Journal of the
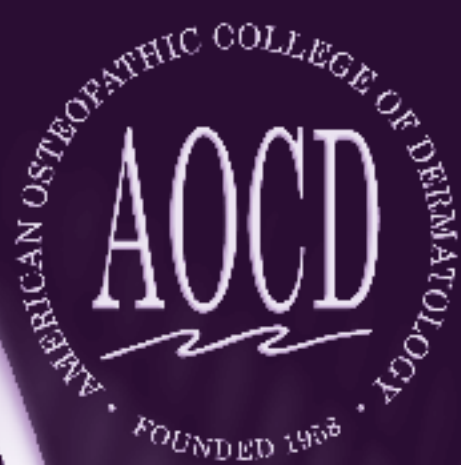# American Osteopathic College of Dermatology

Journal of the American Osteopathic College of Dermatology

Editors
Jay S. Gottlieb, DO
Jon Keeling, DO

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LETTER FROM THE EXECUTIVE DIRECTOR OF THE AOCD

MARSHA WISE

The Board of Trustees and staff of the AOCD would like to thank all of our members for the support given to the AOCD and the JAOCD over the years.

Change is never easy, nor is it inevitable. As the AOCD continues to grow, we must make changes to accommodate that growth. I would like to take this opportunity to update everyone on a few changes that have taken place and future changes that will be taking place in the AOCD office.

In December 2010, long time Executive Director, Becky Mansfield retired from her position and I was named Executive Director in January 2011.

Beginning May 2011, our Division of Corporate Membership will move to our National Office in Kirksville, Missouri. This move will enable us to serve our sponsors better by streamlining resources and communications. This move marks the end of Shirley Gottlieb's term as the Director of Corporate Development. The AOCD is grateful for the work Mrs. Gottlieb has done for the AOCD these past five years and we wish her well in her future endeavors.

Our recent Midyear Meeting in Marco Island, Fla., was a success. It was good to see and meet many of you. Several surveys were handed out asking for your input regarding the College, and how the AOCD can better meet your needs. Regarding members' needs, respondents said they would like to have more communication with the BOT and more industry support at the meetings, among other requests.

Recently the AOCD underwent the mandatory AOA accreditation document survey on our April 2010 Midyear meeting held in Sedona, AZ. I am pleased to inform our membership that we scored 100% on that survey, and have been awarded a continuing 3 year accreditation as a CME Sponsor.

Evidenced based needs assessments is a major requirement of our CME programs and in March of 2010, the AOA distributed a memo to all CME sponsors listing approved sources on where to find the data needed to complete these needs assessments. One source listed was the Journal of the American Osteopathic College of Dermatology! Your support and contributions to this journal are greatly appreciated!

Residents are welcome to submit their yearly papers to the JAOCD. Please remember to have your Program Director review this very important requirement before submitting it.

Plans are being finalized for our upcoming Annual meeting in Orlando. I hope you will all be able to attend. We will again present all physician awards, including the Koprince Award and the Intendis Paper Award to the winners at the AOCD's Annual Business Meeting on Monday, October 31, 2011 from 3pm to 5pm in Orlando.

During the AOA's March 2011 meeting of the PTRC and COPT, I became aware of their "ART" theme:

❖ Accountability
❖ Reliability
❖ Transparency

It is my intention to begin implementing this theme in the AOCD.

I look forward to continuing my work with the AOCD. Coming from a family filled with educators, I feel that maintaining the integrity of our Residency Programs and providing quality CME programs for our members is a priority and is vital to the future of the AOCD.

The AOCD is your organization! Please let the National Office know what we can do to improve communications to you. I welcome your comments and suggestions.

Letter From The Editors
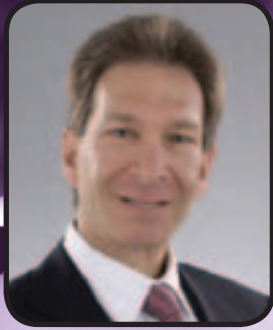
Jay Gottlieb, DO,
FAOCD Senior Editor

Jon Keeling, DO,
FAOCD Editor

Help the JAOCD to grow...

With the summer just about to begin, it is time to take an active role in educating our patients in the importance of sun avoidance and to renew our commitment to our communities to help reduce the incidence of both skin cancer and photo damage.

Recently the FDA has listed tanning beds as 'toxic" and has categorized them in a similar way to cigarette smoking. The tanning bed industry has accused dermatologists of having a vested interest in this campaign. How ridiculous is that? The tanning bed industry is a financial annuity to us! If we were to promote their industry that would be self serving. We must make that point abundantly clear to our patients. We need to step up and let our patients know that we are their advocates. The insurance companies now hire employees and give them the title of "patient advocate." If they are the patient's advocates, what does that make us? As members of the AOCD we need to make sure that our patients know we have their best interests in mind. When our patients truly realize this, they become loyal patients and ambassadors of our practices.

As we train our residents in the field of dermatology, it is incumbent upon us to always let the residents know that patients need to feel and understand that as osteopathic dermatologists, we put our patients' health first.

You will see our new editorial page and notice that we have over 50 Associate Editors on the JAOCD editorial staff. We would like to thank all of them for their commitment to the JAOCD. Julia Layton, the JAOCD copy editor, has done an outstanding job in putting her first issue of the JAOCD together. She has taken each manuscript from the point of submission, through proof reading and correspondence with authors to working with the publisher. We are very fortunate to have her on our staff.

We extend our thanks to all of the members of the AOCD who help improve the quality of the JAOCD.

A special Thank You is in order to **Global Pathology, Galderma Pharmaceuticals, Medicis-The Dermatology Company, Ranbaxy Pharmaceuticals** and to our newest sponsor - **Intendis** for their sponsorship of the JAOCD. The JAOCD would remain just an idea and a dream if we did not have their support.

Sincerely,

Jay Gottlieb, DO. FAOCD
Editor-in-Chief

Jon Keeling, DO, FAOCD
Co-Editor

Letter from the President
of the AOCD

Leslie (Kramer, DO, FAOCD)

It was great to see those of you who attended our midyear meeting at Marco Island. The program was better than promised, thanks to Dr. Neubarers hard work. The luau on the beach was great fun, the food delicious and plentiful. I look forward to seeing all of you in Orlando at our annual meeting in October 2011. What better place to spend Halloween than the Orlando/Disney area. It will be a great time for attendees of all ages.

Our college is definitely going thru some growing pains. As our membership grows, so does the need for regulations/ requirements to be in place and followed.   We need to keep things lucid and transparent in both our meetings and medical practices. Inferences and assumptions cause confusion.   As early as medical school we were told " if its not documented in the chart....it didn't happen". In these litigious times being concise and specific in all our dealings can only help. We are a group of well trained professional dermatologists who work hard. We want both our medical practices and college to be beyond reproach. We come from all different races, religions, and preferences to join together to continue to work to make the AOCD the best it can be.

I had the pleasure of attending DO Day on Capitol Hill for the first time. It was an unexpected enlightening and enjoyable experience. Most all of our Osteopathic Colleges were represented by an impressive group of students. Several specialty colleges were also represented by their presidents or executive directors. The breakfast briefing session was given by our AOA president; Dr. Karen Nichols, and Executive Director John Crosby to name a few. Key "talking points" involved health issues of concern to DO's to be discussed with members of congress and their staff. Each attendee was given a list with specific appointment times to meet with members of Congress and their staff from your registered voting area (zipcode). Meeting with senators, congressman, and their staff individually or in small groups (10 or less) made this experience well worth the time spent. I recommend it highly to each and everyone of you. The AOA organizes this yearly.

I ask you all as members of our college to step forward and go the "extra mile". The AOCD has come thru for all of us to enable us the professions and lifestyles we've worked hard to obtain. We must continue to keep enhancing and improving the college as times and technologies change and as our membership grows.

Thank you

Leslie Kramer, DO, FAOCD
President, AOCD 2010-2011

CALCINOSIS CUTIS: A CASE REPORT AND REVIEW

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ABSTRACT

Calcinosis cutis describes a set of disorders defined by cutaneous calcium deposits. Although generally a benign process, lesions may be painful and may also restrict joint mobility if juxtraarticular. Calcinosis cutis usually presents as firm, gritty white papules, plaques, or nodules which may ulcerate and cause secondary infection. Various forms of calcinosis cutis exist. Proper workup is necessary to find the underlying medical etiology.

Case Presentation

We present a case of calcinosis cutis in a 36-year-old Hispanic male. The patient presented with an enlarging calcific mass in the lower back with multiple draining sinuses, for which he had to keep the area covered with several pads daily. The patient had been on hemodialysis for the past 17 years. He has severe renal osteodystrophy and secondary hyperparathyroidism. The patient is a truck driver, and was complaining of the inability to lean back in his seat due to the large mass. Physical examination showed a calcific mass 15 cm in diameter, protruding approximately 5 cm, with multiple draining sinuses exposing subcutaneous calcium deposits. Upon palpation, the adjacent subcutaneous fat was indurated 5 cm beyond the mass itself circumferentially.

Histologic sections revealed calcified nodule consistent with calcified hemangioma and no evidence of malignancy. Radiologic examination with CT showed sheet-like calcification throughout the subcutaneous soft tissues, with a large calcific mass located posterior to the lumbar spine from the L3 through L5 vertebral bodies.

Due to the purulent drainage from multiple ulcerations in the large calcific mass and the patient's discomfort, a radical excision of the mass was recommended. This procedure included excision of the subcutaneous calcifications and closure with latissimus advancement flaps and skin grafts.

Discussion

Calcinosis cutis (CC) is an uncommon disorder. It is characterized by the deposition of insoluble compounds of hydroxyapatite crystals and calcium phosphates in the skin due to local or systemic factors. Originally described by Virchow in 1855, calcinosis cutis is now classified into four major types: dystrophic, metastatic, iatrogenic and idiopathic.[1] The pathogenesis of calcinosis cutis varies depending on the subtype of the calcinosis.

Dystrophic calcification tends to exhibit calcium deposits in areas where the skin is damaged due to underlying disease, pre-existing lesions, or trauma. In this subtype, there is an absence of metabolic disturbances in calcium regulation. Generally, this form is associated with inflamed or necrotic skin. One hypothesis is that inflammation and injury may cause tissue necrosis that results in alkaline-phosphatase release from lysosomes. This alkaline phosphate in turn acts on organic phosphate that normally inhibits crystal formation, and therefore leads to the precipitation of calcium.[2,3] Dystrophic CC may be localized or generalized. Examples of localized dystrophic CC include acne scars, basal cell carcinoma, pilomatricoma, and epidermal cysts. Examples of generalized tissue damage that may lead to widespread dystrophic CC include connective-tissue diseases including dermatomyositis, lupus erythematosus, and systemic scleroderma. Calcification is found three times more often in juvenile dermatomyositis than in the adult form, and is observed in 40-70 percent of patients.[4] Other, less common examples of generalized dystrophic CC include subcutaneous fat necrosis of the newborn, pancreatic panniculitis, pseudoxanthoma elasticum, and Ehlers-Danlos syndrome.[5]

In contrast to dystrophic calcification, metastatic calcification presents in settings of systemic disturbance of calcium and phosphate homeostasis. Metastatic calcinosis cutis characteristically occurs with widespread calcium deposition, with frequent large deposits around large joints such as the knees, elbows, and shoulders bilaterally.[6] Visceral calcium deposition seen in lungs, kidneys, and blood vessels actually occurs more frequently than cutaneous calcium deposition. Metastatic CC is typically associated with hypercalcemia and/or hyperphosphatemia. Primary and secondary hyperparathyroidism should be differentiated. Primary hyperparathyroidism is due to hyperplastic parathyroid glands. Secondary hyperparathyroidism results in response to hypocalcemia, which may have numerous etiologies, most commonly chronic renal failure.[7,8] Hyperphosphatemia is also commonly associated with chronic renal failure, usually due to decreased renal clearance. Secondary hyperparathyroidism with hypercalcemia subsequently results, playing an important role in the pathogenesis of calcinosis.[9] Elevated serum 1,25-dihydroxycholecalciferol level, due to either excessive intake or sarcoidosis, will also cause hypercalcemia. Hypercalcemia may also be due to malignancy, either from bone metastases or due to paraneoplastic hypercalcemia from production of abnormal hormone.

Calciphylaxis is an ominous clinical finding associated with metastatic calcinosis cutis. This complication usually presents in end-stage renal disease with secondary hyperparathyroidism. Calcification occurs in the intima of the blood vessels and subcutaneous tissue, leading to microthrombi formation, subsequent cessation of blood supply, non-healing necrotic ulcers, and gangrene. Although uncommon, calciphylaxis has also been reported in primary hyperparathyroidism, hypercalcemia of malignancy, and end-stage liver disease.[10]

Idiopathic calcinosis cutis presents in the absence of any known tissue injury or systemic metabolic defect.[11] Subtypes include milia-like idiopathic calcinosis cutis, tumoral calcinosis and subepidermal calcified nodule. Milia-like calcinosis has been reported in association with Down syndrome. Lesions usually are multiple and present on the trunk, limbs and face.[12,13] In a study by Gimenez et al., it was suggested that idiopathic calcinosis cutis lesions could be early findings of connective-tissue disorders.[14] Additionally, Wananukul et al. reported cases of calcinosis cutis occurring years prior to the clinical manifestations of juvenile dermatomyositis.[15] Tumoral calcinosis is an uncommon familial disorder that is associated with hyperphosphatemia.[16] Calcium and crystals are deposited near large joints, presenting as calcified soft-tissue masses most commonly in the hips, shoulders, elbows, feet and buttocks. Although a definite etiology has not been determined, renal failure, genetic disorders and recurrent microtrauma to soft tissue have been reported as various causes.[17] The subepidermal calcified nodule typically affects children, occasionally occurring at birth, and presents most commonly on the face. Clinically, it usually presents as a solitary, white-yellowish papule, but multiple lesions may occur.[18]

Finally, iatrogenic calcinosis cutis is a form of calcification that occurs as a result of a treatment or procedure. Etiologies include parenteral administration of calcium and/or phosphate, repeated heel stick of infants, and tumor lysis syndrome.

Iatrogenic calcinosis cutis may have a multifactorial pathogenesis contributing to the initiation of this disorder, including temporary elevated levels of serum or tissue calcium, local tissue damage resulting from phlebitis, recurrent attempts in peripheral line insertion, and extravasation of solution into the surrounding tissue.[19] Intravenous administration of calcium or phosphate, such as calcium gluconate or calcium chloride, may cause precipitation of calcium salts and lead to calcification.[20] Other agents reported to cause soft-tissue calcifications include quinine, vasopressin tannate, epinephrine, prednisolone, sodium phosphate, prochlorperazine maleate, streptomycin sulfate, amphotericin, sodium bicarbonate, calcium chloride, lead acetate, and vitamin D.[21] Cases have also been reported in low-birth-weight babies in the intensive care unit who have had multiple heel pricks. Tumor lysis syndrome may also lead to a subtype of iatrogenic CC. Tumor lysis syndrome causes hyperkalemia, hyperphosphatemia, hyperuricemia and resultant secondary hypocalcemia due to the rapid production of uric acid. This condition may potentially lead to acute renal failure and multi-organ dysfunction and can be fatal.[22] Parenteral calcium is often required to treat the hypocalcemia, which increases the risk of tissue calcification and consequently calcinosis cutis.

Radiological exam may be used to exhibit the extent of tissue calcification. Non-visceral soft-tissue calcification can further be evaluated by a more sensitive test using bone scintigraphy with radiolabeled phosphate compounds (technetium Tc 99m methylene diphosphonate).[23] Visceral and non-visceral calcification can be evaluated by CT scan.

Medical management of calcinosis cutis has varying benefit. The use of diltiazem has the believed therapeutic effect of antagonizing the calcium sodium ion pump, but it has produced less than ideal results.[24] Other medical treatments that have exhibited some benefits for some individuals include probenecid, colchicine, and warfarin.[25] Additionally, bisphosphates may reduce bone resorption and inhibit the growth of ectopic hydroxyapatite crystals by reducing further calcium deposition.[26]

Indications for surgical removal of such lesions include functional impairment, infection, ulceration and pain. Recurrence is common following excision, and surgical trauma may exacerbate calcification; therefore, it has been recommended to treat a test site prior to having the patient undergo a large excision.

Conclusion

Calcinosis cutis is generally a benign process, but it may lead to numerous complications, such pain, ulceration, infection, and functional impairments. These cutaneous calcium deposits may have various underlying medical etiologies and can present differently depending on the cause. Proper workup of these lesions is necessary to correctly manage patients with this presentation, often requiring a multidisciplinary team of physicians.

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Table 1

Calcinosis Cutis Subtypes	
Dystrophic	Calcium deposits in areas of damaged skin due to underlying disease, pre-existing lesions, or a site of trauma
Metastatic	Systemic disturbance of calcium and phosphate homeostasis with widespread calcium deposition
Idiopathic	Calcification that occurs in the absence of any known tissue injury or systemic metabolic defect
Iatrogenic	Calcification that occurs as a result of treatment or procedure

Table 2

Causes of Hypercalcemia

PTH-mediated
Primary hyperparathyroidism (sporadic)
Familial
MEN-I and –IIa
FHH
Tertiary hyperparathyroidism (acute renal failure)
PTH-independent
Hypercalcemia of malignancy
PTHrP
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Medications
Thiazide diuretics
Lithium
Teriparatide
Excessive Vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk alkali syndrome

MEN: multiple endocrine neoplasia; FHH: familial hypocalciuric hyper-calcemia; PTHrP: parathyroid hormone-related peptide.
Adapted from: Khairallah W, Fawaz A, Brown EM, and El-Hajj Fuleihan G. Hypercalcemia and diabetes insipidus in a patient previously treated with lithium. Nat Clin Pract Nephrol 2007; 3:397.
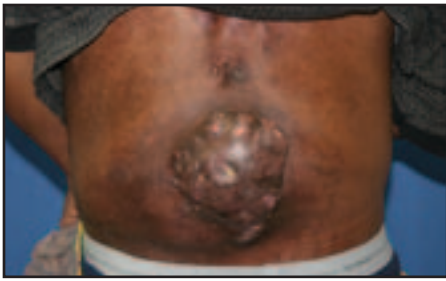
Enlarging calcific mass 15 cm in diameter on the lower back
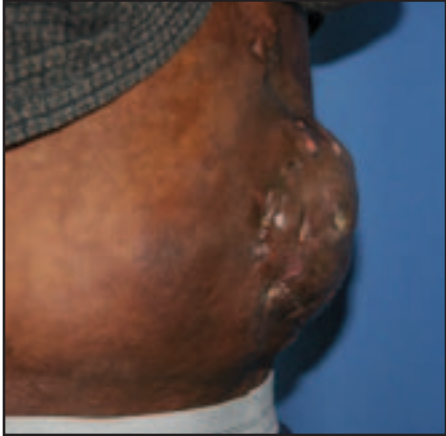
Calcific mass protruding 5 cm with multiple draining sinuses

Radical excision of mass including subcutaneous calcifications

Closure with latissimus advancement flaps and skin grafts

Eccrine Spiradenoma: Not Just Another Painful Nodule

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ABSTRACT

Eccrine spiradenoma is not a clinically distinctive lesion and a biopsy is required for diagnosis. Most examples are either tender or painful. It presents as a usually solitary, intradermal, circumscribed, round or oval, firm nodule. Multiple lesions may be associated with trichoepitheliomas and cylindromas and likely represent a spectrum of the Brooke-Spiegler syndrome. We present a case of a solitary eccrine spiradenoma in a 37 year-old Hispanic female, along with a review of the pathophysiology, immunohistochemistry and histopathology of this adnexal tumor. A review of the literature of the mechanism behind the extremely rare cases of malignant and metastatic transformations is also discussed.

