arm (60%) or wide excision and nodal observation arm (40%). Patients of the sentinel node arm with positive SLNBx underwent immediate complete lymphadenectomy (CLND). Patients of the observation arm underwent CLND only if clinically palpable nodes were noted on follow-up examination. Findings in this interim analysis noted a five-year disease-free survival of 78.3 ± 1.6% for the SLNBx arm versus 73.1 ± 2.1% for the observation arm (95% CI, P = 0.0009). Overall survival between the two study arms was not statistically significant. One possible explanation for this finding, described by Balch, is the “dilutional” effect of the 84% of patients who never had nodal metastatic involvement, making it problematic to demonstrate an overall survival advantage in the remaining 16% of patients with nodal metastases. In the patient subset with nodal metastatic involvement, the sentinel node arm, with confirmed nodal metastasis and immediate CLND, had a significantly higher survival rate (72.3 ± 4.6%) than those of the observation arm with delayed CLND (52.4 ± 5.9%). The survival tumor may be related to amount of nodal tumor burden of each subgroup. In the SLNBx arm, the average burden was 1.4 lymph nodes versus 3.4 lymph nodes in the observation arm. These findings are in keeping with survival statistics demonstrated by Balch et al. for the 2002 AJCC staging criteria, in which there was a significant survival decline in patients with an increased number of involved nodes or with macroscopic (i.e. clinical) nodal metastases.

- The MSLT II trial is currently underway. The primary outcome measure for the trial is melanoma-specific survival, defined as the time between the date of randomization (or date of CLDN for subjects in the CLDN arm) and the date of death from melanoma. The follow-up period extends to 10 years or the date of the subject’s death. Secondary outcome measures are disease-free survival and recurrence during the 10-year follow-up period. Inclusion and exclusion criteria, as well as participating centers, are listed on the National Institutes of Health Web site: http://www.clinicaltrials.gov/show/NCT00297895. It is hoped that this trial may finally answer the outstanding question of whether SLNBx has a positive prognostic impact.

Conclusion

It has been repeatedly demonstrated that SLNBx is a reproducibly accurate modality for identifying microscopic nodal metastatic melanoma. It is a procedure with a low incidence of morbidity, yet it offers a statistically significant survival advantage to those patients for whom it really matters: patients with nodal metastatic involvement. Nevertheless, the debate over SLNBx will, no doubt, continue. It is hoped that this article will help to clarify the issues surrounding SLNBx and help us, the dermatologists, to educate our patients so they can make truly informed decisions in their treatment.

References:


Introduction

The perforating disorders are a heterogeneous group of cutaneous dermatoses that share the transepithelial elimination of a dermal product. These disorders have been classically categorized into four distinct entities: Kyrle’s disease (KD), perforating folliculitis (PF), reactive perforating collagenosis (RPC), and elastosis perforans serpiginosa (EPS). This classification system, though, is not without flaws. Specifically, Kyrle’s disease, perforating folliculitis and acquired RPC show overlapping clinical and histologic features as well as treatment options. To address this issue, the term acquired perforating dermatosis (APD) was suggested in the early 1990s.

The goal of this manuscript is to provide a review of the perforating disorders, including a brief historical review, epidemiology, clinical presentation, histopathologic features and current treatment options. Other cutaneous disorders that may show transepithelial elimination of dermal products will also be reviewed.

Acquired Perforating Dermatosis

History

The term acquired perforating dermatosis (APD) was coined in 1989 to describe the findings previously seen in PF, KD and the acquired version of RPC. All of these entities show similar clinical responses, respond to similar treatment options, and the perforation (penetration) of follicular and peri-follicular inflammation, and the perforation (penetration) of a dermal substance. In 1968, Mehrregan and Coskey described PF, distinguishing it from KD by the follicular unit being the primary focus of inflammation and perforation. To muddy the waters even further, another entity, called acquired reactive perforating collagenosis (ARPC), was suggested by Faver et al. in the JAAD in 1994 with a diagnostic criteria of: 1) eliminated necrotic collagen through a cup-shaped epidermis on histology; 2) umbilicated papules or nodules with a central keratotic plug clinically; and 3) age of onset after 18 years. Since the naming of these entities, multiple authors have concluded that each of these diseases most likely represents a variation of a similar causative event and thus should all fall under the designation of APD.