Introduction

Eccrine spiradenomas are rare, benign adnexal tumors of the eccrine sweat glands with a slow growth pattern, first described in 1956 by Kersting and Helwig.[1] Although extremely rare, preexisting eccrine spiradenomas may potentially undergo malignant transformation into malignant eccrine spiradenomas (MES), as first reported by Dabska in 1972.[2] Malignant eccrine spiradenomas may also arise de novo and have a rate of >50 percent metastasis in reported cases, with high resultant mortality rates.[3]

Case Presentation

A 37-year-old Hispanic female presented to our clinic with a one-year history of a painful lesion on the upper back. The patient denied any history of trauma, change in coloration or bleeding. She reported that the lesion had enlarged slightly over the past six months. Physical exam revealed a 1.0 cm x 0.6 cm, hyperpigmented, slightly firm, poorly circumscribed dermal nodule on the mid-upper back (Fig. 1, 2).

A 2 mm punch biopsy was taken from the mid-upper back. Histological examination revealed discrete tumor lobules located in the subcutaneous fat (Fig 3). Cells with round, hyperchromatic nuclei and minimal cytoplasm were found at the periphery of the lobules, whereas centrally, the cells were larger, with oval or vesicular nuclei, containing a small eosinophilic nucleolus and a pale-staining eosinophilic cytoplasm. Ductal differentiation was also present (Fig. 4, 5). Based on the characteristic histopathology, a diagnosis of a solitary, benign eccrine spiradenoma was confidently rendered.

Discussion

Eccrine spiradenomas are usually solitary nodules but may present as multiple lesions in a linear or grouped pattern or a zosteriform distribution.[4,5,6] They have a slow growth rate and a long clinical history. Eccrine spiradenomas generally manifest as pink, purple, gray or blue nodules, generally in younger patients, often presenting with excessive tenderness or pain on palpation.[7] Spiradenomas range in size from 0.2 to 5 cm, with most about 1 cm in diameter.[8] Most commonly, these lesions develop in the upper torso, but they also have been reported on the scalp, shoulder and face.[9] Additionally, about five cases have been reported on the eyelid, and there has been one case on the proximal portion of the nail fold.[10,11,12] Eccrine spiradenomas are typically covered by normal or blue epidermis and arise mostly in young adults ranging from 20 to 40 years of age, affecting men and women equally.[9,13] Although very rare, occurring in <1% of reported cases, eccrine spiradenomas have also been reported in infancy, but those differ in clinical presentation from traditional spiradenomas by the presence of superficial dermal nodules.[14]

Eccrine spiradenocarcinoma (malignant eccrine spiradenoma) is an extremely rare neoplasm, and fewer than 60 examples have been documented in the English literature. It presents at an average age of 59 years, ranging from 21 to 92 years, and, similar to its benign counterpart, does not show gender predilection.[15] Analysis of MES anatomical distribution in previously reported cases demonstrates tumors preferentially arising on the trunk and extremities, with an average size of 3.9 cm at presentation.[16] The clinical appearance is not distinctive, diagnosis being dependent upon the recognition of a preexistent counterpart.[15] In a study of 12 MES cases by Granter et al., lesions occurred most commonly on the trunk, followed by the extremities and the head and neck, with an average size of 7.5 cm in diameter. Lesions had been present from seven months to 30 years prior to surgical removal.[17] Clinical features of MES in reported literature typically demonstrate sudden growth in a tumor that has been present for many years or even decades, with a stable lesion of more than two years duration occurring in 87.5% of patients and of more than 12 years duration in 66.7% of patients.[3] Other presenting features include a change in color, bleeding and ulceration.[15] Patients may seek medical attention as the previously stable lesion rapidly enlarges, changes color, or ulcerates.[16] Although less common, de novo malignant spiradenomas have been reported and may arise without a preexisting benign counterpart.[18] Malignant eccrine spiradenomas have the potential of recurring following excision and have a risk of metastasis. Tay et al. reported a 57% local recurrence and 39% metastasis and related death.[19] MES most commonly metastasizes to regional lymph nodes, followed by the lungs, brain and liver.[16] Chou et al. reported a case of a 50-year-old male with a 30-year history of asymptomatic, enlarging nodules over the lateral thigh, which transformed into malignant eccrine spiradenoma and metastasized to the lungs bilaterally.[20] Rare cases of MES of the breast and vulva have also been reported.[21,22] MES is considered an aggressive tumor with a reported mortality rate between 20% and 39%.[23,24] Accurate prognostic data are, however, difficult to obtain in such a rare entity.[15]

Pathophysiology

Various etiologies have been postulated for the development of eccrine spiradenomas. Brooke-Spiegler syndrome (BSS), also known as multiple familial trichoepithelioma, is a rare, autosomal-dominant inherited disorder that affects the folliculosebaceous apocrine unit. It is characterized by multiple adnexal cutaneous tumors arising from eccrine and apocrine glands, such as spiradenomas, cylindromas and trichoepitheliomas.[25] Reported cases of Brooke-Spiegler syndrome demonstrate spiradenomas directly adjacent to trichoepitheliomas and in association with follicles, indicating that spiradenomas are apocrine neoplasms because of the embryonic relationship between apocrine glands and follicles.[26] The tumors associated with BSS typically present in early adulthood, typically between 10 and 20 years of age, with multiple flesh-colored papules that may be dense and disfiguring, generally limited to the face and scalp.[27,28] Genetic studies have demonstrated that the defective gene is the CYLD gene, a tumor-suppressor gene on chromosome 16q12-13.[29,30] The

estimated penetrance of the gene has been reported to be between 60% and 100%.[31] The CYLD gene generally suppresses tumor necrosis factor-α (TNF-α) pathway, which leads to an increased expression of nuclear factor-κβ (NF-κβ), resulting in apoptotic resistance and formation of tumors of the folliculosebaceous-apocrine units (Fig. 6).[32,93]

Malignant eccrine spiradenomas have demonstrated over-expression of p53 protein in association with malignant transformation.[23] Biernat et al. demonstrated the overexpression of p53 in the carcinomatous component of different cases of MES, where p53 did not exhibit any positive staining in typical benign eccrine spiradenomas or in the benign areas of the malignant tumors.[32] Therefore, p53 has a substantial role in the transformation from benign to malignant eccrine spiradenomas. Over-expression of Ki67 protein has also been associated with malignant transformation.[33]

Histopathology

Eccrine spiradenoma's histological findings classically demonstrate sharply demarcated nodules of basaloid cells in the dermis or subcutaneous tissue, also described as "cannon balls" or "big blue balls" in the dermis, with no connection to the overlying epidermis.[34] Two types of epithelial cells comprise the multi-lobulated dermal and subcutaneous tumors and are arranged in cords and sheets with evidence of ductal differentiation. The center consists of larger cells with pale-staining eosinophilic nuclei, while the periphery is made up of smaller cells with hyperchromatic nuclei.[35,36] A characteristic histological finding is palisading tumor cells peripherally surrounding central blood vessels, consisting of perivascular spaces.[37] Occasionally, spiradenomas show focal cylindromatous features.[15]

Malignant eccrine spiradenomas commonly reveal areas of low-grade tumor imitating benign eccrine spiradenomas, heterogeneously comprised within sections of high-grade malignant cells. Malignant tumors characteristically feature atypical, large basaloid cells with numerous mitotic figures.[38] Additionally, MES consist of tumor cells with large hyperchromatic nuclei and may demonstrate invasion of surrounding connective tissue, squamous differentiation, and loss of basement membrane.[39]

Malignant transformation in spiradenoma can show two morphologically distinct patterns. The predominant pattern is that of an abrupt transition from a benign-appearing spiradenoma to carcinomatous or sarcomatous states. Carcinomatous change is seen in the form of adenocarcinoma, but squamous differentiation may also be seen. Sarcomatous differentiation may be noted in the form of a spindle cell, leiomyosarcomatous, osteosarcomatous, chondrosarcomatous, osteocartilaginous or rhabdomyoblastic component. A second pattern of MES is characterized by a histologically low-grade tumor in which the lobular architecture of a spiradenoma is observed and retained. These tumors do not show the dual cell population; they are only composed of mildly atypical basaloid cells showing increased mitotic activity.[15] Mitotic rates range from 4 to 32 per HPF (high-power field) in high-grade lesions and from 2 to 12 in low-grade lesions.[40]

Immunohistochemistry

Immunohistochemically, these tumors may demonstrate diverse expression of cytokeratins (CK7, CK8 and CK18), epithelial membrane antigen, carcinoembryonic antigen and S100 protein.[23,41,42,43] Various adnexal tumors, including eccrine spiradenomas, are positive also for DF3, indicating epithelial mucin production by these tumors.[44] Another monoclonal antibody, IKH-4, may be used in differentiating eccrine from apocrine neoplasms and eccrine carcinoma from metastatic adenocarcinoma. IKH-4 stains positive in eccrine spiradenoma because it stains the eccrine secretory coil but does not stain the apocrine secretory segment.[45] Over-expression of p53 has a substantial role in the transformation from benign to malignant eccrine spiradenomas.[23] Cases have demonstrated positive estrogen receptors, as well; therefore, estrogen-receptor status should be assessed for possible treatment options.[63]

Differential Diagnosis

One may remember painful tumors of the skin by using the mnemonic device "BANGLES." The differential diagnosis includes a blue rubber bleb nevus, angiolipoma, neuroma, glomus tumor, leiomyoma, or leiomyosarcoma and eccrine spiradenoma.

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS) is a syndrome that must be considered in the differential diagnosis for painful solitary nodules. BRBNS is a rare vascular anomaly syndrome, characterized by multiple venous malformations in association with visceral lesions, most commonly affecting the GI tract, although they may occur in any tissue.[46] Gascoyen in 1860 first described an association between cutaneous cavernous hemangiomas and similar lesions in the GI tract.[47] BRBNS has also been referred to as Bean syndrome, as in 1958 William Bean further elaborated the association between these skin lesions and the GI tract, and described the compressible characteristic of these cutaneous lesions that would be named blue rubber bleb nevi.[48]

BRBNS clinically may present as three different cutaneous lesions, all blue: soft, rubbery, blood-filled sacs that are easily compressible and refill once pressure is released; large, cavernous lesions that can compress adjacent structures; or irregular macules.[49] These lesions can be spontaneously painful or tender and may exhibit supralesional hyperhidrosis.[50] They are commonly located on the upper limbs, trunk and perineum, but may occur anywhere.[51] Furthermore, in contrast to the cutaneous lesions, intestinal angiomas characteristic of BRBNS commonly bleed, resulting in iron-deficiency anemia in these patients.[49] In addition to intramural hemorrhage, infarction, volvulus and intussusception may result from such lesions affecting the stomach, small bowel and colon.[52] Although rare, central nervous system involvement may occur in BRBNS, consisting of associated cerebral vascular malformations, such as hemangiomas or angiomas, which may correspond to cavernous malformations.[53,54,55] A case has also been reported of pulmonary hypertension, resulting from recurrent thromboembolic events from shunts in visceral lesions.[56] Reported cases have also involved the oronasopharynx, liver, spleen, heart, peritoneum, kidney, thyroid, parotid, skeletal muscle, bone, bladder, penis, vulva, and eyes.[49,57,58] Histopathological examination reveals tortuous, blood-filled ecstatic vessels, lined by a single layer of endothelial cells that are surrounded by a thin layer of connective tissue.[59]

Angiolipoma

Angiolipoma is another diagnosis that must be considered in the differential for painful solitary nodules. Angiolipomas are soft, subcutaneous nodules, which are rarely larger than 2 cm in diameter and are characteristically tender or painful.[60] Most commonly, these lesions are located on the forearm, trunk and upper arm, rarely occurring in the gastrointestinal tract. Clinically, angiolipomas are well-circumscribed and yellowish-white to grayish-purple in coloration, with varying amounts of surface erythema.[61]

Bowen in 1912 first described angiolipomas, and in 1960 Howard and Helig demonstrated the clinicopathologic features that differentiated angiolipomas from lipomas.[62,63] In 1974, Lin and Lin categorized angiolipomas into infiltrating and non-infiltrating groups based on their biologic behavior, as cases had been reported of these rare benign tumors invading skeletal muscle in a locally aggressive manner. Infiltrating angiolipomas are characteristically not encapsulated and typically occur in older patients, whereas non-infiltrating angiolipomas are encapsulated lesions limited to the subcutaneous tissue and are more common in younger patients.[64] Angiolipomas are slow-growing and histologically consist of mature adipose tissue admixed with a vascular component such as arteries, veins, sinusoids or capillaries.[65] Mitotic figures are infrequent, and malignant changes have not been identified.[64]

Neuroma

The differential diagnosis for a solitary, painful nodule also includes a neuroma. One form, traumatic neuroma, was first described by Odier in 1811 as a swelling or enlargement of the distal end of the proximal segment of the peripheral nerve that develops secondary to a partial or complete severance.[66] Proliferation and overgrowth of the nerve fibers in the severed ends of the peripheral nerves comprise these lesions, consisting of endoneural and perineural connective tissue, neurilemma

cells and regenerating neuraxes, but are not neoplastic in origin.[67] Therefore, microscopically, there is a proliferation of nerve fascicles immersed in collagen and scar tissue.[68] Typically following trauma, the proximal region attains a cap of fibroblasts that leads to scar formation, providing protection to the nerves, but also to a fibrosis that prevents further distal growth of the axons.[69] Clinically, traumatic neuroma presents as a firm, flesh-colored nodule, typically not exceeding 2 cm in diameter, which may be tender or painful to palpation, along with a history of trauma to the area, most commonly surgery. This tenderness may be attributed to the strangulation of proliferating nerves by scar tissue, local trauma or infection.[66,70]

Palisaded encapsulated neuroma (PEN), also referred to as solitary circumscribed neuroma, is another form of neuroma. PEN was first described in 1972 by Reed et al. as a benign, solitary, firm, skin-colored and dome-shaped papule that predominately presents on, but is not limited to, the face.[71] These lesions range in size from 2 to 6 mm and have a predilection for the mucocutaneous junctions of the face in adult patients. Histologically, PEN is an intradermal nodule that is solitary and well-circumscribed, partially encapsulated and composed of spindle cells grouped in fascicles.[72] In palisaded encapsulated neuromas, only the peripheral capsules contain perineural cells, unlike traumatic neuromas, which have these cells surrounding each fascicle. Numerous mast cells are also demonstrated, since they are tumors of neural origin.[69]

Glomus Tumor

Glomus tumors must also be considered in the differential diagnosis for solitary painful nodules. Glomus tumor (GT) is a rare, benign neoplasm consisting of cells that resemble modified smooth-muscle cells of the normal glomus body, which is a specialized form of arteriovenous anastomosis related to thermoregulation. The glomus body is located in the stratum reticularis of the dermis and is most commonly in the subungual region, lateral aspects of the digits, and the palm, which encompass the regions that GTs are most frequently encountered.[73] Masson, in 1924, first described the clinical presentation of glomus tumor as excruciating pain out of proportion to size, localized tenderness and cold sensitivity that subsided abruptly after tumor removal.[74] GTs typically are characterized by paroxysmal attacks of pain, often triggered by environmental stimuli such as touch, pressure and changes in temperature, especially cold exposure. This pain usually radiates away from the lesion.[75] Glomus tumors most commonly measure 5 mm to 2 cm in diameter, are characteristically reddish-purple in color and have a smooth, round-to-oval surface, compromising less than 2% of all soft-tissue tumors.[76,77] Most GTs are diagnosed between 20 and 40 years of age, and approximately 70% of solitary tumors occur by 30.[78] The malignant counterpart of GT is an extremely rare neoplasm with only a few reported cases, representing only an estimated 1% of glomus tumors. These malignant glomus tumors may arise from a previously benign GT, or may develop de novo.[77]

Histological examination of glomus tumors typically demonstrates lesions that are well-circumscribed, consisting of tight convolutes of capillary-sized vessels encompassed by glomus cells within a hyalinized or myxoid stroma that may display a highly vascular appearance.[73] Glomus cells intersperse the branching vascular channels lined by endothelial cells, and characteristically are uniformly round to ovoid, forming nests, sheets and trabeculae.[77] Glomus cells are regularly shaped with sharply rounded, punched-out nuclei with well-demarcated borders, which with periodic acid-Schiff (PAS) stain are accentuated.[79]

Leiomyoma

Finally, leiomyomas are also in the differential diagnosis for solitary painful nodules. Virchow first described leiomyomas in 1854, and in 1958 Kloepfer et al. first reported the hereditary form of leiomyomas, which causes multiple lesions.[80,81] Leiomyomas are benign, soft-tissue tumors that arise from smooth muscle and may originate from the arrector pili muscle of hair follicles (piloleiomyomas), tunica dartos of the scrotum, mammillary muscle of the nipple (genital leiomyomas), and the smooth muscles of blood vessels (angioleiomyoma). Leiomyomas clinically present as firm, skin-colored to brown papules and nodules, ranging in diameter from 3 mm to 13 mm. They may present as a solitary lesion or as multiple clustered lesions (piloleiomyomas), linear or segmental in a dermatologic distribution.[82,83]

Leiomyomas are most commonly found on the extremities, followed by the trunk and face.[82] Clinically, patients most commonly present with pain that is induced by cold, tactile or emotional stimuli. Some authors suggest this is due to local pressure by the tumor on neurofibrils or to the constriction of local vessels leading to ischemia.[84] An autosomal-dominant syndrome has been described in cases of early uterine leiomyomatosis and cutaneous leiomyomas, a condition known as Reed syndrome or multiple leiomyomatosis.[85] Renal-cell carcinoma has also been associated with the syndrome of hereditary leiomyomatosis due to the germline mutation in gene encoding of fumarate hydratase (FH).[86,87] Histopathology of leiomyomas demonstrates well-differentiated, interlacing bundles of smooth muscle fibers with nuclei that are elongated with blunted ends, appearing as cigar-shaped.[88]

Treatment

The treatment of choice for eccrine spiradenomas is complete resection, with recommended follow-up because of the potential for malignant transformation.[89]

Management of MES should include wide local excision with regional lymph node dissection, especially if metastasis is clinically suspected. Wide local excision with 1 cm to 3 cm margins and margin sampling has demonstrated most therapeutic in MES patients.[3] Recurrence of the lesion may occur, and MES has the potential to metastasize. Therefore, close follow-up is necessary. Radiation therapy has generally been proven unsuccessful in the management of MES, as sweat-gland tumors are typically radioresistant.[90] The chemotherapeutic agent tamoxifen has demonstrated symptomatic improvement and reduction of MES in estrogen-receptor-positive eccrine adenocarcinomas.[16,91]

Conclusion

In summary, malignant eccrine spiradenoma generally consists of a pre-existing benign eccrine spiradenoma and a transformed malignant component. However, MES may arise de novo and has the potential to metastasize, leading to high mortality rates. Clinically, eccrine spiradenomas commonly present as solitary, intradermal, well-circumscribed nodules, typically exhibiting excessive tenderness or pain to palpation. Painful solitary nodules are a challenging clinical presentation to diagnose and appropriately manage. A proper work-up and a complete differential diagnosis are important, as these lesions may have various etiologies with ranging severity. Blue rubber bleb nevus syndrome, angiolipoma, neuroma, glomus tumor and leiomyoma should be included in the clinicians' differential when managing patients with such clinical presentation.

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Figure 1

Figure 2
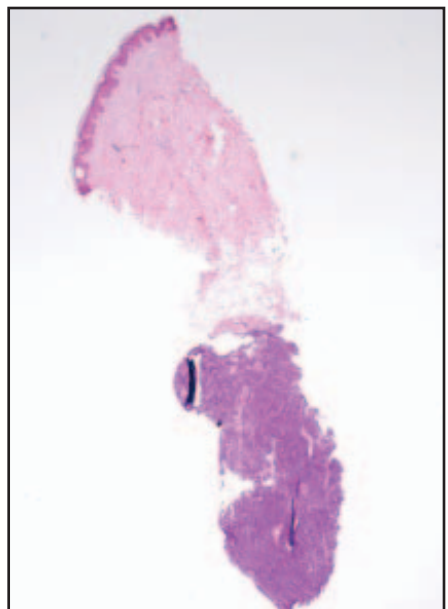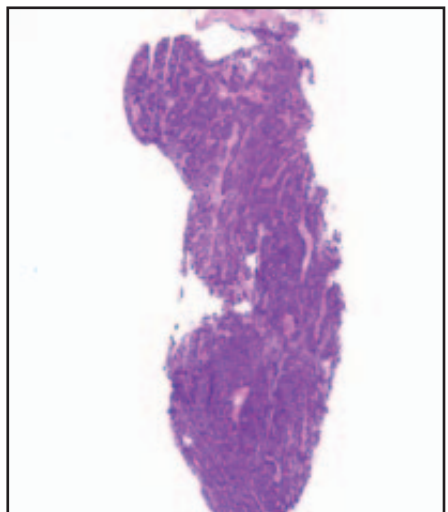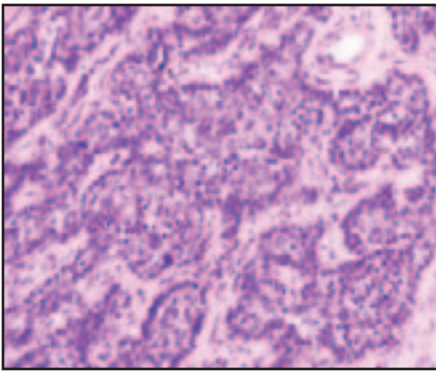
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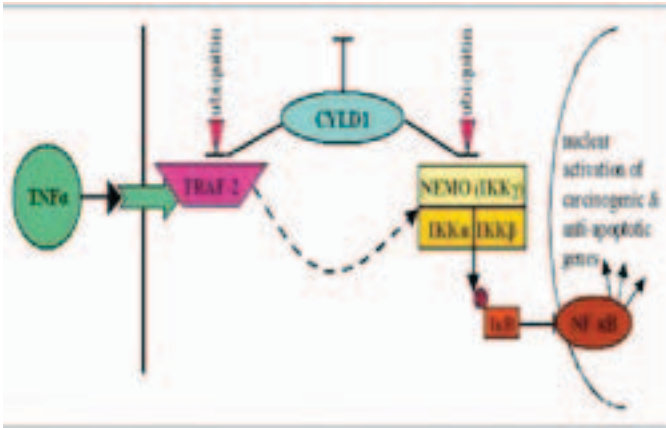
Figure 4

Figure 5

Figure 6
Interactions between CYLD, tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF-2) and NEMO [inhibitor κB (IKK)] in a part of the regulatory NF- κB signaling pathway.[93]

Goltz-syndrome Patient with Condyloma: Case Report and Review

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ABSTRACT

This is a case report of a 27-year-old female who was referred to the dermatology clinic for treatment of peri-oral and genital warts. On evaluation, the patient had multiple papules around her mouth as well as on her groin. Further history and physical found the patient to have features consistent with Goltz syndrome. Biopsies of representative lesions were taken. Pathology confirmed focal dermal hypoplasia, papillomas of the mouth, and condyloma of the genitals. Patents with Goltz syndrome commonly develop papillomas in the oral and genital region. These lesions are often confused with condyloma. Given the widespread lesions, our patient presents a diagnostic and treatment conundrum. We review the recent literature on Goltz and discuss the therapeutic challenge presented in our patient.

Patient History

We present a 27-year-old female referred to our dermatology clinic by her primary physician for warts of the mouth and genitals. Our patient reported lesions around her mouth present for approximately one year and lesions in her genital area for over three years. She reports no symptoms of her oral lesions, and describes itching and burning of the lesions in the genital area. The patient denies any history of STDs and was HIV-negative during her recent pregnancy. She is currently married and monogamous. Her husband was present and denied having any oral or genital lesions or history of STDs. The patient did report being rather promiscuous in her late teens and early twenties. Current medications include an OBC and ibuprofen prn.

On physical exam, the patient was noted to have two 4mm, flesh-colored, verrucous papules on the left commissure, with a few scattered 2mm pink papules periorally (Fig. 1A). There were many 2-8mm, flesh-colored, pedunculated and verrucous papules scattered bilaterally in the genital area and inner thighs (Fig. 1B). Further examination noted atrophic, telangiectatic plaques with soft, orange nodules in a Blaschko distribution on both the arms and legs (Fig. 2A). Both hands and feet were dysmorphic, showing syndactyly and oligodactyly (Fig. 2B).

When asked if she had ever been given a diagnosis of Goltz syndrome, the patient was unable to recall but remembered being told she had "some disorder" when she was young. Further questioning of family history was negative. The two larger papules on the mouth were biopsied, and two representative lesions in the groin, one from the thigh and one from the labia majora, were biopsied with a ddx of condyloma acuminata vs. benign papilloma. A punch biopsy was performed on the right arm to confirm dermal hypoplasia.

The slides were read by a dermatopathologist. The histopathology of the oral lesions showed acanthosis with fibrous submucosa, and no viral changes were noted (Fig. 3A). Both biopsies from the genital area showed acanthosis, hypergranulosis, and koilocytes without atypia, with a vascular-rich stroma and delicate collagen bundles (Fig. 3B). The punch biopsy confirmed dermal hypoplasia, with sparse collagen bundles and subcutaneous fat up near the epidermis (not shown). On return visit, the pathology results were discussed, and the areas were re-examined. Both lesions from the groin had pathology consistent with condyloma; however, given the various morphologic lesions present, we felt that not every lesion present in the groin was condyloma. Attempting to clinically distinguish all condyloma acuminata from Goltz papillomas would be difficult. We discussed this with the patient and considered treatment with imiquimod 5% cream as a first-line therapy. Unfortunately, given the large area needing treatment, her insurance coverage and her financial situation, it was economically unfeasible to attempt. We came to the general agreement to treat a handful of the genital lesions on that day's visit with podophyllin and LN2. The patient returned four weeks later with moderate improvement of the lesions treated. The patient was treated on this return visit and has subsequently been lost to follow-up.

Discussion

Goltz syndrome, or focal dermal hypoplasia, is a widespread dysplasia of mesodermal and ectodermal structures, with characteristic underdevelopment of the dermis.[10] The main feature is profound dysplasia of connective tissue, especially the skin and bones.[4-7]

There is a wide variety of physical findings in Goltz syndrome. Cutaneous manifestations of the disease are numerous and include linear, cribriform, or reticular areas of hypoplasia of the skin represented as striae distensae, verrucoid papillomas of the skin and mucous membranes, and soft, yellowish nodules representing the presence of fat in the dermis.[1] Other cutaneous manifestations include pink or red, angular, atrophic macules which may be raised or depressed, telangiectasias, and raspberry-like papules.[13] The raspberry-like papillomas can show up at any time in life and are commonly found at the junction of mucosa and skin, lips, vulval and perianal areas and around the eyes, but they can also be seen in other areas such as the ears, fingers and toes, groin, umbilicus, mouth, and esophagus.[3,13] Many of these cutaneous lesions will follow the lines of Blaschko. There has also been reported an early inflammatory vesicular eruption in some patients.[11] The hair may also be involved and is usually sparse and brittle. Nail dystrophy and anonychia are present when contiguous with linear skin lesions.[13]

Skeletal anomalies are also numerous, the most common being syndactyly. This usually involves the third and fourth fingers and often affects both the hands and the feet.[12] Polydactyly, adactyly, scoliosis, and hypoplasia of the distal extremities may also be found.[12] Approximately 80% of patients will have other skeletal anomalies, which may include dental defects such as dysplastic or absent teeth, enamel defects, and high-arched or cleft palates.[14] Facial asymmetry, reduced bone density or osteoporosis, and fibrous dysplasia of the bone may also be present.[2] Radiographic changes, osteopathia striata, may also be present and are characterized by the presence of asymptomatic, fine, linear densities parallel to the axis of the long bones, but they are not pathognomonic for Goltz syndrome.[6]

There are numerous other physical manifestations that are highly variable from patient to patient. Ocular involvement occurs 20% of the time and includes defects of the anterior chamber, coloboma of the iris, aniridia, choroidoretinal colobomata, microphthalmos, anophthalmos, asymmetry, and strabismus.[13] Renal involvement can present as horseshoe kidney or mild cystic dysplasia.[7] Multiple hernias have also been reported as complications including exomphalos, inguinal, and epigastric hernias. IQ is usually normal in these patients; however, in severe cases, microcephaly and mental retardation may be present.[13]

Goltz syndrome has a variety of histopathologic findings. A normal epidermis is usually found overlying a hypoplastic, collagen-scarce dermis.[14] The fatty herniations are consistent with the histologic findings of islands

of adipose tissue found in the superficial dermis, which impinges on the epidermis.[1] A narrow dermis is found along most of the dermal-epidermal junction and peri-appendageal areas; however, in areas with no dermis, ulceration presents, and the epidermis isn't able to survive.[14] Under electron microscopy, the dermis shows long, filamentous strands that are probably immature collagen.[15] It is postulated that collagen synthesis is occurring at a normal rate but is unable to form mature bundles.[13]

The genetic pattern for Goltz syndrome has been widely studied. The majority of cases have been in females, suggesting that there is an X-linked dominant inheritance pattern. This is consistent with male inheritors of the trait not being able to survive. Approximately 90 percent of cases have been female, with only approximately 30 male cases reported worldwide.[14] All of the male cases have been sporadic, without any male-to-male transmission.[6] New research has found a link to the PORCN gene, which is a regulator for Wnt signaling.[8,16]

Supportive therapy is the mainstay for treatment in Goltz syndrome. Reconstructive surgery is occasionally used. Cryotherapy has been studied for control of the papillomas associated with Goltz syndrome.[9] Most patients are able to live normal lives with a normal lifespan.

Conclusion

In conclusion, we present a 27-year-old female with an extremely rare genodermatosis, Goltz syndrome, who required treatment for an extremely common condition, genital warts. Unfortunately, our patient was eventually lost to follow-up. However, the lesions being treated were showing some response to our treatment of podophyllin and LN2. It would have been impractical and extremely painful to remove all the lesions in the groin at one time. It is difficult to assess without histologic confirmation whether all lesions we did treat were condyloma and not related to the patient's Goltz syndrome. The use of topical imiquimod 5% cream would have optimized our treatment of these lesions by "lighting up" those with viral infection. Given that the papillomas associated with Goltz syndrome can be easily confused for condyloma clinically, and that both lesions were present on this patient, we were challenged to identify and treat the patient's condyloma acuminata.

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Figure 1A

Figure 1B

Figure 1A: Perioral lesions, located primarily at the muco-cutaneous junction and along the mental crease.
Figure 1B: Lesions in the groin (note various morphologic types on thighs and labia).

Figure 2A

Figure 2B

Figure 2A: Blaschko distribution of soft, orange nodules. Similar lesions were noted on all extremities.
Figure 2B: Syndactyly of both feet, which was also seen on the hands.

Figure 3A

Figure 3B
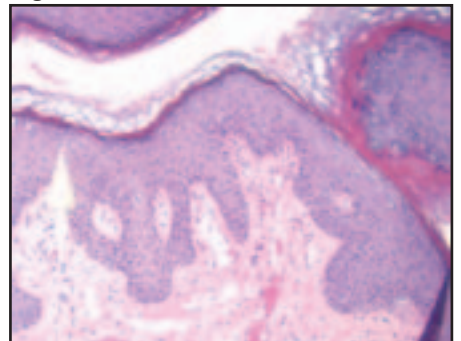
Figure 3A: Oral papillomas showing acanthosis with fibrous submucosa; no viral changes were noted.
Figure 3B: Koilocytes without atypia (arrow) and vascular-rich stroma with delicate collagen bundles.

Lichen Planus Pigmentosus: Case Report and Literature Review

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ABSTRACT

Lichen Planus Pigmentosus (LPP) is a rare variant of Lichen Planus which predominates in India and the Middle East. LPP is characterized by dark brown macules and/or papules in sun-exposed and non-exposed areas. The etiology is unknown. This condition should be considered in the differential diagnosis of hyperpigmented skin lesions. To date, attempted therapies have been marginal and inconsistent. We describe a 26 year old Pakistani-American female with a three year history of LPP.

Case Report

A 26-year-old, Pakistani-American female presented with a three-year history of hyperpigmented macules and patches on the face, thorax, and upper and lower extremities. The affected areas were asymptomatic other than mild pruritus of the lower extremities. The eruption began as a few dark-brown macules, which gradually progressed. At onset, the patient noted slight pruritus, but denied erythema or any other symptoms. There was no history of prolonged sun exposure or cutaneous trauma. The course of the hyperpigmented areas was not affected by seasonal changes. There was no family history of a similar skin eruption. Physical examination revealed hyperpigmented macules and patches on the upper eyelids, nasal tip, perioral area, buccal mucosa, chin and anterior neck. Confluent, violaceous to dark-brown macules, papules, patches and plaques were noted on the abdomen, lower back, and upper and lower extremities. Nails were uninvolved. Figures 1 and 2 show the clinical appearance of the patient's hands and feet. The patient reported self treatment with an over-the-counter "bleaching cream." Routine laboratory examinations did not reveal any abnormalities. Although the history was unremarkable for known predispositions, both clinical and histologic findings led to the diagnosis of lichen planus pigmentosus.

History

Lichen planus pigmentosus (LPP) is uncommon and one of many variants of lichen planus. Although Shima is credited with being the first to use the LPP designation in 1956,[1,3] it was not until 1974 that the disease was clinically and microscopically described by Bhutani et al. in a study of 40 patients diagnosed with LPP.[2]

Etiology

To date, there have not been any definite inciting agents of LPP. In studies of Indian patients with LPP, Kanwar et al.[5] and Bhutani et al.[2] reported that although no definite link between LPP and an inciting agent could be established, mustard oil, amla oil, henna and hair dye could be precipitating factors in predisposed individuals. In their report, Bhutani et al. noted that most patients had been using mustard oil for variable periods.[2] Mustard oil contains allyl thiocyanate, a potential photosensitizer, and is used for cooking and as a topical emollient in India.[5] Kanwar et al. also noted that approximately 18% of patients with LPP experienced increased pigmentation upon sun exposure and that the exposed sites were frequently the first to be involved.[5] As such, he proposed that sunlight may play a role in inciting LPP.

In our patient, the only association that we were able to draw from the medical literature was her occasional use of henna as a skin-coloring agent used for ceremonial purposes. However, the significance of this is unknown.

Although the cause of LPP is unknown, it is postulated that immunologic mechanisms mediate its development. Cho et al. suggest that, like LP, type IV hypersensitivity reactions play an important role in LPP pathogenesis.[3] Likewise, various authors attribute the inflammatory response of the lichenoid reaction seen in both LP and LPP to a cell-mediated immunity, in particular, T-lymphocytes. These cells regulate epidermal cell recognition, the lichenoid response and epithelial destruction.[4] For example, T-lymphocytes are thought to mediate apoptosis of basal keratinocytes, resulting in the formation of Civatte bodies in the lower epidermis and papillary dermis, histologic changes characteristic of lichenoid tissue reaction.[4]

Clinical Presentation

LPP occurs most often in India and the Middle East. Although primarily described in Indians, this disorder has subsequently been seen in other racial and ethnic groups.[6,7,12] LPP differs from classic lichen planus by exhibiting mottled or reticulated, dark brown macules and/or papules and patches in a non-characteristic distribution on sun-exposed areas such as the face, neck, and upper limbs, and on non-exposed areas such as flexural folds, including the axilla, inguinal, and submammary regions.[3,7-9] LPP has a longer clinical course, characterized by exacerbations and remissions.[1,3] It should be noted that the lesions may be local or generalized, pruritic, and associated with typical LP papules.[1-3,8,12] Most commonly, LPP is without scalp, nail or mucosal involvement.[2,3,8] However, Laskaris et al.[10] and Kanwar et al.[5] have reported patients diagnosed with LPP involving the oral mucosa.

Bhutani et al. reported 40 patients, aged 12 to 50 years, seen at a pigmented-lesion clinic in India over a two-year period.[2] The pigmented lesions first appeared as small, ill-defined macules which later became confluent to form uniform sheets of pigmented patches. The distribution of the slate-blue to steel-grey hyperpigmented areas was most commonly on the face, upper extremities, abdomen and upper back. Preauricular regions and the forehead were almost always affected. Pigmentation was progressive and varied in duration from two months to 12 years. One-half of the patients were asymptomatic, with the rest experiencing pruritus at the onset.

In a study by Vega et al. of 11 Mexican patients with LPP, the average age at onset was 46 years; 54% had a symmetrical distribution; 54% had a localized distribution, particularly on the face and abdomen; 62% had associated pruritus; and 46% had a generalized dermatosis, primarily on the face, axillary, submammary and inguinal folds.[11] LPP duration was one to six months and six to 48 months in 45% and 55% of the patients, respectively. In these patients, LPP presented as black-brown macules or patches, without elevated active borders and with a chronic course.

Studies involving a large number of patients with LPP were lacking from the literature prior to the current decade. In efforts to fill this void, Kanwar et al. performed a retrospective analysis of medical records of Indian patients who had attended a pigmentary clinic over a 12-year period.[5] Of the 3,020 patients referred to the clinic, 124 (4.1%) were diagnosed with LPP. The average age of onset was 30 years; 91% had symmetrical involvement; 79% had lesions present at more than one anatomical site; 88.7% had involvement of the face and neck; and 77.4% had a diffuse distribution. LPP duration was six months

to three years and greater than three years in 48.4% and 32.3% of patients, respectively. The majority of these patients presented with grey to bluish-black pigmented areas without elevated active borders.

Most case reports in the literature describe cases of LPP more commonly in ethnicities with darker skin. However, a case report by Pock et al. describes seven Caucasian patients with clinical and histological diagnosis of LPP.[7] The authors deny any causal relationship to the use of drugs or sun exposure. All patients had a striking predominance of lesions in the intertriginous locations, with most occurring in the axilla and inguinal regions. There were only a few cases with lesions outside the intertriginous areas. The lesions were brown macules of variable size and were sharply demarcated with smooth surfaces. This group of patients differed from the aforementioned studies, as well as from most studies, in that all patients were Caucasian from central Europe, and 90-100% of their involvement was located in intertriginous regions.

Less typical, LPP has been reported in association with acrokeratosis of Bazex, a paraneoplastic condition. In this case report by Sassolas et al., the authors describe a patient who developed LPP and acrokeratosis of Bazex simultaneously.[12] Treatment of the cancer resulted in resolution of both acrokeratosis and LPP. The authors believe this to be a noteworthy association, as both LPP and acrokeratosis of Bazex are rare. Furthermore, they suggest that LPP in the reported patient was a paraneoplastic phenomenon, as it regressed with no relapse after the treatment of the inciting cancer.

From our case report, it can be appreciated that our patient shares very similar characteristics to what has been reported. Our patient is from Pakistan, a country which is located in South Asia and borders Central Asia and the Middle East. The hyperpigmentation has progressed from localized areas of pigmented macules and papules to more generalized pigmented patches and plaques on the face, thorax, and upper and lower extremities. Consistent with the findings of Laskaris and Kanwar, our patient also has involvement of the oral mucosa.