Epidemiology/Etiology

APD is not an uncommon disorder. It is typically seen in middle-aged individuals, with no gender or racial predominance. APD is not a primary disorder, but instead is seen in association with a systemic disease or prior pruritic cutaneous eruption. The most common association is with patients with diabetes mellitus and/or chronic renal failure. Approximately 10% of patients on hemodialysis for chronic renal failure are affected. Other associations include sclerosing cholangitis and other hepatic diseases including hepatocellular carcinoma and hepatitis C, as well as HIV, hyperthyroidism, hyperparathyroidism, healed lesions of herpes zoster, post laser hair removal, Hodgkin's disease, IgA nephropathy, pulmonary fibrosis, myelodysplastic syndrome, cutaneous CMV infection and scabies. The underlying etiology of this disease is still unknown. Possible reasons why lesions occur include: a reaction from chronic pruritus/scratching, dermal microangiopathy from diabetes leading to necrosis, abnormal action of fibronectin within the dermis, increased levels of matrix metalloproteinases, immature keratinization, accumulation of advanced glycosylation end products in the dermis from elevated blood glucose levels, or the over-expression of TGF-β3.

Clinical Presentation

Lesions of APD present as 2mm-8mm hyperkeratotic papules with a central, cone-shaped plug. The lower extremities are the most common site of involvement, followed by the upper extremities, trunk, head and neck. The mucosal surfaces, palms and soles are typically spared. The lesions can occur as a group of single follicular or extra-follicular papules/nodules or can coalesce into verrucous-appearing plaques. Pruritus is variable, although excoriations are commonly appreciated, and the Koebner effect can be seen.

Histopathology

The classic finding is a keratotic plug, with the apical portion of the plug pointing toward the dermis, imbedded in a cup-shaped epidermal invagination. The keratotic plug contains parakeratosis and variable cellular debris, and occasionally includes degenerated collagen and elastin fibers. The presence of collagen and elastin fibers within the plug is not a diagnostic criterion for APD, as most lesions do not show evidence of elimination of this material. The presence of this material in the proper clinical context should not dissuade the clinician in making the diagnosis of APD.

A mixed inflammatory infiltrate of lymphocytes, neutrophils and foreign body giant cells are seen at the base of the disruption. If follicular structures are involved, the disruption normally occurs at the infundibulum, and a coiled hair is often seen. Dyskeratotic keratinocytes and vacuolization of the basal layer around the epidermal invagination can occur.

Treatment

Treatment for APD is frustrating for the patient and for the physician. Topical therapies such as ultra potent corticos-
teroids, the “soak and smear” method with mid-potency ointments, retinoids and bland emollients are first-line treatments, but they rarely control all but the mildest forms of disease. Systemic options are varied, with no one treatment considered effective in all patients. Oral antihistamines, oral retinoids, PUVA and thioldiome have shown some success. A small study by Ohe et al. showed near complete clearing of all lesions in five patients after 10-15 treatments with NB-UVB at a starting dose of 400mJ/cm² and a maximum dose of 1500mJ/cm².²² Another option is allopurinol at a dose of 100mg daily, which has shown, in multiple separate case studies, marked improvement in lesions within two weeks.²³,³⁴ Doxycycline, at a dose of 100mg daily for 14 days, was shown in a case study by Brinkmeier et al. to stop formation of new lesions within five days and to affect complete clearance of lesions by five months with the addition of a urea-based cream.²⁵ In patients with end-stage renal disease, skin lesions have cleared post renal transplant.² In summary, only small case reports exist that show agents beneficial in the treatment of this disease.