Histopathology

Most studies report typical histopathologic findings of LPP consisting of hyperkeratosis; increased granular cell layer; atrophic epidermis; vacuolar alteration of the basal cell layer; and lichenoid infiltration of the papillary dermis with lymphohistiocytes, pigmentary incontinence and the presence of melanophages.[1,3,8,11-13] Kim et al. observed marked hydropic degeneration of the basal cell layer, with separation of the epidermis producing a small cleft (i.e., Max Joseph space), and multiple apoptotic bodies (i.e., Civatte bodies) at the dermo-epidermal junction.[9] Cho et al. examined a specimen by direct immunofluorescence, which revealed linear deposition of anti-fibrinogen antibodies.[3] Electron microscopy of the same specimen revealed several layers of basal lamina due to reduplication.

A punch biopsy of an affected area overlying the left lateral malleolus in our patient was performed and sent for interpretation. The dermatopathology report described the specimen features as lichenoid dermatitis with regression and pigment incontinence, consistent with LPP (Figures 3 and 4).

Differential Diagnosis

The differential diagnosis for LPP includes pigmentary disorders with similar features, such as erythema dyschromicum perstans (EDP), Riehl melanosis, fixed drug eruptions (e.g., carbamazepine, minocycline), actinic lichen planus, occupational dermatosis with hyperpigmentation (e.g., argyria, caloric melanosis) and acanthosis nigricans.[3,5,8,9,12] Most of these can be differentiated by history and clinical findings, but EDP is perhaps the most difficult.

Various authors have reported that while LPP and EDP are similar histologically, clinically, they are distinct entities.[1,2,11] The similar histology has resulted in much confusion between these two conditions.[1,11] EDP has a high incidence in Latin America and occurs mainly in dark-skinned people, predominantly in women.[11] EDP is clinically characterized by ashy-colored to blue-gray hyperpigmented macules, sometimes with an elevated red border, and the absence of pruritus. Distribution tends to be symmetric and commonly involves the face, neck, trunk, and upper extremities.[1,2,11,12] Histologically, Vega et al. proposed that the structural and immunofluorescent findings in EDP are manifestations of prolonged damage to the basal cell layer, which is also present in other conditions with a lichenoid pattern.[11]

Treatment

Thus far, no specific treatment is available for LPP. The reported effectiveness of the variety of therapies employed in the literature for the treatment of LPP has been inconsistent and marginal at best. Indeed, effective therapy for LPP is challenging. It is important to tailor the therapy to the patient's symptoms and presentation, while reconsidering alternate treatment options when standard approaches yield less-than-desired outcomes. Also of importance are the psychological sequelae that can result from the cosmetic disfigurement. Hence, the clinician should exercise therapeutic persistence and offer reassurance to the patient. Although the mainstay of therapy seems to be corticosteroids, other treatment options in LPP patients have consisted of keratolytics, topical dimethyl sulfoxide, griseofulvin, retinoids (etretinate), or chloroquine.[1,3] Bhutani et al. suggest that in the absence of any other effective therapy, vitamin A offers gratifying results.[14]

Initial therapy for our patient was fluocinonide cream 0.1% applied twice daily and hydroxyzine as needed for pruritus. Additionally, the patient was advised to use moisturizing bath soap and lotion, and daily sun block and other protective measures (e.g., protective clothing). At her three-month check up, the patient reported decreased pruritus, but examination revealed little to no improvement of the LPP areas. Current therapy for our patient includes fluocinonide cream 0.1% applied twice daily to new areas, tacrolimus ointment 0.1% applied twice daily, methotrexate 7.5 mg each week with folic acid 1 mg, loratadine 10 mg as needed for pruritus, and hydroquinone 4% cream applied at bedtime. After six months of therapy, there has been little to no regression of the affected areas. However, it is important to note that the progression of the LPP has been suppressed.

Conclusion

LPP is an uncommon variant of lichen planus that has no identified definitive etiologies. The medical literature provides reports of uncommon presentations of LPP, yet conveys what is most typical. Although LPP most commonly affects darker-skinned persons in the warmer climates of India and Latin America, LPP should be on the list of differential diagnoses for any patient presenting with hyperpigmented, maculopapular skin eruptions. As LPP can easily be confused with other hyperpigmented skin conditions, the history and clinical presentation is of particular importance in guiding the clinician to the most appropriate diagnosis. Many therapeutic agents have been attempted, with inconsistent results. Should therapy yield limited benefit, reassurance and the tincture of time may prove to be the most efficacious approach.

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Figure 1: Violaceous-to-brown, maculopapular plaques on the medial aspect of the left foot.

Figure 2: Violaceous-to-brown, maculopapular plaques involving dorsum and digits of hands.
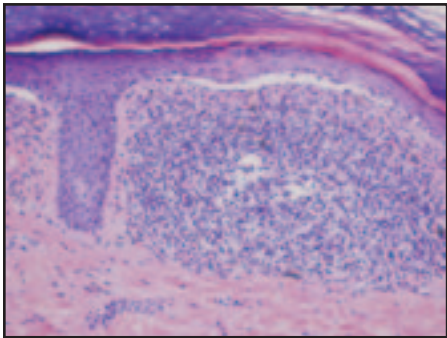
Figure 3: Dermatohistopathology revealed compact hyperkeratosis, hypergranulosis, vacuolar alteration of basal cell layer and a superficial, bandlike lymphohistiocytic infiltrate with scattered melanophages (H&E, original magnification X20).
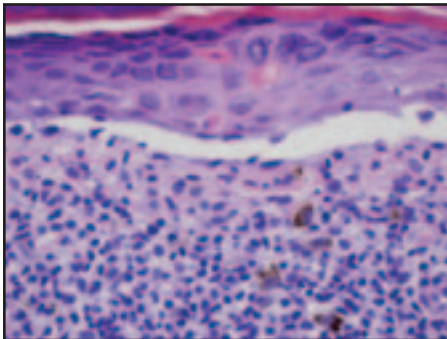
Figure 4: Further examination demonstrates the wedge-shaped hypergranulosis, vacuolar alteration and band-like lymphohistiocytic infiltrate with dermal melanophages. Rare Civatte bodies and a Max-Joseph space are seen (H&E, original magnification X40).

When the flares of dermatitis strike…

On target relief

KENALOG®
SPRAY
Triamcinolone Acetonide Topical Aerosol USP

Precision application when treating hard to reach areas

- Indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

- Systemic absorption of topical corticosteroids has produced reversible, hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. (See the Precautions section in Full Prescribing Information)

- Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

The Nozzle Makes the Difference!

For topical use only
Please see Brief Summary on reverse side.

KENALOG® SPRAY
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For dermatologic use only
Not for ophthalmic use

Brief Summary. Please see full prescribing information for complete product information.

DESCRIPTION

Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.3%), and isobutane propellant.

INDICATIONS AND USAGE

Kenalog Spray (Triamcinolone Acetonide Topical Aerosol USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, substitute a less potent steroid, or use a sequential approach when utilizing the occlusive technique.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see **PRECAUTIONS, Pediatric Use**).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only; avoid contact with the eyes and inhalation of the spray.

2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.

4. Patients should report any signs of local adverse reactions especially under occlusive dressing.

5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone showed negative results.

Pregnancy: Teratogenic Effects

Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers

It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

DOSAGE AND ADMINISTRATION

Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided.

Three or four applications daily of Kenalog Spray (Triamcinolone Acetonide Topical Aerosol) are generally adequate.

Occlusive Dressing Technique

Occlusive dressings may be used for the management of psoriasis or other recalcitrant conditions. Spray a small amount of preparation onto the lesion, cover with a pliable nonporous film, and seal the edges. If needed, additional moisture may be provided by covering the lesion with a dampened clean cotton cloth before the nonporous film is applied or by briefly wetting the affected area with water immediately prior to applying the medication. The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply the spray under an occlusive dressing in the evening and to remove the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional spray should be applied, without occlusion, during the day. Reapplication is essential at each dressing change.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

Store at room temperature; avoid excessive heat.

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November 2007

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Pernox® salicylic acid and sulfur cleanser

Sebulex® salicylic acid and sulfur shampoo

Balnetar® therapeutic tar bath

RANBAXY

Mycosis Fungoides with Plantar Keratoderma – A Case Report

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ABSTRACT

The accurate and early diagnosis of cutaneous T-cell lymphoma (CTCL) is often challenging. Mycosis fungoides (MF)-in which the skin is invariably affected by flat patches, thin plaques, or tumors-is the most common form of CTCL. Often it takes a certain level of evolution of the initial lesion, and multiple biopsies to identify the characteristic histologic features of MF. Though, there are clearly defined clinical features that can help guide the decision making process for the clinician, when faced with a non-specific clinical AND histologic picture of early or atypical MF lesions, accurate diagnosis commonly become a challenge. Presented here is a case of MF involving only the plantar surfaces of bilateral feet, initially diagnosed as eczema. The disease proved to be painful, significantly life altering for this young patient who became bed bound until a correct diagnosis was established and appropriate treatments undertaken.

Introduction

The accurate and early diagnosis of cutaneous T-cell lymphoma (CTCL) is often challenging. The diagnostic process relies heavily on clinical assessment, particularly in providing a supportive history, confirming one of several typical or suspected clinical presentations of CTCL and directing the choice of the critical biopsy sites.[1] CTCL is a rare, extranodal non-Hodgkin's lymphoma with a stable incidence of approximately 0.36 per 100,000 person-years.[2] Mycosis fungoides (MF) -- in which the skin is invariably affected by flat patches, thin plaques, or tumors -- is the most common form of CTCL. MF and SS represent approximately 65% of the cases of CTCL.[2] Both are characterized by CD4+/CD46Ro+ helper T-cells and the loss of mature T-cell antigens in the skin and involved organs.

Infectious agents, occupational exposures, and genetic mutations have been evaluated as etiologic factors in relation to MF, but evidence of causation has not been readily forthcoming.[2,3] Whereas viruses have been identified as etiologic agents in at least two cutaneous lymphomas (human T-cell lymphotropic virus-associated adult T-cell lymphoma-leukemia and Epstein-Barr virus-associated nasal NK T-cell lymphoma), no such relation has been confirmed for mycosis fungoides.[2] Interestingly, a report by Duvic et al. supports that 97 percent of patients with late-stage MF or the Sezary syndrome (SS) are seropositive for cytomegalovirus, in contrast to healthy bone-marrow donors, whose seropositivity rate is 57 percent.[4]

There are several benign inflammatory dermatoses that mimic early patch and plaque stage MF. Often, it takes a certain level of evolution of the initial lesion and multiple biopsies to identify the characteristic histologic features of MF. Though there are clearly defined clinical features that can help guide the decision-making process for the clinician, when faced with a non-specific clinical AND histologic picture of early or atypical MF lesions, accurate diagnosis commonly becomes a challenge.

The International Society of Cutaneous Lymphoma (ISCL) Task Force has identified several criteria that are most important for recognizing classic MF at initial patch stage.[1] According to the ISCL task force, there should be a higher clinical suspicion of CTCL if the following lesional characteristics are identified:

- Persistent and/or progressive patches/thin plaques
- Particularly those with:
  - Non-sun-exposed location
  - Size/shape variation
  - Poikiloderma

Of course, if the classic histologic features of a superficial lymphoid infiltrate, epidermotropism without spongiosis, and lymphoid atypia are identified, the diagnosis is clearly established. In addition, the molecular studies are key in establishing the specific diagnosis, including TCR gene rearrangement. The positivity of CD2, CD3, and loss of CD7 are also helpful confirmatory clues to diagnosis when present.

Presented here is a case of MF involving only the plantar surfaces of bilateral feet, initially diagnosed as eczema. The disease proved to be painful and significantly life-altering for this young patient who became bedbound until a correct diagnosis was established and appropriate treatments undertaken.

Case Report

Patient is a 33-year-old African American woman who initially presented with complaints of chronic, scaly, itchy feet and legs. She stated that skin lesions appeared three years ago, initially as erythematous patches on the plantar feet. The patches evolved over the course of three years to involve most of the bilateral plantar surfaces. The condition was significantly painful, interfering with her activities of daily living and employment. Patient was initially treated with topical steroids, with a presumptive diagnosis of plantar eczema versus psoriasis based on initial biopsy findings. There was no improvement.

Eventually, patient presented to the Boston University Department of Dermatology. On examination, patient had normal and clear skin on head and neck, trunk, and extremities, with the exception of significant bilateral plantar keratoderma. Patient was staged as T1; however, in spite of a limited involvement of skin (<4% body surface area), the level of debilitation was significant for this patient. The plantar skin was exquisitely painful (patient arrived in a wheel chair) and pruritic (10/10). There was no lymphadenopathy. An additional right plantar skin biopsy was completed and finally revealed findings consistent with cutaneous T-Cell lymphoma (CTCL): psoriasiform epidermal hyperplasia, papillary dermal fibrosis, epidermotropism of atypical lymphocytes with Pautrier microabscesses.

Over the course of the next few years, the CTCL treatment regimens at the Boston University Skin Oncology Clinic included the following: oral bexarotene (Targretin) and denileukin diftitox (Ontak). The combination of the two medications cleared her plantar skin entirely over the course of six months, and she remained on the regimen for over a year. However, the painful plantar keratoderma would recur with attempts to wean off the treatment.

In efforts to prolong the remission period, external beam radiotherapy (EBT) was planned during one of the CTCL flares. However, after five radiation treatments, there was very little improvement. EBT was subsequently stopped.

Unfortunately, over the next year, the plantar keratoderma became increasingly difficult to clear in spite of excellent control in the past. Given clear evidence of CTCL progression, a more aggressive plan of management was initiated, consisting of: bexarotene, extracorporeal photopheresis, and liposomal doxorubicin (Doxil).

The combination proved to be significantly more effective in halting disease progression and improving the plantar keratoderma: After three infusions of Doxil, the patient experienced significantly decreased pain and pruritus (4/10), and she was able to return to her employment soon thereafter. As of last patient visit (April 2010), she is tolerating the treatment regimen and continues to be functional at home and work.

Discussion

As classically described, our patient had involvement of the non-sun-exposed areas of the soles. Given the much higher prevalence of eczematoid dermatosis, contact dermatitis and psoriasis, the initial diagnosis was presumed to be of a benign inflammatory entity. Given the young age of the patient, the acute clinical presentation and localization of the lesions, it was indeed a reasonable first impression. In addition, the early biopsies were more reflective of an

inflammatory spongiotic dermatosis. There is a well-recognized paradox of histologic correlation in MF: Despite the fact that skin biopsy is considered a cornerstone of diagnosis, a reported false-positive diagnosis rate of 44% and false-negative rate of 40% highlights the difficulty of correct diagnosis of MF and underscores the importance of careful review of the MF simulators.[3] In regard to the common clinical mimickers of MF, the following entities ought to be considered during the diagnostic decision-making process:[3]

- Pseudolymphoma syndrome
- Persistent nodular arthropod-bite reaction
- Secondary syphilis
- Inflammatory lymphomatoid dermatoses
- Nodular scabies
- Chronic actinic dermatitis (actinic reticuloid)
- Fungal Infections
- Lichen sclerosis et atrophicus
- Lichenoid keratosis (solitary lichen planus or lichen-planus-like keratosis)
- Pigmented purpuric dermatosis
- Chronic cutaneous lupus erythematosus
- Inflamed vitiligo
- Regressed malignant melanoma

Ultimately, the clinicopathologic correlation would distinguish MF from other mimickers. Though our patient's clinical presentation is not classic for MF, the clinopathologic correlation over time led to an accurate diagnosis. The lesions evolved both clinically and histologically to warrant doubt about the initial diagnosis. Basic science research supports the clinical challenge of accurate diagnosis of MF. Complexity (tendency to evolve and progress) of MF may be best appreciated as a cancer of T-cells that continue in many respects to function as T-cells under normal physiologic conditions, but the behavior of which is dominated by their propensity to home to the skin, be activated and persist in an activated state, and achieve clonal dominance, thereby accumulating in the skin, lymph nodes, and peripheral blood.[2] In other words, it is a dynamic disease process, evolving over time, yet the responsibility of early and accurate diagnosis ultimately lies with the dermatologist.

Keratoderma has been described as a common feature of SS (but not MF), along with lymphadenopathy, erytheroderma, nail dystrophy, alopecia, ectropian, and intractable pruritus. However, localization of patch-stage MF to plantar areas, as our case demonstrates, is rather uncommon and presented a diagnostic and management dilemma. Though the lesions remained localized to the plantar areas, they evolved significantly, becoming hypertrophic, coalesced to a point of mimicking keratoderma, and became increasingly refractory to topical treatment options.

Ideally, the treatment algorithms are dictated by the initial stage of MF, which is based largely on the degree of skin involvement. For limited-patch or plaque MF, the treatment of choice is often a skin-directed therapy, which potentially can simultaneously target both the malignant T-cells and the stimulating Langerhans' cells.[2] External beam radiotherapy (EBT) in a localized field for limited disease, and total-skin electron-beam therapy (TSEBT) for more advanced stages, have been shown to be associated with relatively high rates of response and disease control. EBT clearly has been shown to have a direct effect on the death of T-cells and may effectively modulate the cutaneous milieu in a manner that is conducive to slowing the progression of MF.[2,6,7] In our patient, EBT had a very limited response. Perhaps there is a variation in response to EBT based on body areas involved or the extent of the hypertrophy of the lesions. Our patient had significant confluence and hypertrophy of her plantar skin at the time of EPT trial, which could have limited the penetration of electron-beam radiation. Consequently, as the case demonstrates, she responded much better to a systemic therapy of oral bexarotene, Doxil infusions and monthly sessions of extracorporeal photopheresis.

Several other skin-based therapies, such as psoralen in combination with UVA light, narrow-band UVB light, nitrogen mustard, bis-chloronitrosourea, topical corticosteroids, and bexarotene gel, have been used with success.[8] Again, these topical therapies are capitalizing on the skin-homing behavior of malignant T-cells in MF and preferentially targeting them. Likewise, the activated state of the cells in MF also makes them a semi-selective target for systemic therapy. These therapeutic options include: oral methotrexate, interferon (alfa 2b and gamma), denileukin diftitox, histone deacetylase inhibitors (vorinostat), and liposomal doxorubicin. According to National Comprehensive Cancer Network practice guidelines published in 2009, successful combination therapies include:

- Phototherapy with either retinoid, interferon, or photopheresis
- Total electron-beam therapy + photopheresis
- Variety of systemic combinations:
  - Retinoid + interferon
  - Bexarotene + dinileukin diftitox
  - Photopheresis + retinoid, or interferon, or both

In summary, MF should be considered an appropriate differential of palmo-plantar dermatoses, especially if a presumed benign inflammatory entity does not fit the clinical history, presentation, or response to therapies. Appropriate biopsies, gene rearrangement and molecular studies are valuable tools and should be employed early if there is a suspicion of a cutaneous malignancy.

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Figure 1

Figure 2

Figure 3

Figure 4

Piebaldism: A Historical and Clinical Tale from Slaves to c-Kit

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ABSTRACT

Piebaldism is a rare congenital autosomal dominant leukoderma. It is due to the mutations of the KIT proto-oncogene, which plays a role in the differentiation and migrations of the melanoblasts. Typically patients display a white forelock and symmetrical hypopigmented macules and patches. We report a patient with the characteristic features and the family lineage to support the diagnosis of piebaldism and discuss this condition from a historical perspective.