**Reactive Perforating Collagenosis**

**History**

Mehregan et al. first described RPC in their article in the Archives of Dermatology in 1967.²⁶ Some authors divide RPC into a rare genodermatosis with childhood onset and a more common acquired form in adults associated with renal disease and diabetes. As previously discussed, the acquired form “fits” better under the label of APD, and therefore the term RPC should refer to the childhood-onset disease.

**Epidemiology/Etiology**

RPC is a rare genetic disorder that has shown autosomal-dominant, autosomal-recessive and sporadic modes of inheritance.²⁷ Onset of disease is in early childhood, often before the age of five, and males and females are equally affected. Systemic disease is not known to be associated with the skin lesions, although a case report of RPC in a child with the Treacher Collins syndrome was noted.²⁸ One thought on the etiology of this disease is that it is a reaction to superficial trauma to the skin, as lesions often appear in cold weather, after an insect bite or in areas of folliculitis.²⁷ Herzinger et al. suggest an alternate theory involving antibodies to type IV collagen, as shown via immunohistochemical staining in their study with two patients diagnosed with RPC.²¹

**Clinical Presentation**

The lesions of RPC present as small, 1mm-10mm flesh-colored papules with a central umbilication and a keratin plug. The most frequent sites of involvement are areas of high incidence of trauma: dorsal hands, forearms, elbows and knees. Lesions classically occur after a superficial injury to the skin and then resolve spontaneously within six to eight weeks, leaving behind a hypopigmented scar. Koebnerization of lesions can be observed, although pruritus is often not present.²²

**Histopathology**

Histopathology reveals a cup-shaped depression in an acanthotic epidermis, filled with parakeratotic debris, degenerated collagen and inflammatory cells, similar to APD. What differentiates RPC from APD is the presence of a thinned, disrupted epidermis underlying the depression with thin, vertically oriented streaks of basophilic collagen streaming into the depression.²⁵ These vertically oriented collagen fibers are essential in making an RPC diagnosis.

**Treatment**

Treatment options for RPC and APD are quite similar. For most cases of RPC, the lesions are transient and asymptomatic and may not require treatment at all. In more resistant cases, topical retinoids have shown some success.

**Elastosis Perforans Serpiginosa**

**History**

EPS was first described in 1953 by Lutz, who dubbed the entity keratosis follicularis serpiginosa due to its clinical appearance.²⁹ In 1955, Meischer identified elastin fibers penetrating into the epidermis along with other degenerated dermal material in these lesions, and suggested the name elastoma intrapapillare perforans verruciforme.³⁰ Since then, the name has been abbreviated to its current form.

**Epidemiology/Etiology**

Young adults are the most common portion of the population to be affected, with a male-to-female ratio of 4:1. The etiology is unknown, but an autosomal-dominant mode of inheritance has been suggested by one author.³¹ Fujimoto et al., in the British Journal of Dermatology in 2002, described a defect in the 67 kD elastin receptor that could result in the clinical findings.³² As with the other perforating diseases, the role of focal irritation of the skin cannot be discounted.

EPS has been divided into three general categories. Type 1 EPS is the idiopathic type, with no associated systemic disease. Type 2 is referred to as reactive EPS, with associated connective-tissue disease. These associated diseases include: Down syndrome (the most frequently associated disease, with 1% of these patients showing EPS lesions), Ehlers-Danlos, osteogenesis imperfecta, Marfan’s, Rothmund-Thompson, acrokeria, systemic sclerosis, morphea, XYY karyotype, renal disease, diabetes mellitus and cutis laxa.²⁶,³⁷,³⁸ The final category is type 3, which is associated with penicillamine use for the treatment of Wilson’s disease, cystinuria or juvenile rheumatoid arthritis.³⁹

**Clinical Presentation**

Typically, EPS presents as 2mm-5mm, flesh-colored-to-red papules with a central invagination, arranged in an arcuate-to-serpiginous manner and located on one region of the body. The most common location is the nape of the neck, followed by the face, upper extremities, lower extremities and, rarely, the trunk. Lesions are often asymptomatic and run a variable course, lasting anywhere from six months to five years and often resolving spontaneously with scarring.³¹

**Histopathology**

The epidermis in EPD is acanthotic with hyperkeratosis. A central, narrow channel can be seen coursing through the epidermis in a follicular or parafollicular location, giving a funnel or corkscrew-like appearance. Parakeratosis, degenerated keratinocytes, inflammatory cells and, most important, elastic fibers are found within this channel. Chronic inflammation is seen at the base of the perforation with the presence of multinucleated giant cells, and increased amounts of elastic fibers within the papillary dermis are seen with elastic stains.³¹

**Treatment**

Treatment options for EPS are varied. Topical medications include potent corticosteroids, calcipotriene ointment, and glycolic and salicylic acids.³¹ A case report by Kelly and Purcell showed complete clearing of a chin lesion with daily use of imiquimod for six weeks and then three times weekly for four weeks.³² Another case study of two patients with EPS showed moderate improvement with nightly use of tazarotene 0.1% gel for eight weeks, although the disease relapsed
shortly after discontinuing the medicine. Systemic treatments with oral isotretinoin and narrow-band UVB have shown some success. Destructive methods include cryotherapy, cellophane tape stripping, electrodermosis and curettage and laser therapy. The flashlamp pulsed dye laser seems to be the most effective laser modality, according to two studies, while the Erbium:YAG and pulsed CO2 lasers have shown minimal benefit.

An important part of treating patients with EPS is to recognize the possible association of a coexistent systemic disease. Vearrier et al. performed a survey of pediatric dermatologists in order to determine the prevalence of systemic disease among patients with lesions of EPS. The results of the study indicate that the history and physical exam of the entire patient should guide the clinician on whether further workup, i.e. imaging or blood work, should be obtained. The routine ordering of lab tests in patients with EPS and no other stigmata is not warranted.

**Other Perforating Dermatoses**

There are myriad dermatologic entities that on histology may show evidence of transepidermal elimination of a dermal product. One of the better documented conditions is periumbilical perforating pseudoxanthoma elasticum. This is an entity usually seen in multiparous, middle-aged, obese females, and it presents with hyperpigmented, firm papules surrounding the umbilicus. Microscopically, the elimination of calcified elastic fibers is seen.

Various other case reports exist for commonly seen dermatologic disorders that show perforation on histology. Some of these entities include granuloma annulare, lichen nitidus, morphea, pilartrichomatosis, chondrodystrophic nodularis chronica helicis and perforating verruciform collagenoma.

**Conclusion**

In conclusion, the three primary perforating disorders have been discussed in detail. Making sense of this often-confusing topic will enable the clinician to render a correct diagnosis, giving the patient an accurate prognosis and provide rational treatment options for these often difficult-to-treat entities.

**References**

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TREATMENT OF LYMPHANGIOMA CIRCUMSCRIPTUM WITH IMIQUIMOD 5% CREAM

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ABSTRACT

Lymphangiomas are common benign vascular tumors often found in children. The treatment of choice for lymphangiomas has traditionally been complete surgical excision. However, incomplete resections are frequent, with a high rate of recurrence. Several nonsurgical interventions have been proposed, all with unsatisfactory results. In this case, we sought to examine the role for imiquimod (AldaraTM) in the treatment of lymphangioma circumscriptum. Imiquimod 5% cream was prescribed nightly, as a therapeutic trial, due to its ability to induce antiangiogenic cytokines. Resolution of superficial vesicles was noted, but more studies need to be done to investigate the role for imiquimod in the treatment of lymphangiomas.