Introduction

Piebaldism is a rare congenital leukoderma. It is due to the mutation of the c-KIT proto-oncogene, which plays a role in the differentiation and migration of the melanoblasts. This condition has been recognized throughout history, from the times of the ancient Egyptians and Romans to the West Indies slave trade. It follows an autosomal-dominant inheritance pattern and is not usually associated with any systemic issues. Typically, patients display a white forelock and symmetrical hypopigmented macules and patches. When considering congenital leukodermas, it is important to differentiate piebaldism from Waardenburg's syndrome. We report a patient with the characteristic features and the family lineage to support the diagnosis of piebaldism.

Case Review

A four-year-old, developmentally normal, Caucasian girl was found to have sharply demarcated, hypopigmented patches demonstrating islands of normal pigmentation on both posterior legs and midline abdomen (Photos 1 and 2). The patches had neither expanded nor regressed since first noted at birth. The lesions demonstrated no linearity or Blaschkoid pattern. A frontal white forelock was also present at birth. Around the age of six months, the white forelock fell out and was replaced with normal hair. No underlying pigment abnormalities were appreciated in the area of the previously noted forelock. Physical exam findings included normal irises and cranio-ocular facial features. A recent school hearing examination was reported to be normal, and there was no history of bowel obstruction or chronic constipation.

The child had three maternal cousins (two girls and one boy) with similar findings, who were not available for exam. The patient's parents declined the offer for any further studies, biopsies, or treatment. A presumed diagnosis of piebaldism was made based on the history of the white forelock, hypopigmented patches containing islands of normal pigmentation, and the characteristic distribution of the lesions.

Discussion

Piebaldism is a congenital disease that is transmitted through families in an autosomal-dominant pattern. The Office of Rare Diseases of the National Institutes of Health classifies piebaldism as "rare," meaning it affects less than 1 in 200,000 Americans. There is no sex predilection. The word fragment of "pie" is believed to be a reference to the black-and-white winged magpie. The "bald" possibly refers to the white head plumage of the bald eagle. The striking white forelock passing from generation to generation led to surnames like Whitlock, Horlick, and Blaylock.

The first modern description and pedigree of piebaldism was made by Dr. James Morgan in 1786. The patient was a West Indies slave reportedly owned by "the dentist of the King of France."[1] In 1740, a painting of a young slave girl by an unknown Columbian artist appeared in Histoire Naturelle by Buffon. It is believed to be the first artistic depiction of piebaldism. The girl was owned by Jesuit missionaries. Since race was a challenging philosophical issue at the time, the presence of her white patches of skin invoked the fear that "interbreeding" among the races was occurring. To preserve the honor of the monks, Buffon put forth the hypothesis that piebald individuals were the offspring from "the union of slaves and albinos."[2] Mentions of individuals with features consistent with piebaldism can also be found in ancient Roman and Egyptian writings. In the age of the circus sideshow, individuals with either piebaldism or vitiligo earned their livings as "Leopard" or "Zebra" people.

Piebaldism affects the migration and differentiation of melanocytes from the neural crest. It results from a mutation in the c-KIT proto-oncogene and is located on chromosome 4q12.[3] The c-KIT gene itself is responsible for the encoding of the cell surface membrane receptor tyrosine kinase. This receptor is the critical factor for melanoblast migration, proliferation, differentiation, and ultimately survival.[4] Point mutations, deletions, nucleotide splits, and insertion mutations have all been described but are beyond the scope of this discussion. Various phenotypic expressions have been well-correlated with specific mutation sites on the KIT gene. The most severe are seen when they affect the intracellular domain, and the mildest affect the extracellular ligand-binding domain.

The clinical manifestations of the disease can be seen from birth and are usually stable throughout life. The typical piebald lesions are described as well-circumscribed, irregular macules and patches that often have hyperpigmented islands within the areas of hypopigmentation. The lesions can be observed on the central forehead, anterior trunk, flanks, arms, knees, and legs. Sparing of the dorsal midline, hands, feet, and peri-oral areas is typical.[5] Mucosal surfaces and ocular structures are not involved. The clinically distinctive white forelock can be seen at birth and is present in 80-90% of affected individuals. The underlying skin, eyelashes, and brows may also display the hypopigmented features seen elsewhere on the body. Regression of the white forelock, as occurred in our patient, has previously been described but is unusual.[6]

Typically a stable condition, there are reports of spontaneous repigmentation, either partial or complete, especially after injury.[7] A progressive form of piebaldism was also recently described in a mother and daughter.[4] Piebald areas may differ immunologically from surrounding skin, as graft-verses-host disease has been observed within the lesions while normal skin was spared.[8] Rare associations include: Hirschsprung's disease,[9] neurofibromatosis type 1,[10] Diamond-Blackfan anemia,[11] and Grover's disease.[12]

Histopathological evaluations of skin samples taken from piebald lesions show areas of absent or significantly reduced melanocytes. When the areas of adjacent hyperpigmentation have been examined, there are a normal number of melanocytes but an increased number of melanosomes in the melanocytes and keratinocytes.[13]

The primary condition to be differentiated from piebaldism is Waardenburg's syndrome. It is another congenital autosomal-dominant disorder that affects multiple cells that arise from the neural crest, including the enteric plexus ganglion cells, melanocytes, and neural and connective tissues of the head and neck. These patients typically have similar hypopigmented macules but also a constellation of hypertrophic nasal root, lateral displacement of the medial canthi (dystopia canthorum), partial or total heterochromia of the iris, and deafness.[14] Additional diagnostic considerations are nevus depigmentosa, hypomelanosis of Ito, and other chromosomal mosaicisms.

Treatment of piebaldism can be difficult and frustrating. The lesions themselves do not typically respond to the treatments used in vitiligo. Sunscreens

protecting against both UVA and UVB are recommended for the entire skin but especially for the hypopigmented areas. Camouflage make-up and pigmented tanning products can offer the option of covering existing lesions, but the daily application can lead to frustration and noncompliance from the patient. Surgical procedures have offered mixed results for repigmentation. Thin split-thickness grafts, minigrafting, transplantation of autologous melanocytes, and a combination of dermabrasion and grafting pigmented skin have all been used.[15] Excellent repigmentation following epidermal graft transplantation has been reported but is rarely utilized.[16] While piebaldism patients usually have no further co-morbid medical conditions and can lead otherwise normal and healthy lives, the stigma of the hypopigmented lesions can be detrimental to the self-esteem of an individual. Online forums for persons with piebaldism are available and offer clinicians insight into the psychosocial spectrum of their lives. Clinicians should remain aware of any psychological distress and refer appropriately.

In summary, we describe a young female with piebaldism and offer a review of the condition's history, pathogenesis, clinically distinguishing features, and existing treatment options.

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Photo 1

Photo 2

Photo 3

Photo 4

POLYPOID GIANT BASAL CELL CARCINOMA

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ABSTRACT

Basal cell carcinoma (BCC), is the most common cutaneous malignancy, however the giant type (greater than 5cm) is considered a rare form.[1] While the majority of BCC's are located on the head and neck, the giant forms show a predilection for the trunk.[2] These tumors are frequently described as vegetative plaques. Here we describe a case of a polypoid giant BCC (GBCC) and a brief review of the literature.

Introdustion

Basal cell carcinoma (BCC) is the most common cutaneous malignancy; however, the giant type (greater than 5cm) is considered a rare form.[1] While the majority of BCCs are located on the head and neck, the giant forms show a predilection for the trunk.[2] These tumors are frequently described as vegetative plaques. Here we describe a case of a polypoid giant BCC (GBCC).

Case Report

An 81-year-old female presented with a 15-year history of a slowly growing lesion on her left shoulder. The patient stated that the lesion did not hurt but had begun to bleed regularly and was staining her clothing. Past medical history included MI, COPD, HTN and osteoarthritis. She denied drinking alcohol but admitted to smoking one pack per day for 60 years. She denied any personal or family history of non-melanoma skin cancers.

A 7.2cm, firm, pedunculated polypoid lesion on the left posterior shoulder was found on physical examination (Figure 1). The stalk connecting the lesion was approximately one half the width of the lesion. The lesion was undulating, with a pink/red shiny surface and an area of necrosis on the inferior aspect. There were no other suspicious lesions.

An excisional biopsy was performed and sent for histological evaluation. The microscopic diagnosis was basal cell carcinoma, nodular variant. The patient was sent to a surgeon for complete excision with clear margins.

Discussion

GBCC has been recognized as a rare tumor with a high rate of recurrence. It represents less than 1% of all basal cell carcinomas.[3] It is found to occur more often in elderly male patients and on sun-protected sites.[4] One study found that 38.3% of patients develop local recurrence or metastasis even with optimal treatment.[3] GBCCs have been shown to have an aggressive course, with local destruction and metastatic disease.[5]

There are four recognized clinical subtypes of GBCC: exophytic (polypoid), noduloulcerative, morpheaform, and extensively ulcerated.[6] The polypoid type tends to be less aggressive, with lower risk of metastasis.[7] The size of the lesion correlates with risk of metastasis.

Although the majority of GBCCs are between 5 and 10cm, only approximately 9% of metastases arise from lesions smaller than 10cm.[8] The histologic subtypes are the same as with other BCCs, and the aggressive subtypes are the morpheaform, micronodular and metatypical lesions. The less aggressive nodular variety is most common in GBCC.[4]

Neglect of an initially small tumor, mostly due to fear of the diagnosis, is generally accepted as the reason most of these tumors grow to such large sizes.[4,9,10] Randle et al. have shown that people with GBCC are more likely to have had radiation exposure than those with small tumors. They also have shown that GBCCs that are recurrent from previously treated BCCs tend to be of the aggressive histological types.[9] Northington et al. report a case of GBCC associated with HPV expression.[11] A retrospective study demonstrated that cigarette smoking is associated with greater risk of GBCC.[12]

The treatment for GBCC is complete excision with histologically clear margins.[4,13] This is often difficult due to the size of these lesions. There is a report of a case of a GBCC of the left shoulder treated successfully with radiotherapy.[14] Reiger et al. report on two incompletely excised GBCCs that regressed spontaneously, and they propose a wait-and-see approach on incomplete excisions where re-excision is not an option.[15]

Overall, the GBCCs that arise as a result of neglect can be treated with several methods, including complete excision, radiotherapy and partial excision with clinical follow-up. Patient education to decrease the fear of an evaluation of smaller, earlier lesions should be a goal of clinicians in both primary care and dermatology.

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Figure 1

Case Report: Ulcerated Midfacial Segmental Hemangioma Treated with Surgery, Propranolol and Vascular Dye Laser

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ABSTRACT

Hemangiomas of infancy (HOI), the most common tumors of childhood, are typically benign and self-limiting. In some cases, these lesions may herald underlying developmental anomalies and, rarely, may compromise vital organ function. Ulceration is one of the most frequent complications observed in the proliferative phase of HOI, particularly with segmental hemangiomas. Appropriate work-up and intervention is required for hemangiomas complicated by ulceration, bleeding or aesthetic deformity, and where developmental anomalies or vital organ impairment is suspected. Early recognition of problematic lesions, coupled with prompt intervention, may help minimize future complications. Here, we report the treatment of a segmental hemangioma with propranolol, surgical intervention and PDL. The successful outcome in our case report suggests that a multimodal, multidisciplinary approach can achieve a good cosmetic result in a complicated HOI.

Case Report

A two-month-old, Hispanic female presented to the pediatric dermatologist's office in a tertiary care hospital with an ulcerated segmental hemangioma of the midface. The patient's mother reported that the hemangioma appeared two weeks after birth and grew rapidly over the subsequent weeks, with ulceration appearing one week prior to evaluation. The patient was initially seen by a plastic surgeon from an outside hospital, who administered corticosteroids intralesionally. One week following this treatment, ulceration of the upper lip was reported by the patient's mother. Upon initial evaluation by the pediatric dermatologist, the patient presented with mild bleeding, irritability, and difficulty feeding secondary to the upper-lip ulceration and pain. On physical examination, a large, 4x3 cm, maxillary segmental hemangioma extended from the nasal prominence, columella, philtrum and upper lip, with a central necrosis and ulceration between the philtral columns and upper lip extending down into gingival buccal sulcus (see Figures 1 and 2). Patient's past medical history was non-contributory. She was born 40-weeks gestation weighing 8lbs 2oz to a gestational-diabetic mother without complications.

The patient was admitted to the tertiary care hospital due to the ulceration of a midfacial hemangioma that required treatment secondary to pain and difficulty feeding. A complete work-up was done to rule out any other associations. Multiple specialties were consulted, including cardiology, otolaryngology, and plastic surgery, for their evaluation and recommendation. Because the hemangioma was facial, a PHACES (see Figure 2) work-up was performed. An MRI/MRA with and without contrast of the face, brain, neck and great vessels was done. Results were normal except for a lobulated soft-tissue proliferation in the upper lip and nose consistent with proliferating capillary HOI. A direct laryngoscopic examination ruled out upper airway involvement. EKG and ECHO showed normal cardiac rhythm and no congenital heart disease. PHACES was thus ruled out.

After obtaining parental informed consent and approval from cardiology, off-label use of propranolol was started on day 2 of hospitalization. The starting test dose of 0.5 mg/kg was tolerated without any side effects; therefore, on day 3, the full dose of 2 mg/kg/day was given. The patient's vitals, blood pressure and glucose were closely monitored for the potential side effects of bradycardia, hypoglycemia, bronchospasm and hypotension, of which the patient had none. Within 48 hours of full-dose propranolol, softening and lightening of the tumor was noted.

In addition to treatment with propranolol to reduce the size of the hemangioma, she was also started on Duricef on day 3 after the culture of the upper lip ulceration grew MSSA. The upper lip ulceration was of significant concern due to its effect on oral motor function and potential for significant cosmetic deformity. The patient was experiencing difficulty feeding secondary to both the pain and deformity of the upper lip. Acetaminophen was required around the clock to control the pain.

Plastic surgery was consulted early on admission and recommended that the once the lesion began to regress they would reevaluate and perform surgical closure to prevent further spreading of the upper lip. On hospital day 9, the patient successfully underwent surgical closure of the upper lip ulceration (see Figure 3).

The patient was discharged on the 10th day of hospitalization, tolerating bottle feeds well and without evidence of pain. Medications prescribed were: oral propranolol at 2mg/kg/day in three divided doses and Duricef to complete 10 days.

After about seven weeks of propranolol therapy (when patient was about five months of age), significant thinning of the lesion was observed. While maintaining propranolol therapy, the patient was then started on approximately monthly treatments of PDL therapy (Candela VBeam Perfecta). After four PDL treatments and seven months of propranolol therapy, significant regression of the lesion was noted (see Figure 5).

Discussion

HOI are benign tumors of endothelial cells that usually appear within the first few weeks of life. HOI are the most common tumors of childhood, with an estimated occurrence of between 3% and 10% in white children.[1] Dysregulated vascular homeostasis has been implicated in the pathogenesis of this condition. GLUT1, a glucose transporter normally expressed in the microvascular endothelia of blood-tissue barriers (such as the brain, retina, placenta and endoneurium barriers), but not of normal skin, was recently described as a specific marker for HOI in all phases of development.[2] Hemangiomas of infancy are associated with low birth weight, prematurity, female sex, and multiple gestations and are increasing in incidence as the rate of preterm, low birth-weight deliveries increases.[3,4]

In 1982, Mullikin and Glowacki[5] proposed a classification system of vascular birthmarks that was refined and then adopted in 1996 by the International Society for the Study of Vascular Anomalies (ISSVA) (see Table III). This classification system divided vascular birthmarks into two categories: 1) tumors, or 2) malformations of varying vascular origin. Infantile hemangiomas are the most common type of vascular tumors. They are usually absent at birth, grow rapidly during early infancy, and then regress. In contrast, vascular malformations are present at birth, grow in proportion to the child and do not regress. This classification system provided a framework for understanding vascular birthmarks and is the basis for continued study into the causes of these lesions and their therapy.

Infantile hemangiomas clinically demonstrate an early proliferative phase during the first three to six months (usually reaching maximum size by 9 to 12 months of age), followed by a stationary phase, and then by an involution phase that in most cases begins at 12 to 18 months of age. Completed involution of HOI occurs at an estimated minimum rate of 10% per year -- approximately 50% involute by 5 years of age, 70% by 7 years of age, and 90% by 9 years of age.[2] The growth or involution characteristics of any individual HOI are difficult to predict because a small minority may continue to grow until 18 to 24 months of age and therefore begin and complete involution at a later time.

HOI demonstrate a striking

predilection for the head and neck region but can occur in any part of the body. Waner et al.6 described facial infantile hemangiomas occurring in two distinct patterns of tissue involvement: 1) focal type with tumor-like appearance (showing a predilection for embryological fusion lines); and 2) diffuse type (less common) with plaque-like or segmental distribution. The diffuse (segmental) lesions were more likely to be complicated by ulceration or airway obstruction. Facial hemangiomas have been reported to occur with various anomalies such as central nervous system defects (posterior fossa malformation), arterial anomalies, coarctation of the aorta, eye abnormalities and occasional sternal defects. These hemangiomas are sometimes designated PHACE(S) syndrome (Posterior fossa malformation, Hemangioma, Arterial abnormalities, Coarctation of the aorta, Eye abnormalities and Sternal defects). The diagnosis of PHACE(S) requires a large facial segmental hemangioma as well as at least one of the aforementioned extracutaneous manifestations. Therefore, it is important to consider the appropriate work-up in any patient with facial segmental hemangioma: 1) history and physical with review of systems; 2) cardiac evaluation consisting of echocardiogram and all four extremity blood pressures; 3) MRI/MRA of head and neck; 4) neurologic exam; and 5) ophthalmologic exam. Patients with segmental hemangiomas located in the mandibular region (preauricular, chin, anterior neck and lower lip) are at risk for life-threatening upper airway obstruction and should therefore be evaluated by direct laryngoscopy.

Although most HOI are benign and innocuous, some tumors may threaten function or life or be associated with structural congenital anomalies.[2] Intervention is required for lesions that interfere with vital structure and function. Among these hemangiomas that warrant treatment are those that cause ocular compromise, respiratory distress, congestive heart failure, gastrointestinal bleeding or extensive ulceration[7] (see Table II for location and morphology of HOI and associated risks).

Ulceration is the most frequent complication of infantile hemangiomas, occurring in nearly 16% of patients, most often by 4 months of age, during the proliferative phase.[1] Studies have shown that a subset of hemangiomas are at greatest risk for ulceration: those of mixed superficial and deep subtypes, with a segmental pattern, and occurring in certain anatomic sites of mechanical trauma, namely perioral, perineum, and intertriginous areas.[1,2] This observation can guide a primary care physician to give anticipatory guidance and refer a patient to a pediatric dermatologist earlier for treatment.

Ulcerations, depending on the depth and location, can be treated with different modalities. No singular treatment form is uniformly effective, and several goals of management must be addressed: local wound care, treatment of infection, specific treatment modalities and pain control.8 First-line treatment is local wound care with antiseptic compresses with .25% acetic acid and/or topical antibiotics (polysporin, mupirocin and metronidazole) and/or systemic antibiotics, which will often result in healing of small ulcerations. Occlusive dressings can also help accelerate the healing process. Second-line treatment is topical becaplermin gel and pulse dye laser. Becaplermin gel, a recombinant human-platelet-derived growth factor, has been reported to heal ulcerations when local wound care has not been successful.[9] Pulse dye laser (PDL), for the past two decades, has been used to heal and decrease pain in ulcerated hemangiomas and treat non-ulcerated hemangiomas, post-involutionary erythema and/or telangiectasia.[2,8] Third-line treatment is systemic treatment with oral corticosteroids, intralesional corticosteroids, propranolol, interferon alpha, and surgery. Pain control in ulcerated hemangiomas, especially those in the lip and perineum, is an important consideration. Pain is effectively managed with oral acetaminophen, acetaminophen with codeine, and topical 2.5% lidocaine.[8]

The approach for treating HOI should be determined on a case-by-case basis depending on each patient's particular circumstance. The potential for complications of the hemangioma should be weighed against the risks associated with treatment. As outlined in the 1997 guidelines of the care of hemangiomas of infancy by the American Academy of Dermatology, goals of treatment are: 1) preventing or reversing life-threatening complications, 2) preventing permanent disfigurement, 3) minimizing psychosocial stress for patient and family, 4) avoiding aggressive, potentially scarring procedures, and 5) preventing or adequately treating to minimize scarring, infection and pain.[2]

In the case presented here, there was no doubt that the central upper-lip ulceration and large segmental hemangioma of the midface required treatment. This patient failed intralesional corticosteroid therapy and successfully responded to propranolol, with partial involution of the lesion prior to surgical intervention for the deep ulceration of the upper lip that would have disfigured the patient if left to heal by secondary intention. Patient after surgery continued on propranolol for a total of seven months. In addition to propranolol, the patient was also treated with the pulse dye laser to enhance resolution of hemangioma and residual scarring and telangiectasia.

Beta-blocker treatment using agents such as propranolol is revolutionizing therapy because of its impressive results. Up until recently, the mainstay of treatment was oral corticosteroids. Systemic corticosteroids have proven effectiveness in most cases, but the risks of long-term and high-dose use include growth disturbances and immune dysfunction, as well as ulcerations causing severe tissue loss.[10] Other therapeutic options like interferon alpha, vincristine, and cyclophosphamide are used less frequently because of side effects and toxicity. Propranolol, a non-selective beta blocker, inhibits the growth of infantile hemangioma via these potential mechanisms: vasoconstriction, decreased expression of vascular endothelial growth factor and basic fibroblast growth factor, and/or triggering apoptosis of endothelial cells.[11] The use of propranolol in the treatment of hemangiomas was accidentally discovered in 2008 when two children were reported to show rapid regression and involution of their hemangioma after treatment with propranolol for cardiac conditions. Leaute-Labreze et al.[11] replicated these effects in nine other children with disfiguring hemangiomas. These results led to larger observational studies by Sans and Dumas de la Roque et al.[12] using propranolol at 2-3 mg/kg/day in 32 patients with severe hemangiomas that threatened life or function or were at high-risk for local complications or cosmetic involvement. Rapid therapeutic effects were noted in all cases, with considerable shortening of the natural course of infantile hemangioma with good clinical tolerance.

Prior to starting propranolol, a baseline work-up by a pediatric cardiologist should be performed where EKG, echo, and baseline vitals measuring blood pressure, heart rate, blood sugar and temperature are evaluated. Propranolol is contraindicated in congestive heart failure, airway disease (severe asthma, bronchospasm, lung disease), irregular heart beat, and renal and cardiac failure. Patients on this medication need to be monitored closely for severe adverse effects, which include hypoglycemia, hypotension, bronchospasm, and bradycardia.[12]

In addition to propranolol, the patient was also treated with the pulse dye laser to enhance resolution of hemangioma and residual scarring and telangiectasia. The use of lasers for the treatment of HOI can be divided into three separate indications: treatment of the proliferative phase, treatment of the ulcerated hemangiomas, and treatment of residual telangiectasias that may remain after involution.

Conclusion

Ulcerated hemangiomas represent a therapeutic challenge, especially in hemangiomas affecting the face, where scarring and permanent disfigurement can lead to psychosocial implications. This case describes an example of a work-up that should be considered in any segmental hemangioma affecting the face. The patient, in this case, did not meet the criteria for the diagnosis PHACES syndrome. Early recognition of problematic hemangiomas of infancy, such as those that can potentially cause ulceration, bleeding and aesthetic deformity, coupled with prompt intervention can reduce the chances for future complications. The multidisciplinary, multimodal approach described herein incorporated surgery, propranolol and pulse dye laser and resulted in a successful cosmetic outcome for our patient.

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Fig 5. Patient at 9mo of age after 7 months of propanolol therapy and after 3 PDL treatments.

Fig 1. and Fig 2. 2mo old infant with midfacial hemangioma with ulceration when she first presented to pediatric dermatologist.

Fig 3. Patient is six days post surgical closure of the upper lip and 14 days after starting propanolol therapy. Note the softening and the color change of the hemangioma.

Fig. 4 Patient at 7mo of age and after 5 months of propanolol therapy and 1 PDL treatment.

Table 1

P	Posterior fossa malformation
H	Hemangiomas, large segmental facial
A	Arterial anomalies
C	Cardiac anomalies and coarctation
E	Eye abnormalities
S	Sternal cleft and/or supraumbilical raphe

Table 2
Location and morphology of hemangioma of infancy and associated risks

Anatomic Location, Morphology	Associated Risk
Facial, large segmental	PHACES syndrome
Beard and neck, segmental	Airway hemangioma
Perioral, lips	Ulceration and disfigurement
Nasal tip, ear	Permanent scarring and disfigurement
Perineal, axillae, and neck	Ulceration
Lumbosacral spine	Tethered spinal cord, GU anomalies
Multiple hemangiomas	Visceral involvement (commonly liver and GI tract), high risk of CHF
Periorbital and retrobulbar	Ocular axis occlusion, astigmatism and amblyopia

Table 3
Vascular tumors and malformations of childhood

Vascular Tumors	Vascular Malformations
Hemangioma of infancy	Capillary (port wine stain, salmon patch) (CM)
Rapidly involuting congenital hemangioma (RICH)	Venous (VM)
Non-involuting congenital hemangioma (NICH)	Lymphatic (LM)
Kaposiform hemangioendothelioma	Arterial
Tufted hemangioma	Arterial venous (AVM)
Pyogenic granuloma	Combined (capillary/lymph/venous)

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Folliculotropic Mycosis Fungoides – A Case Report

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ABSTRACT

Folliculotropic mycosis fungoides is a distinct subtype of mycosis fungoides. There are significant differences in clinical presentation, histologic features, therapeutic responses, and outcomes in FMF compared to the conventional MF, that it is widely accepted as a distinct subtype of MF. Early stages of FMF (stage IA or IB) are more refractory to treatment and has worse prognosis compared to conventional MF. Skin lesions in FMF can present as patches, plaques, or grouped papules, nodules, tumors, erytheroderma, acneiform lesions, mucinorrhea, as well as leonine facies.). There is often associated alopecia. Head and neck are most common locations involved in FMF, however trunk and extremities are often involved as well. Pruritus is a major symptom, and a burden on patients' quality of life. Here is presented, a case report of FMF, reviewing the clinical course and the treatment response to various regimen.

Introduction

Mycosis fungoides (MF) is a well-known and the most common type of cutaneous T-cell lymphoma, characterized clinically by an evolving dermatosis, often mimicking other inflammatory papulosquamous entities such as eczema and psoriasis. In classic MF, the lesions initially present as patches, plaques, and tumors. Classic MF is histologically defined by infiltration of the epidermis by medium-sized to large, atypical T-cells with cerebriform nuclei. There are various clinical and histologic variants of MF that have been defined. These include hypopigmented MF, vesicular MF, pustular MF, and granulomatous MF, along with a few more.[1] These entities are not classified as subtypes of MF because the clinical course, response to treatment, and prognosis does not vary among the variety of clinical presentations. On the contrary, pagetoid reticulosis and folliculotropic MF (FMF) and are the only two distinct subtypes of MF defined by the European Organization for Research and Treatment of Cancer (EORTC) and the World Health Organization (WHO).[1] There are significant differences in clinical presentation, histologic features, therapeutic responses, and outcomes in FMF compared to conventional MF, so it is widely accepted to be a distinct subtype of MF.

Even at early stages, FMF (stage IA or IB) is more refractory to treatment and has worse prognosis compared to conventional MF.[1,2] Skin lesions in FMF can present as patches, plaques, grouped papules, nodules, tumors, erytheroderma, acneiform lesions, mucinorrhea, and leonine facies.[1] There is often associated alopecia. Head and neck are the most common locations involved in FMF; however, trunk and extremities are often involved as well. Pruritus is a major symptom and is a burden on a patient's quality of life. Follicular mucinosis is present in over 90% of FMF cases.[1] There is a significantly higher male-female ratio in FMF compared to classic MF. FMF is predominantly CD4+ and CD8-. Histologically, five patterns are considered highly characteristic: folliculolymphoid hyperplasia with folliculotropism, granulomatous dermatitis (closely associated with a destructive process of the follicular unit) and folliculotropism, eosinophilic folliculolitis-like presentation with folliculotropism, formation of dilated follicular cyst with folliculotropism, and lastly, the prototypical FMF, with intact follicles and folliculotropism with or without mucinosis.[3] Epidermotropism is classically absent in FMF. Large-cell transformation is possible, though not common.

Case Report

Presented is a case report of a 55-year-old Hispanic man with stage IB folliculotropic mycosis fungoides (FMF). Prior to the diagnosis of the FMF, our patient had a longstanding history of atopic dermatitis, well controlled with topical corticosteroids. Starting in 2006, his skin condition began to change, in that skin areas affected were not typical of his previous eczema, lesions became more refractory, and pruritus increased significantly (9/10). The worst areas of "rash" and pruritus now included scalp and posterior neck. On initial physical examination, there were scaly, mildly erythematous, somewhat hypopigmented patches and plaques involving the posterior neck and scalp with alopecia. There was no lymphadenopathy. The rest of the skin was clear. Given the atypicality of his "eczema flare," additional skin biopsies were undertaken. They showed the following features: no epidermotropism, mild spongiosis, superficial perivascular and interstitial lymphocytic infiltrate, peri-follicular lymphocytic infiltrate with admixed eosinophils, and colloidal-iron-confirmed mucin within follicular epithelium. Immunoperoxidase staining with T-cell marker CD3 revealed T-cells within the follicular units as single cells and small collections. Additional skin biopsies confirmed a diagnosis of FMF. Patient was diagnosed as having FMF stage IB disease.

Initially, a regimen of oral bexarotene (Targretin) and topical corticosteroids was initiated. However, after a short period of improvement in follicular plaques, the lesions became refractory, with recurrence of plaques and formation of nodules within the first eight months of treatment. There were additional plaques noted on the trunk at this time. In addition, pruritus became severe and difficult to control. Given the clear progression of disease, a more aggressive approach to treatment management was undertaken. In addition to continuation of oral bexarotene, there was inclusion of PUVA and eventually liposomal doxorubicin (Doxil). With the more aggressive combination regimen, the patient reported a significant decrease in the size of his lesions and severity of pruritus (6/10). At the time of this writing, though the disease has waxed and waned, the patient remains mostly stable on a combination treatment of bexarotene, PUVA, Doxil and topical corticosteroids. His severe pruritus remains an ongoing challenge and currently is being managed on hydroxyzine, mirtazapine, and gabapentin, with reduction of symptoms to tolerable levels.

Discussion

Our patient followed the well-described profile of an FMF patient: male gender, involvement of head and neck regions, and refractory response to therapies typically utilized for early MF, necessitating early aggressive therapy with a combination regimen of light, oral retinoid, and chemotherapy. The studies that have been published in the last 15 to 20 years essentially agree on clinical and prognostic trends in FMF. In a study published by Northwestern University's cutaneous lymphoma group, 65% of the patients had alopecia secondary to the FMF, and 71% of these patients had alopecia of the face involving the brows. In regards to alopecia, there was a range of clinical findings, from scarring alopecia without prominent papules to keratosis-pilaris-like papules to large papulonodular or boggy lesions.[2] Though head and neck are typically considered the classic locations of involvement, some studies have shown that the incidence of FMF lesions involving the trunk is actually higher.[2,4,5] Though there is a varied presentation of types of lesions that can present, patches, plaques and papules remain the most common types of initial presenting lesions in FMF.[4] Clinical mimickers of FMF include comedonal and cystic acne, rosacea, and keratosis pilaris. Histologic mimickers include scarring alopecia, severe nodulocystic acne, eosinophilic folliculitis, granulomatous dermatitis and granulomatous MF.

Treatment and management of FMF is significantly more challenging as compared

to classic MF. There is very limited response to topical therapies. It is a commonly accepted fact among the experts that because of the peri-follicular localization of the dermal infiltrates, patients with FMF should always be considered to have a tumor-stage disease, regardless of the clinical appearance of lesions.[1,2,4] Therefore, even early lesions are treated with more aggressive combination regimens including light therapy, radiation, and chemotherapy. However, despite early initiation of a more aggressive treatment regimen, the patients with FMF have a greater challenge in achieving remission compared to classic MF.[1] Accordingly, disease-specific survival is much lower versus classic MF. For instance, Northwestern University's cutaneous lymphoma group recommends psoralen plus UVA (PUVA) and narrowband UVB (NBUVB) early in their stage IA and IB patients, along with oral retinoids (bexarotene, acitretin), interferon therapy, or radiation.[2] Their experience shows that narrow-band UVB therapy is not optimal for FMF, since the photons in this wavelength cannot penetrate the deeper follicular unit, leaving residual disease and therefore rendering treatment inadequate and often misleading. The role of chemotherapy in FMF is also very important. Essentially, any FMF with a stage IIB or higher disease is a candidate for, and should be seriously considered for, systemic chemotherapy (CHOP, liposomal doxorubicin, or gemcitabine).[2]

In general, FMF patients are indeed a lot more refractory to treatment and have a much worse prognosis compared to their conventional MF counterparts. For instance, the overall five-year survival has been described as somewhere from 62-67%.[1,2,4] Management of pruritus is another important but challenging goal. Commonly used agents include hydroxyzine (higher doses), doxepin, mirtazapine, gabapentin, and emollients. Finally, superimposed infections (a common complication of altered and compromised cell-mediated immunity in MF and FMF patients) should be detected and treated early. Chlorine-bleach baths can help with prevention of secondary bacterial infections. Oral antibiotics can be used if there is evidence of a superimposed infectious component.

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Figure 1

Figure 2

Elephantiasis Nostras Verrucosa

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ABSTRACT

Elephantiasis Nostras Verrucosa (ENV) is a disease at the end stage of lymphedema. It can be caused by either primary or secondary lymphedema. Treatment is difficult and not always effective. Stewart-Treves syndrome, a form of angiosarcoma, can be a fatal complication of ENV. Here we present a case report and review of the literature.

Case Report

A 44-year-old, African-American male presented to the emergency department complaining of lesions on his bilateral lower extremities for the past year. The patient stated that the lesions started out as vesicles, which subsequently burst and formed nodules. The patient denied any bleeding but reported a chronic, clear-yellow fluid seeping from the nodules. He visited the ER several times for this same problem.

During previous emergency room visits, the patient was given oral antibiotics and topical steroids, which did not result in improvement. He denied any recent travel or pets in the home. The patient is on disability but formerly worked as a corrections officer. His past medical history includes type II diabetes mellitus, hypertension, peripheral vascular disease, gout and morbid obesity.

On physical exam, there were verrucous nodules on the anterior, medial and lateral aspects of both lower extremities (Figure 1). Clear-yellow fluid wept from many of the nodules (Figure 2). There was yellow crust overlying a few of the nodules (Figure 3). No vesicles were noted. There was non-pitting edema to the groin without any lymphadenopathy. Stemmer's sign was positive. No pedal pulse was detected.

A biopsy showed pseudoepitheliomatous hyperplasia with dermal fibrosis. The papillary dermis had edema with clusters of capillaries. A PAS stain was negative for fungal elements, and a fungal culture was negative. These findings are consistent with a type of lymphedema called elephantiasis nostras verrucosa (ENV).

Discussion

Lymphedema is a condition characterized by an abnormal collection of lymph fluid in the interstitium from damage to, or a defect in, the lymphatic channels. It is divided into primary and secondary types. Primary lymphedema (PL) is caused by an intrinsic abnormality of the lymphatic system. Secondary lymphedema (SL) results from an acquired defect due to an extrinsic factor.[1]

There are multiple known causes of PL. It was originally classified by age of onset, but in many cases the genes responsible were elucidated, which allowed for further classification. The genetic defect can cause lymphedema at birth or can manifest at puberty or even later in life (Table 1).

Secondary lymphedemas are due to an acquired obstruction or obliteration of the lymphatic pathways. The causes are myriad and may be a combination. The causes can be categorized as neoplastic (from tumors or therapy), infectious (with lymphatic filariasis being the most common cause of SL worldwide), inflammatory (collagen vascular disorders or recurrent cellulitis), vascular (obstruction from morbid obesity or varicose vein surgery), and traumatic.[2-4] SL can also be localized to a small area like the vulva.[2,5]

Elephantiasis nostras verrucosa can be a result of either PL or SL. It is characterized by hyperkeratosis and papillomatosis of the epidermis with underlying woody fibrosis of the dermis and subcutaneous tissue. The typical clinical features of cobblestoning, verrucous nodules and grotesque enlargement are late findings of chronic lymphedema.

The pathophysiology of ENV begins with dysfunction of lymph transport and subsequent leaking of protein-rich fluid into the interstitium, causing the collagen fibers to swell and separate. At this stage, the edema is soft and clinically pitting. This excess fluid and the accompanying inflammatory infiltrate eventually cause the interstitial connective tissue to fibrose. The overlying epidermis becomes acanthotic, and the dermis demonstrates an increase in collagen but generally a loss of elastic fibers.[5] There is also significant angiogenesis in the upper dermis, seen histologically as a proliferation of capillaries.[1]

ENV can occur anywhere on the body where a chronic lymphedema is found. The clinical course is often complicated by repeated infections, with both bacterial and fungal species causing a foul odor.[1,3] The weeping lesions are a good portal for bacteria, which can cause a cellulitis, osteomyelitis, or even a septicemia.[6] These infections can also do more damage to an already impaired lymphatic system. As this disease progresses, the limb gets enlarged, which can impede movement enough to impair a patient's quality of life.[13]

A rare but usually fatal complication of chronic lymphedema is the Stuart-Treves syndrome. It is an aggressive angiosarcoma most commonly seen in post-mastectomy lymphedema but also reported in ENV.[3,7,8] The lesions are usually purple or blue nodules, but have been known to present as non-healing eschars. If a patient develops lesions that are unusual or an existing lesion begins to change, a biopsy is warranted to rule out this malignancy.

The main differential diagnosis for ENV includes chromoblastomycosis, filarial infection, lipedema, lipodermatosclerosis, papillomatosis cutis carcinoides and pretibial myxedema. A good history and physical exam can usually provide the diagnosis, but biopsy and bloodwork can confirm it.[4]

The treatment options for ENV have been satisfactory at best. The main goal is to prevent or minimize complications such as infection, odor, restriction of movement and poor wound healing. Any contributing factors to the lymphedema should be addressed immediately. For example, weight loss in our patient should be a focus.

Initial treatment should include compression garments (most helpful in early stages), manual lymphatic drainage, exercise and good skin care and hygiene. Patient compliance is crucial to successful treatment. It is important to get the family involved as well, because it will have to become a lifestyle change.[13]

Surgical treatments are helpful if the patients are carefully chosen.[9] Surgical debulking and debridement are used to help with the aesthetic and/or functional complications but do not address the underlying problem. The use of lymphatic anastomosis has been reported in the literature but is not a widely used technique.[10]

Different drugs have been used for treatment of ENV. Diuretics such as thiazides have been used but are not helpful in improving the lymphatic flow. Antibiotics are used to treat the common infectious complications.[11] Oral etretinate was tried on three patients with obesity-related ENV and showed promising results. Topical tazarotene has been reported to be beneficial in a reported case.[12]

Overall, ENV is not an easily treated disease. Once the diagnosis is made, a team effort including the patient, family, physician and lymphedema therapist is necessary. The underlying cause should be sought and treatment tailored to the individual. The team must remain vigilant for complications such as infections, joint restriction and Stewart-Treves syndrome and address these issues appropriately.