Introduction

Lymphangiomas, resulting from an abnormal proliferation of lymphatic vessels involving the skin and subcutaneous tissues, are common benign vascular tumors in children. The term “lymphangioma” is used when lymphatics are distended to tumor-like proportions, and “lymphangioma circumscriptum” (LC) for lymphatic malformations that are localized to an area of skin, subcutaneous tissue or even muscle. LC may present at any age, but is usually noted at birth or appears during childhood. Common sites include the axillary folds, shoulders, flanks, proximal extremities and perineum. LC manifests with fluid-filled vesicles, which are mostly translucent but may vary in color from red to blue-black. Vesicles are well defined, discrete or grouped, resembling frogspawn. The treatment of choice for lymphangiomas has traditionally been complete surgical excision to ensure removal of the superficial as well the deep components. However, incomplete resections are frequent, with a high rate of recurrence. Several nonsurgical interventions have been proposed, such as electrocautery, carbon-dioxide laser ablation, superficial X-ray therapy, cryotherapy, and injection sclerotherapy, all with unsatisfactory results. In this case, we sought to examine the role for imiquimod (AldaraTM) in the treatment of lymphangioma circumscriptum. Imiquimod 5% cream did reduce the number and size of superficial lesions and may require more treatments when compared to treatment with cryotherapy. Side effects included local pain and irritation immediately after treatment with cryotherapy. Imiquimod cream was tolerated well, with no side effects reported.

Materials and Methods

Imiquimod 5% cream was applied topically, at night, to the right side of the skin lesion. Cryotherapy using liquid nitrogen (temperature -196°C) was used on the left side of the skin lesion. The patient was evaluated at baseline, at weeks six and 12. She used imiquimod 5% cream for a total of 12 weeks, had three cryotherapy treatments (baseline, six, and 12 weeks), and was then lost to follow-up. Physical examination was performed by the dermatology residents and attending faculty, and pictures were taken at each visit to assess improvement and resolution of skin lesions.

Results

Topical application of imiquimod cream nightly for six weeks resulted in minimal improvement of skin lesions when compared to baseline evaluation, and initial treatment with cryotherapy caused only mild erythema with no resolution of superficial vesicles. At 12 weeks, a reduction in the number of superficial vesicles and erythematous macules were observed at the imiquimod treatment site, while slightly atrophic, erythematous and hyperpigmented macules were observed at the cryotherapy treatment site. Standard treatment with cryotherapy did provide superior results when compared to treatment with imiquimod. However, imiquimod did reduce the number and size of superficial lesions and may require more treatments when compared to treatment with cryotherapy. Side effects included local pain and irritation immediately after treatment with cryotherapy. Imiquimod cream was tolerated well, with no side effects reported.

Discussion

Lymphatic malformations are due to a hyperproliferation of the lymphatic vessels. Lymphangiomas constitute approximately 4% of all vascular tumors and approximately 26% of all benign vascular tumors in children. Lymphangiomas can occur anywhere in the skin and the mucous membranes. They may be localized or generalized, and the most common sites are the head and
the neck, followed by the proximal extremities, the buttocks, and the trunk. These tumors rarely regress spontaneously, and if untreated they persist and often expand.\(^1\)

For the treatment of lymphangioma circumscriptum, the main indications are usually cosmetic but can also be to control complications such as infection, hemorrhage, and pain. The only cure is to remove the superficial component as well as the deeper lymphatic cisterns through surgical destruction or laser ablation of lesions. All other treatments are palliative to control symptoms. Electrocautery, cryotherapy, carbon-dioxide laser, and sclerotherapy can also be used to reduce the risk of infection and to reduce lymphorrhea.\(^10\)

Imiquimod (imidazoquinoline 5%) is a topical immune-response-modifier agent that inhibits angiogenesis. Previous studies have shown imiquimod to be a strong inhibitor of tumor-cell-induced angiogenesis through the production of a wide range of immunomodulatory and antiangiogenic cytokines.\(^11,12\) Additionally, imiquimod down-regulates several pro-angiogenic factors, increases endogenous angiogenesis inhibitors, and induces endothelial apoptosis.\(^12\) Imiquimod specifically induces interferons (IFN) $\alpha$, $\beta$, and $\gamma$, which inhibit angiogenesis independently of their immunomodulatory functions.\(^3,11,12\) Imiquimod is used clinically for its antiangiogenesis activity to treat and regress vascular proliferative lesions such as hemangiomas of infancy, pyogenic granuloma, hemangiosarcoma, and Kaposi’s sarcoma.\(^12\) Since lymphangiomas are due to hyperproliferation of lymphatic vessels, imiquimod may promise a non-invasive treatment option for the condition.

References:
CUTANEOUS METASTASIS OF ADENOCARCINOMA

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ABSTRACT

Cutaneous metastases of adenocarcinoma are rare at the time of diagnosis. These cancers carry a significant prognostic importance. Diagnosis of these tumors should be made before the patient presents. Clinical suspicion for these tumors should be high, opposite squamous-cell carcinomas. Clinical presentations vary greatly but usually present as a painless, firm, skin-colored pink papule or nodule. The peak incidence is in patients in the fifth to seventh decades of life. The site of cutaneous metastasis depends on the source of the primary cancer. When cutaneous metastases are present at the time of diagnosis, the patient’s outcome is much grimmer. The average patient survives only three months after the diagnosis is made. This study describes a case of cutaneous metastasis, likely from a bronchoalveolar primary malignancy.

Introduction

Skin metastases of internal malignancies are rare at the time of diagnosis. These cancers carry a significant prognostic importance. Because of the varied presentation of these tumors, they must be diagnosed histologically. Clinical suspicions for these tumors are low, and they are usually thought to be basal-cell carcinomas as opposed to squamous-cell carcinomas. We observed this rare occurrence in a 68-year-old Caucasian male who presented with three cutaneous growths, lymphadenopathy, syncope, and malaise. The patient was referred by the primary care physician (PCP) to the dermatology clinic for evaluation.

Presentation of Case

A 68-year-old white male presented with "knots" on the back of his scalp. He was referred by his PCP to the dermatology clinic for evaluation of the suspicious areas. Three lesions had developed on his scalp within a few weeks of each other. The patient did not remember the exact onset, but thought the nodules occurred approximately four to six weeks prior to presentation to the dermatology clinic. The lesions were originally asymptomatic but then progressed and changed in their appearance. Upon presentation to the dermatology clinic, the lesions had recently become warm and started bleeding when palpated. The patient admitted to having scratched these areas at times. The lesions also bled when towel drying his hair.

The patient, two weeks prior to presentation at the dermatology clinic, had felt a "knot" on his left clavicle and went to see his PCP. The PCP asked the patient about the cutaneous lesions on his scalp and the enlarged supravacular lymph nodes. He referred the patient to the dermatology clinic and to an internal medicine clinic. Approximately two weeks after seeing his PCP, the patient noticed two more "knots" along the left side of his throat, which were tender to palpation. The internist ordered a chest X-ray, computed axial tomography (CT), and a positron emission tomography (PET) scan. The patient’s chest X-ray showed a lobular infiltrate in the mid left lung. The CT and PET scans were recommended, but the results were not obtained at the time of presentation to the dermatology clinic.

The patient had a family history of non-melanoma skin cancer and a brother who died of throat cancer. He also had a history of hypertension, hyperlipidemia, and stomach disease. He quit smoking tobacco in 1978; prior to that he had a history of 40 to 50 packs per year. The patient drank two alcoholic beverages per day. He was a divorced, retired construction worker who never wore a shirt, hat, or skin protection. Current medications included Accupril, Lipitor, Aciphex, fish oil, Bayer, garlic, niacin, and Centany (2% mupirocin ointment).

The patient had experienced a 3-pound weight loss over the previous two to three months, and he had chills and hot flashes periodically. He denied any chest pain, discomort or shortness of breath. His appetite and bowel and bladder functions were unchanged, although reports of a kidney stone were identified on the CT scan. The patient denied dysuria and hematuria. The patient denied an artificial heart valve, mitral valve prolapse, artificial joint replacement or past history of endocarditis.

On initial evaluation the patient was weak but in no acute distress. Three lesions were found on the scalp. They were erythematous-based papules with scale and crust. Site A was on the left occipital region of the scalp, measuring 0.8cm x 1.0cm (Fig. 1). Site B was located at the mid-occipital area, measuring 1.3cm x 1.3cm (Fig. 2). Site C was located in the mid-parietal area measuring 0.5cm x 0.4cm (Fig. 3). Hyperkeratotic scaly lesions, with erythematous bases consistent with...
malignant melanoma, metastatic carcinoma, dermatofibroma, dermatofibrosarcoma protuberans, cutaneous lymphoma, sarcoidosis, and foreign body granuloma. The etiology of the lymphadenopathy was unknown.