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Figure 1. Verrucous nodules on the anterior, medial and lateral aspects of both lower extremities

Figure 2. Weeping of clear-to-yellow fluid from many of the nodules

Table 1: Types of Primary Lymphedema

Disease	Age of Onset	Gene Association	Comment
Milroy Disease	Birth	VEGFR-3	Lymphedema below the knees from failure of lymphangiogenesis
Meige's Disease	Puberty	FOXC2	Females, most common type of primary lymphedema, hypoplasia of distal lymphatics
Turner's Syndrome	Birth-20s	Loss of X chromosome	Transient lymphedema of hands and feet
Noonan's Syndrome	Birth-Adult	PTPN11	Lower-extremity lymphedema
Klippel-Trenaunay Syndrome	Birth		Lymphatic malformation
Proteus Syndrome		?PTEN	Lymphatic malformation
Amniotic Bands			Obstruction of lymph channels
Maffucci's Syndrome	Birth-early childhood		Venous cavernous malformations, cavernous lymphangiomas
Lymphedema-distichiasis Syndrome	Puberty	FOXC2	
Hypotrichosis-lymphedema-telangiectasia Syndrome		SOX-18	Bilateral lower-extremity lymphedema

Tuberous Xanthomas in Childhood:
A Case Report and an Endocrinological Perspective

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ABSTRACT

Cutaneous xanthomas are lipid-containing papules, plaques, nodules or tumors that often represent clinical manifestations of an underlying lipid-metabolism dyscrasia. There are several forms of cutaneous xanthomas, but few types can be representative of these lipid-metabolism disorders and merit a thorough investigative evaluation to prevent further systemic sequelae. The authors present a case of a 9-year-old Hispanic female with multiple tuberous xanthomas on her elbows and knees associated with hypercholesterolemia, as well as an in-depth review of the pathophysiology of hyperlipidemia with special attention to the pediatric population.

Case Report

A 9-year-old, non-obese, Hispanic female of Mexican descent presented to an outpatient office with her parents for the evaluation of "warts" to her elbows and knees, present for two years (Figures 1-4). The child had a history of controlled asthma, for which she occasionally used a rescue inhaler without corticosteroids, and had no other associated symptoms or complaints. The child stated that the lesions did not itch and were not painful. The patient's father was diagnosed with hypercholesterolemia in his third decade of life, without any known cardiovascular events. The child's mother and sibling had no similar known medical history, and nobody else in the family had similar lesions. The mother stated that the lesions had a tendency to occur at sites of minor trauma, and that some had resolved or waned spontaneously throughout this time.

A shave biopsy of one of these papules from the patient's right elbow showed an aggregate of foam cells with few Touton giant cells, consistent with tuberous xanthoma (Figures 5-7).

Subsequent evaluation of the patient's fasting lipid status showed elevated triglyceride levels (130 mg/dL), elevated total cholesterol (643 mg/dL), low high-density lipoproteins (HDL: 26 mg/dL) and very elevated low-density lipoprotein level (LDL: >350 mg/dL; estimated calculated LDL 591 mg/dL). The results were verified with repeat fasting laboratory testing. The patient was then referred to her pediatrician and eventually also consulted with a pediatric cardiologist and a nutritionist for further workup and dietary recommendations. Thyroid studies, genetic evaluation and endocrinological workups were also recommended.

Repeat evaluation of the patient's fasting lipid status ordered by the patient's pediatrician 10 months later showed normal triglyceride levels (105 mg/dL), elevated total cholesterol (704 mg/dL), low high-density lipoproteins (HDL: 30 mg/dL) and very elevated low-density lipoprotein level (LDL: >350 mg/dL; estimated calculated LDL 653 mg/dL). The patient was suspected to have a form of familial hypercholesterolemia (likely Fredrickson type IIa) with associated cutaneous tuberous xanthomas. Based on the level of the LDL elevation and the early development of the xanthomas, it was also considered that the patient may have the homozygous form of familial hypercholesterolemia.

Pathogenesis

Though the exact mechanism of xanthoma formation is not fully understood, it is believed that it results from permeation of circulating plasma lipoproteins through dermal capillary vessels. These lipoproteins are then phagocytized by macrophages, forming lipid-laden cells known as foam cells.[1] Approximately 80% of LDL cholesterol is metabolized by receptor-mediated endocytosis. The remaining LDL is removed from circulation by a macrophage scavenger receptor pathway, as in familial hypercholesterolemia and familial dysbetalipoproteinemia. However, xanthomas seen in Tangier disease and familial HDL deficiency are formed from altered macrophage cholesterol reflux mechanisms. These latter two disease entities show that the formation of cutaneous xanthomas can reflect its dependence on the macrophage scavenger pathway.[2]

Most plasma lipids are transported in structures called lipoproteins. This complex structure helps deliver triglycerides and cholesterol to peripheral cells to be metabolized. On the outer shell of lipoproteins are specialized proteins known as apolipoproteins. One of the more significant apolipoproteins, due to its invaluable role in hepatic lipid metabolism, is the B-100/E receptor that is found on the surface of hepatocytes. This receptor helps recognize lipoproteins for uptake and processing in the liver. Apolipoproteins allow binding of the lipoproteins to their receptors on the target organs and also activate enzymes that metabolize the lipoproteins.[3]

Lipoproteins are synthesized by two major pathways: exogenous (dietary intake) and endogenous. In the exogenous pathway, dietary triglycerides are degraded by pancreatic lipase and bile acids, and are then absorbed by the intestinal epithelium to become part of the central core of a chylomicron.

A chylomicron then enters the lymphatic system and later the systemic circulation via the thoracic duct, where it will then be hydrolyzed in muscle and adipose. This triglyceride-depleted chylomicron remnant will then be taken up by the liver to be part of hepatic storage.

The endogenous pathway involves the hepatic formation of VLDL particles. Lipoprotein lipase regulates the hydrolysis of the VLDL molecule and removes the majority of its triglyceride content. The remaining portion of the VLDL is known as intermediate-density lipoprotein (IDL) and is taken up by the liver. Those IDL molecules that are not taken up by the hepatocytes enter the circulation as LDLs after the remaining triglycerides are removed by extracellular hepatic lipases. LDL is mostly composed of a core of cholesterol esters and expresses apolipoprotein B-100 on its surface. These cholesterol esters are metabolized in the peripheral tissues and converted to free cholesterol. Also a component of the endogenous pathway is the presence and activity of HDL. One of the main functions of HDL molecules is the removal of cholesterol from the peripheral tissues.

Clinical

Lipid disorders can be associated with specific types of cutaneous xanthomas along with other systemic findings and manifestations (Table 2).

Eruptive xanthomas typically present as small, soft, yellow papules and have a tendency to arise on the buttocks and the posterior thighs. These xanthomas are most commonly associated with chylomicronemia and secondary forms of hyperlipoproteinemia. Eruptive xanthomas wax and wane as chylomicron levels fluctuate and are mostly made of triglycerides, which are more rapidly metabolized than cholesterol. Often the triglyceride levels in patients with eruptive xanthomas may exceed 3000 mg/dL and can be due to primary or secondary causes such as diabetes mellitus, obesity, high caloric intake, alcohol abuse, oral estrogen replacement and retinoid therapy.[4] Therefore, in these cases the treatment of eruptive xanthomas involves the identification and treatment of the cause of hypertriglyceridemia.

Tuberous and tuberoeruptive xanthomas are yellow to pink-yellow papules most commonly found on the elbows, knees, fingers and buttocks and are usually associated with elevated levels of LDL and VLDL, as in dysbetalipoproteinemia and familial hypercholesterolemia. The prominent lipid form in tuberous xanthomas is cholesterol. These lesions have a tendency to slowly regress after appropriate therapy has been started.[5]

Tendinous xanthomas are firm, smooth nodules that have a tendency to occur on the Achilles tendon and the extensor tendons of the fingers, knees or elbows. They occur most frequently in patients with elevated LDL levels, as in familial

hypercholesterolemia, but can also be seen in patients with dysbetalipoproteinemia, hepatic cholestasis, familial defective apolipoprotein B-100 and, rarely, in the absence of a lipoprotein disorder, as in cerebrotendinous xanthomatosis and β-sitosterolemia.[6] Ultrasound can serve as an aid in the diagnosis of these lesions, especially when they are subtle and over the Achilles tendon.[7]

Plane xanthomas present as yellow-orange papules, patches or plaques that usually develop in skin folds, commonly occur on the palmar creases, and are diagnostic of dysbetalipoproteinemia, especially when associated with tuberous xanthomas.[8] Intertriginous plane xanthomas of the antecubital fossa or the web spaces of fingers are suggestive of homozygous familial hypercholesterolemia. Plane xanthomas that are associated with primary biliary cirrhosis, biliary atresia and cholestasis are usually plaque-like and usually extend past the palmar creases. Plane xanthomas can also occur in normolipemic patients and may indicate the presence of an underlying monoclonal gammopathy (as in multiple myeloma), lymphoproliferative disorders such as B-cell lymphoma or Castleman's disease, or chronic myelomonocytic leukemia.[9]

Xanthelasma are small, yellow, soft plaques on the eyelids and are the most common form of cutaneous xanthomas. This form is not very specific for hyperlipidemia and commonly occurs in normolipemic patients. However, the presence of xanthelasma should still warrant an investigation of the patient's lipemic status, especially in younger patients and those with a strong family history of hypercholesterolemia. Xanthelasma is commonly considered a form of plane xanthoma and is sometimes categorized in the family of macrophage disorders.[10]

Finally, verruciform xanthomas are solitary plaques that usually occur in the mouth without an associated hyperlipidemia, possibly seen in the setting of lymphedema, epidermolysis bullosa, graft-versus host disease and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome. Surgery is usually curative.

Histopathology

Histologically, xanthomas are thought to represent a cutaneous focus of infiltrated serum lipids that are phagocytized by macrophages and then form lipid-laden foam cells within the dermis. Most xanthoma cells are mononuclear, but Touton giant cells are occasionally seen. The most diagnostic finding that is suggestive of an internal lipid metabolism abnormality is the presence of free lipids that have not been taken up by macrophages yet. Special fat stains such as scarlet red and Sudan red can help visualize these lipid droplets on frozen sections or formalin-fixed sections. Most xanthoma specimens have some form of fixation artifact such that the lipids are removed in sample processing, represented by artifactual clefting.[11]

When extracellular lipid is present in a lesion with an infiltrate of foam cells, the physician should suspect an underlying hyperlipidemia. If, however, the serum lipid levels are within normal range and this has been confirmed on repeat analysis, one can then extend the differential diagnosis to include xanthogranulomas, non-cholesterol lipid disorders (sitosterolemia, cholestanolemia), paraneoplastic disorders, post-inflammatory or post-traumatic lesions and storage disorders.[12]

Early eruptive, tuberous and tendinous xanthomas can have a mixture of non-foamy cells such as lymphocytes, macrophages and neutrophils. Well-developed lesions, however, are more likely to show mostly foam cells. Eruptive xanthomas typically have fewer foam cells compared with the other types of xanthomas. The histopathologic differential diagnosis for eruptive xanthomas includes non-Langerhans cell histiocytosis, xanthomatous lesions of Langerhans cell histiocytosis and disseminated granuloma annulare.

Tuberous xanthomas often have fibrotic changes along with large aggregates of foam cells. The differential diagnosis for tuberous xanthomas includes erythema elevatum diutinum and multicentric reticulohistiocytosis.

Tendinous xanthomas have even larger foam cells along with polarizable cholesterol esters.

The histologic differential diagnosis for tendinous xanthomas includes giant cell tumor of tendon sheath, rheumatoid nodule and subcutaneous granuloma annulare.

Palmar plane xanthomas and xanthelasma are easily identified by their pathological location-specific characteristics.[13] The histologic differential diagnosis for xanthelasma includes syringomas, necrobiotic xanthogranuloma, adult-onset asthma and periocular xanthogranuloma and sebaceous hyperplasia.[14]

Discussion

Early atherosclerotic disease is present in up to one in six American teenagers.[15] Familial hypercholesterolemia represents the most common type of primary hyperlipidemia and is due to a genetic defect which causes various mutations in the LDL receptor. This is inherited by an autosomal-dominant pattern and can present as homozygous and heterozygous types (the latter being more common). Homozygous patients will begin to manifest cardiovascular disease within the first two decades of life, while heterozygotes will begin in early to mid-adulthood.[16] Heterozygote patients rarely manifest cutaneous xanthomas, and generally not until older adulthood. However, homozygotes may have xanthomatous lesions generally by the age of 5 years and can show LDL levels that are five to six times normal. These patients may experience a cardiovascular event as early as the first decade of life.[17]

Hyperlipidemia in the pediatric population is traditionally defined as an LDL level greater than 130 mg/dL, and triglycerides greater than 100 mg/dL for ages 0-9 years and over 130 mg/dL for children over 10 years of age.[18] Once identified, secondary contributing factors must also be ruled out, including diabetes mellitus, hypothyroidism, nephrotic syndrome, HIV/AIDS, biliary and liver disease, illicit drugs, alcoholism, obesity and potentially causative medications (corticosteroids, retinoids, estrogens).[19]

Xanthomas can be found anywhere on the skin or mucous membranes and often represent the dermatologic manifestation of a lipid metabolism disorder, although they can also be seen in normolipemic states as in monoclonal gammopathy.[20] Moreover, cutaneous xanthomas can serve as clues that a patient may have an associated lipid abnormality and thus herald the initiation of identifying factors that can prevent future sequelae, namely premature cardiovascular disease.

Though most people with hyperlipidemia do not have cutaneous xanthomas, the clinical or dermatopathologic presence of xanthomas should alert the physician to pursue internal causes, and the evaluation of the patient's lipemic state is warranted. Lipid levels can be quantified after a 12-hour overnight fasting blood test.

Plasma lipoproteins can be separated by electrophoresis into four major fractions: chylomicrons, β-lipoproteins, pre-β-lipoproteins and α-lipoproteins. Ultracentrifugation allows for further separation into four major groups: chylomicrons and very low density lipoproteins (VLDL; both of which make up the pre-β-lipoproteins), low density lipoproteins (β-lipoproteins) and high density lipoproteins (α-lipoproteins).

These levels of lipoproteins allow for classification of the familial hyperlipidemias known as the Frederickson classification system, types I through V. Types I and II are the most common presenting types in childhood.[21] All five types of familial hyperlipidemias are characterized by elevated total cholesterol and VLDL levels, but can be classified by other specific laboratory findings (Table 1). Type I hyperlipidemia is an autosomal-recessive inherited disorder that is caused by a lipoprotein lipase deficiency or a dysfunctional apolipoprotein C-II. Type II hyperlipidemia is an autosomal-dominant disorder that can be further sub-classified into types IIa and IIb based on their slight variations of lipid-profile abnormalities. This type is typically caused by an LDL-receptor defect or dysfunctional apolipoprotein B-100. Type III hyperlipidemia is an autosomal-recessive inherited disorder caused by apolipoprotein E abnormalities. Type IV hyperlipidemia is an autosomal-dominant inherited disorder caused by renal disease and diabetes. Type V hyperlipidemia is an autosomal-recessive disorder that is similar to type I in that it can also be caused by apolipoprotein C-II deficiency.

Treatment

Pediatric patients with cutaneous xanthomas associated with hyperlipidemia represent a disease spectrum that is best managed by a multidisciplinary influence. Therefore, patients with this presentation would best be managed and evaluated by first identifying the underlying lipoprotein disorder and other possible secondary causes, and then evaluating and treating based on the systems involved.

Diet modification remains a cornerstone therapy for patients with cutaneous xanthomas and hyperlipidemia. However, this is only recommended to lower lipid levels in patients greater than two years of age. The initial treatment protocol (Step 1 diet) includes dietary-fat restriction to less than 30% of total caloric intake with less than 10% of calories from saturated fat and less than 300mg per

day of cholesterol. If necessary, further dietary restrictions (Step 2) can be instituted, including less than 7% of calories as saturated fat in the diet and less than 200mg of cholesterol per day. Carbohydrates should be approximately 55% of the total calories and should be high complex with little refined carbohydrates.[22] Alcohol avoidance and achieving ideal body weight is also of high importance.

The American Academy of Pediatrics recommends beginning pharmacotherapy in patients eight years of age or older with LDL levels greater than 190 mg/dL, greater than 160 mg/dL in patients with cardiovascular disease or two or more additional risk factors, or LDL levels greater than 130 mg/dL in patients with diabetes mellitus. The LDL goal should be less than 160 mg/dL initially, but targets should be more aggressive for patients with a strong family history of early cardiovascular disease, diabetes mellitus, metabolic syndrome and obesity.[23-24]

One of the pharmacotherapeutic agents used to treat hyperlipidemia in pediatric patients is the group of bile acid-binding resins. These agents act by binding to bile acids in the small intestine and preventing their absorption in the terminal ileum. This leads to an increase in LDL receptors on the hepatocyte surface and an increase of the HMG-CoA reductase activity, leading to a net decrease in the total LDL levels. Based on the existing pediatric guidelines published in 1992 by the National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents, bile acid-binding resins are considered to be the primary medication class to consider in those pediatric cases with type IIa hyperlipidemia that also meet recommendation for drug therapy.[25] This is likely to be associated with the fact that they are not systemically absorbed. However, their poor compliance, poor tolerability profile and modest decrease of LDL levels make them less likely to result in target levels being reached.[26] Also, these medications are not recommended in patients with type IIb hyperlipidemia since they can potentially raise triglyceride levels.

Nicotinic acid or niacin is a water-soluble B-complex vitamin that mostly lowers VLDL synthesis and LDL levels. Triglyceride levels are also lowered by decreasing lipoprotein production and increasing lipoprotein clearance. HDL levels are raised as well, but the mechanism by which this happens is unknown. This class of medications is considered second-line pharmacotherapy by the NCEP for the treatment of LDL elevation. This class of medication is effective in patients with combined hyperlipidemia and isolated hypertriglyceridemia due to elevated VLDL. Adverse effects such as facial flushing, gastrointestinal upset and the need for frequent monitoring of liver transaminases often leads to poor compliance with this medication in children. Currently, there are few dosing guidelines for pediatric patients.

HMG-CoA reductase inhibitors, also known as "statins," work by competitively inhibiting the rate-limiting enzyme of hepatic cholesterol synthesis, HMG-CoA reductase. This leads to decreased hepatocellular stores of cholesterol, increased expression of LDL receptors, increased LDL clearance and decreased VLDL synthesis. HDL levels may also increase slightly. The use of this class of medication

in the pediatric population has recently increased. It is approved for children at least 10 years of age, and at least 8 years of age with pravastatin. Safety studies of the use of statins in children and adolescents have ranged in duration from six months to two years.[27] Limits of the use of statins include hepatocellular toxicity and risk for rhabdomyolysis, though most adverse events were reversible upon discontinuation of the medication. Teratogenicity also raises a major concern when treating adolescent females, and they should be made aware of the importance of avoiding pregnancy while taking these medications.