The treatment plan for the neoplasms of the skin was to be determined by shave biopsy of the three lesions on the scalp. The actinic keratoses were treated with liquid nitrogen. The patient was given information and was encouraged to use sunscreen and protective clothing. The patient was also advised to do self-exams from head to toe. The patient was to follow up with his primary care physician and internist for follow-up diagnostic, lab, and additional testing. The pathologist was consulted, and stains were ordered based upon her discretion.

The three lesions on the scalp were positive for CK7 and CK20. The CEA stain showed some background staining and positive-rimming tumor cells, but the tumor cells themselves were not positive. PSA and TTF1 stains were negative. The pathology report from all three lesions revealed nests of metastatic adenocarcinoma from an unknown origin (Fig. 4-6). Possible primary sites include gastric, pancreatic, urothelial and salivary gland.

The patient followed up with an oncologist. The CT scan showed mediastinal lymphadenopathy or a possible left perihilar mass. There were two well defined pleural-based lesions involving the superior left upper lobe. PET scan was recommended and revealed extensive subcutaneous metastatic nodules, hilar lymphadenopathy, and a large hepatic metastatic deposit. There were retroperitoneal, pericaval and periaortic lymph nodes, pelvic lymphadenopathy, and rib metastases. After the patient’s visit to the dermatology office, he progressively got weaker and experienced a greater decrease in appetite and weight loss and extreme right hip pain. The oncologist ordered a magnetic resonance imaging (MRI) of the brain as well as an X-ray of the right hip. He suggested starting the patient on chemotherapy for the metastatic disease. The therapy would most likely consist of Avastin, Taxol, and Carboplatin. Based upon the results of the X-ray, he would possibly add radiation therapy. The patient was unable to decide whether he wanted therapy. He passed away before starting any of the treatment options.

Discussion

Cutaneous metastases are a rare phenomenon that occurs in approximately 0.7% to 10% of internal malignancies. Carcinoma can spread through vascular or lymphatic embolization, contiguous spread, or direct implantation through surgical procedures. Cutaneous metastases most commonly occur with breast cancer in women and lung cancer in men, followed by melanoma. They can occur at anytime of life, but the greatest incidence is the fifth through the seventh decades.

Tumors most likely to metastasize to the scalp are from the breast, lung, stomach, pancreas, and kidneys. The tumors usually appear as firm, asymptomatic, erythematous, skin-colored nodules, but they have been known to appear in many different manners. At the time of diagnosis of internal cancers, only 1.3% of patients have a skin metastasis present. Diagnosis with cutaneous metastases leads to a much bleaker outcome. Reingold reported that his patients only survived an average of three months after the development of cutaneous metastasis.

Immunohistochemistry can be used to help differentiate between carcinomas from different origins. Cytokeratin 7 is found in tumors of the lung, ovary, endometrium, and breast, but not in tumors of the gastrointestinal tract. Cytokeratin 20 is detected in 68% of the gastrointestinal tumors, but in none of the metastatic lung carcinomas. Thyroid transcription factor 1 (TTF-1) is typically positive for lung and thyroid cancers. PSA is positive in prostatic pathology. A positive CK20+/CK7+ and TTF-1 have been reported in colorectal adenocarcinoma and mucinous bronchoalveolar carcinoma. Given the lung mass found on chest X-ray and the immunohistochemistry of the biopsy specimens, our patient most likely had a rare mucinous bronchoalveolar carcinoma with subsequent cutaneous metastasis to the scalp.

Skin metastases are rare and can be very difficult to diagnose. Histological evaluation is very important in determining the diagnosis and treatment. Diagnosing skin metastasis as early as possible is crucial to the treatment and overall outcome of an internal malignancy.

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