Fibric acid derivatives are most often used for treating hypertriglyceridemia. These medications work by decreasing lipoprotein production, increasing lipoprotein clearance and decreasing VLDL synthesis. Fibric acid derivatives can be used to treat patients with dysbetalipoproteinemia and chylomicronemia syndrome. In the pediatric population, these medications are usually used for patients with levels of triglycerides persistently greater than 350 mg/dL or a random level greater than 70 mg/dL to prevent pancreatitis. Fibrates are not recommended for use with statins and in patients with liver disease.[28]

Cholesterol absorption inhibitors represent a new class of lipid-lowering agents. Their primary mechanism of action is to inhibit the absorption of cholesterol at the level of the brush border of the small intestine. This class of medications is primarily considered adjunctive therapy in patients who have not reached LDL goal with statins alone. However, this class of medications also has limited data in the pediatric population.

Cutaneous xanthoma lesions can also be treated surgically by excision or destructive methods such as laser surgery, chemical agents and cryosurgery. In many cases, unfortunately, there is a high rate of reoccurrence.[29-30]

In patients with confirmed familial hypercholesterolemia, a thorough cardiovascular risk stratification should be assessed as a way to determine the therapeutic strategy for the patient. Homozygous patients should receive a complete cardiovascular assessment at the time of diagnosis as well as consideration for treatment with regular plasma LDL apheresis. The use of statins is recommended in combination with a cholesterol absorption inhibitor. Heterozygous patients should begin a lifestyle modification program as well as statin therapy as first-line therapy in males greater than 10 years old and females greater than 1 year postmenarchal with familial hypercholesterolemia. However, a select group of patients with extremely high LDL can be initiated at a younger age.

Pediatric patients with cutaneous xanthomas and hyperlipidemia should have a general pediatrician who can help coordinate the care of these patients. This includes the identification of any secondary causes of the hyperlipidemia such as thyroid disease, insulin resistance and other common causes of hyperlipidemia in childhood. The patient should be evaluated by a nutritionist who can help manage any hyperlipidemic state with an appropriate diet and exercise regimen. A pediatric cardiologist should also evaluate the patient to quantify the cardiovascular state of

the patient and thereby follow any progress or changes to this system as the potential for cardiovascular sequelae are a real threat to these patients' health and prognosis. Pediatric endocrinologists can also help manage and coordinate the appropriate therapies, which in many cases is specific for the severity of the associated hyperlipidemia and the age of the patient.

Finally, a genetic evaluation may also be warranted in order to establish potential risk of inheritance to the patient's siblings and potential future offspring. Weigman and colleagues studied 1,034 children from families with familial hypercholesterolemia for genetic evaluation and stated that even in the absence of genetic testing, a clinical diagnosis of familial hypercholesterolemia could be made if the LDL cholesterol was above the 95th percentile for age and gender in a family with premature cardiovascular disease and the presence of a tendon xanthoma.[31]

Conclusion

As dermatologists, we are often presented with a wide spectrum of systems involved with cutaneous pathology. One example of this is the cutaneous xanthomas and their multisystemic correlation. It is therefore important for dermatologists to become familiar with the many presentations of cutaneous xanthomas as well as the pathophysiology of hyperlipidemia, since the early recognition of these lesions can help determine the management, treatment and prognosis of patients who may have a systemic disease. The paramount importance of early identification of pediatric patients with cutaneous xanthomas and hyperlipidemia should therefore be aimed to prevent cardiovascular morbidity and mortality in adulthood.

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Table 1: Laboratory findings in lipid disorders[32]

Disorder and Inheritance	Total Cholesterol	Triglycerides	VLDL	Chylomicrons	LDL	HDL
Type I / AR	↑	↑↑↑	↑	↑	↓	↓↓↓
Type II / AD	↑	Normal (IIa) ↑ (IIb)	↑ (IIb)	Normal	↑	↓
Type III / AR	↑	↑	↑	↑	↓	Normal
Type IV / AD	↑	Normal to ↑	↑	Normal	↓	↓↓
Type V / AR	↑	↑↑↑	↑	↑	↓	↓↓↓

Table 2: Xanthoma types seen in lipid disorders and other associated clinical findings[33]

| Disorder	Xanthomas	Cardiovascular	Other Findings
Type I	Eruptive Tendinous Xanthelasma	None	Diabetes Lipemic plasma
Type II	Planar (intertriginous) Tendinous Tuberous	Generalized atherosclerosis	None
Type III	Planar (palmar) Tuberous	Atherosclerosis	Abnormal glucose tolerance Hyperuricemia
Type IV	Eruptive Tuberous	Atherosclerosis	Obesity
Type V	Eruptive Tuberous	Atherosclerosis	Obesity Hyperinsulinemia

Figure 1

Figure 2

Figure 3
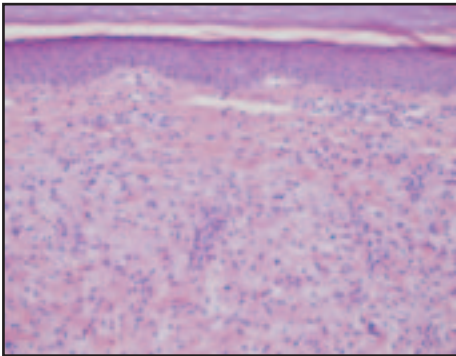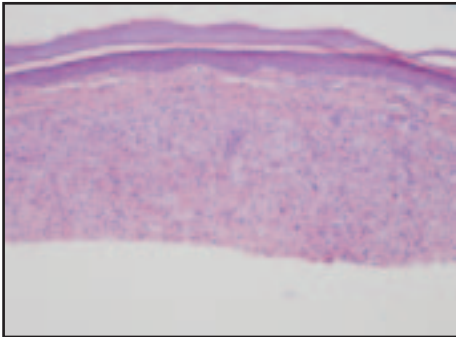
Figure 4

Figure 5

Figure 6

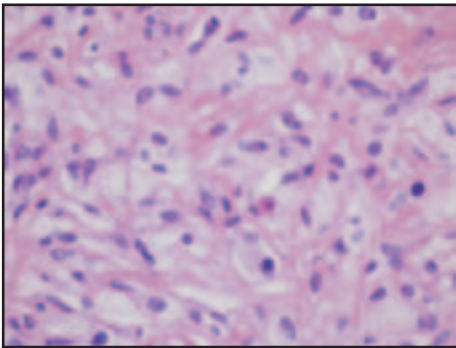Figure 7

Dermatitis Herpetiformis: A Case Report and Discussion

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ABSTRACT

Dermatitis herpetiformis (DH) is an autoimmune bullous disease characterized by symptomatic skin lesions and a gluten-sensitive, often asymptomatic, enteropathy. Cutaneous findings are characterized by an intensely pruritic papulovesicular rash predominately on symmetrical extensor locations. The diagnosis of DH is made with the utilization of histology, serology and direct immunofluorescence. DH patients may have multiple associated comorbidities including autoimmune conditions. Disease treatment may be with pharmacologic agents and a gluten-free diet. While Dapsone is the drug of choice used to treat DH, modifications must be made in patients with a sulfa allergy. We describe a 58 year old sulfa-allergic male with a six month history of dermatitis herpetiformis.

Case Report

A 58-year-old Caucasian male presented to the clinic with a chief complaint of "red spots" and "water blisters" that began six months prior on his face, abdomen, genitalia, and bilateral elbows and knees. He stated that these lesions then quickly spread to his buttocks and scalp. He described them as feeling "itchy and burning." Review of systems was positive for a 10-year history of occasional flatulence, bloating and "floating stool" after heavy meals. He reported recent blood in his stool that he attributed to his past history of hemorrhoids. Also, he noted having generalized fatigue and paresthesias in his fingers, which he attributed to his job. His past medical history was significant for hypertension, hypercholesterolemia and gastroesophageal reflux disease. His medications included irbesartan, esomeprazole, simvastatin, ibuprofen, Sudafed, aspirin and antihistamines. His allergies included sulfa and eggs. He had a family history of a brother with Hodgkin's lymphoma. His social history was significant for social use of alcohol, which often caused him to feel ill.

Physical examination revealed an erythematous papulovesicular rash with "honey crusting" and secondary excoriations on the face, neck, elbows, knees, waistline and buttocks. His complete blood cell count was unremarkable. Pertinent laboratory values included an ANA of 1:160, gliadin IgG Ab of 24 and a gliadin IgA Ab of 29. A punch biopsy from a lesion on the right buttock was taken. Histological examination demonstrated a subepidermal blister associated with a ragged epidermal undersurface and a dense upper dermal neutrophilic infiltrate with microabscess formation at the tips of the dermal papillae and karyorrhexis. Direct immunofluorescence (DIF) of perilesional skin on the left elbow demonstrated a dense granular IgA deposition along the basement membrane zone. This IgA granular pattern was more intense at the tip of the dermal papillae and percolated along the papillary dermal microfibrils. No IgG, IgM, C3, C5b-9 or fibrinogen deposits were identified in this specimen. Assessment of the clinical and histological features supported a diagnosis of dermatitis herpetiformis (DH).

A treatment plan was determined taking into account the information above. First, a trial of oral and topical steroids was attempted in conjunction with a gluten-free diet. After four weeks, the patient had no change in his condition, so the topical steroids were stopped and the oral steroids were tapered. Since the patient had a sulfa allergy, dapsone and other sulfa-containing medications were avoided. Instead, he was prescribed nicotinamide 500 mg three times daily and tetracycline 500 mg two times daily. It should be noted that the patient was having difficulties adhering to a gluten-free diet. At a three-week follow-up examination, the patient had noticed a decrease in the quantity of lesions as well as a decrease in pruritis.

Discussion

Dermatitis herpetiformis is a chronic skin dermatosis characterized by pruritic papulo-vesicular lesions.[1] The rash of DH is considered to be an external presentation of underlying intestinal sensitivity, and a clinical or subclinical form of celiac disease (CD) is thought to be present in most patients with DH. Although there is this association, in the majority of patients with DH gastrointestinal symptoms are minimal or absent.[2] The rash of DH may occur at any age, with most common onset during the second through fourth decades of life.[1,3,4] Several studies have reported a familial incidence of 2.4-6.5%, and it typically affects men more frequently than women (1.36:1).[5]

DH and CD are multifactorial disorders that share a common pathogenesis from an intestinal reaction to gluten. This is most likely a result of molecular mimicry between autoantigens of the gut, known as tissue transglutaminase, and those of the skin, called epidermal transglutaminase.[6] In the gut, wheat peptides may interact with tissue transglutaminase within the mucosa.[1] Tissue transglutaminase is the autoantigen responsible for gluten-sensitive disease. Recent findings indicate that epidermal transglutaminase is the major autoantigen responsible for the skin lesions of DH.[1,7] Cross reactivity to both of these antigens may occur, as they both belong to the transglutaminase family.

Both environmental and genetic factors seem to be important in the pathogenesis of DH. Environmentally, initiating factors include circumstances that may create a loss of tolerance to gluten in the gut. These include pregnancy, recent enteric infections, development of lymphoma or increased intake of gluten-containing grains.[1] Other environmental triggers not involving the gut include local factors in the skin, such as trauma, sun exposure or iodine. These triggers may cause direct activation of T cells in the gut or neutrophils in the skin.[1] Genetically, the pathogenesis is influenced by the fact that both DH and CD share the same association with HLA-B8, HLA-DR3, HLA-DQ2 and HLA-DQ8.[9]

Clinically, DH has various signs and symptoms. It presents as grouped lesions in a herpetiform arrangement with symmetric distribution over extensor surfaces. The most commonly affected sites include elbows (90%), knees (30%), shoulders, sacrum, buttocks and posterior nuchal area.[1,10] Some cases involve the scalp, face and groin. Lesions are usually polymorphic, initially presenting as erythematous, urticarial plaques, papules, herpetiform vesicles or blisters.[10] These lesions have a tendency to become erosive, excoriated and/or hyperpigmented. Lesions may be excessively pruritic. The sensation of pruritis and burning may precede the appearance of lesions.[9] While oral lesions are rare, they may present as easily ruptured vesicles that leave ulcerations of the mucosa.[1] These lesions often bleed easily and heal slowly. While adults with DH and small-bowel involvement tend to be asymptomatic, they may suffer from weight loss, bloating, anemia, malabsorption and diarrhea.[1,2,6] Children with DH and small-bowel involvement tend to be more symptomatic, presenting with abdominal pain, diarrhea, iron deficiency and decreased rate of growth.[10] The main differential diagnoses to consider include autoimmune bullous disorders, transient acantholytic dermatosis, urticaria, scabies, eczema and prurigo nodularis.[1]

While the clinical picture of DH can vary, the use of histology, DIF and serology may help confirm the diagnosis.[3] Histologically, an erythematous papular lesion in DH demonstrates subepidermal blisters and distinctive neutrophilic microabscesses in the dermal papillae.[1,2,10] These neutrophils are seen in association with fibrin, leukoclastic debris and edema.[1] Findings in the upper and mid-dermis include perivascular infiltrates containing lymphocytes, neutrophils and eosinophils. There are granular IgA deposits in the dermal papillae by DIF in the perilesional skin of patients with DH, which is the hallmark of the disease. Direct immunofluorescence of perilesional skin is the gold standard for establishing the diagnosis of dermatitis herpetiformis.[5,10,11] Patterns consistent with DH include granular IgA deposits located in the dermal papillae or along the basement membrane.[10] Serology tests

such as IgA anti-tissue transglutaminase and endomysial autoantibodies are used as initial detection of gluten sensitivity and DH.[2,9] Endomysial autoantibodies are directed against smooth-muscle reticular connective tissue and can be detected with indirect immunofluorescence assay.[1] Antigliadin antibodies are also detected in 30% to 60% of DH patients; however, they are not considered disease-specific.[13] Detection of IgA antibodies against epidermal transglutaminase is a sensitive test for the diagnosis of DH, and may be superior to tissue transglutaminase assays at establishing the diagnosis of DH.[8]

There are many comorbidities associated with DH and CD. DH patients have an increased incidence of autoimmune disorders including thyroid disease, pernicious anemia and insulin-dependant diabetes mellitus. Other associated disorders include connective-tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis and Sjogren's disease.[5] Patients with CD may have comorbidities including weight loss, dyspepsia, infertility, bone disease, and consequences of intestinal inflammation, such as strictures.[1] They also may develop nutritional deficiencies, such as B12, folate, and iron.[1,2,3] While patients with CD may have a predisposition to malignancy, fracture or mortality, there is conflicting data regarding the association of DH with malignancy and mortality.[1] Recent studies have failed to find an excess in mortality or malignancy in DH patients compared to the general public. Explanations of the difference in risk factors between CD and DH patients can be attributed to possible variations in expression or activity of tissue transglutaminase phenotype as well as the fact that the enteropathy present in DH is milder and less inflammatory than that found in CD.[14] Due to these potential comorbidities, a workup including a small-bowel biopsy, HLA testing, evaluation of malabsorption and screening for autoimmune conditions should be included in the diagnosis of DH.[10]

Since there are currently no curative treatments for DH, treatment is based on disease management with dietary restrictions and pharmaceuticals. A gluten-free diet is the mainstay of treatment if these patients have celiac disease. Specific foods to be avoided include wheat, rye and barley, as they contain proteins considered to be toxic to patients with celiac disease and DH.[10,15] While gluten exclusion from the diet seems to lessen enteropathy relatively quickly, the lesions of DH respond slowly, taking up to two years to completely resolve.[10] With strict elimination of gluten from the diet, IgA antibodies may even disappear from the dermal-epidermal junction after many years.[10,16] First-line pharmacologic treatment for DH is dapsone. Dapsone is effective in controlling itching and decreasing inflammatory lesions within 48-72 hours.[16] However, dapsone treatment carries many potential, severe adverse effects and requires strict monitoring.[10,16] Hemolysis is the most common adverse effect due to the strong oxidizing ability of the drug and the stress it puts on erythrocytes. Other potential side effects include agranulocytosis, methemoglobinemia, hypersensitivity syndrome, malaise, Stevens-Johnson syndrome, photosensitivity, neurological side effects, nephropathy, hypothyroidism, nausea, vomiting, fever, rash, and lymphadenopathy.[16,10] These side effects seem to be dose dependent and are more likely to occur in those patients with comorbidities such as anemia, cardiovascular disease and glucose-6-phosphate dehydrogenase deficiency. Discontinuation of dapsone results in rapid recurrence of vesicles and pruritis.[16] In patients allergic, intolerant or non-responsive to dapsone, other treatment methods have been met with varying levels of success. Sulfasalazine, sulphamethoxypyridazine and sulfapyridine act as alternative medications.[1,10,16] Sulfapyridine, however, may not completely control symptoms, and in some cases may be entirely ineffective. In patients with sulfa allergies, oral or potent topical corticosteroids may be used in combination with anti-histamines. Although oral corticosteroids show disappointing results, topical corticosteroids may be more beneficial in terms of controlling pruritis. The third-generation anti-histamines have greater activity on eosinophils and may be helpful to alleviate itching.[10] Combination therapy with heparin, tetracycline and nicotinamide has been reported to effectively treat DH in cases of intolerance to dapsone and sulfa. This combination treatment has proved effective in a case study even once heparin therapy was discontinued. Intensive heparin therapy has lead to rapid improvement in skin lesions over 2-13 days. The mechanism by which heparin alleviates the rash of DH remains unknown, but it is thought to inhibit proteolytic enzymes that are activated in DH lesions. Tetracyclines have also been found to act at the basement membrane, suppressing complement-mediated inflammatory reactions and leukocyte chemotaxis. Nicotinamide, a free-radical scavenger, inhibits neutrophil and eosinophil chemotaxis and secretion, and also acts to decrease protease release from leukocytes. Heparin therapy may be difficult to maintain; however, the literature demonstrates that once heparin is discontinued, a combination of tetracycline plus nicotinamide continues to be effective.[17]

Conclusion

This case study describes a patient with cutaneous findings consistent with DH who realized a reduction in lesions and symptoms with tetracycline, nicotinamide and a gluten-free diet. In summary, DH is a cutaneous manifestation of gluten sensitivity, and a clinical or subclinical form of celiac disease (CD) is thought to be present in most patients. DH is characterized clinically by an intensely pruritic papulovesicular rash distributed predominantly on the elbows, knees, buttocks, and scalp. The pathogenesis of DH is multifactorial and includes environmental and genetic predisposing factors. Patients with DH have an increased predisposition to autoimmune and connective-tissue disorders. Because of an increased risk for comorbid conditions, accurate diagnosis and treatment are imperative. Diagnosis is based on history and physical examination and confirmed by histology and DIF studies. While a gluten-free diet is the mainstay of treatment in CD, this has been shown to alleviate cutaneous manifestations. First-line pharmacologic treatment for DH is dapsone, which effectively controls skin findings and pruritis but may be associated with adverse effects. As seen in our patient, patients unresponsive or intolerant to dapsone have several therapeutic options.

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Figure 1

Figure 2

Figure 3

Multiple mechanisms of action of AzA[1]

Continuous improvement in lesions and erythema[2,3]

24-week maintenance data[4]

Additional patient benefits*
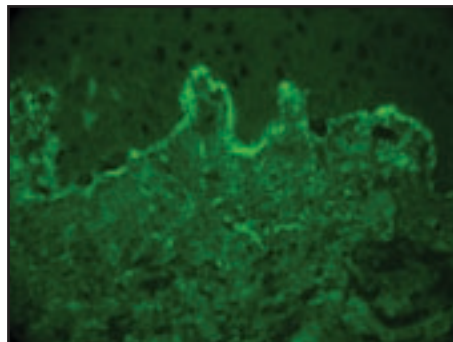
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offering more
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Finacea is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

Finacea is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use. Finacea is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation. In clinical trials, sensations of burning/stinging/tingling occurred in 29% of patients, and itching in 11%, regardless of the relationship to therapy. Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure to the eye. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

Please see following page for brief summary of full Prescribing Information.

References: 1. Draelos ZD, Kayne AL. Implications of azelaic acid's multiple mechanisms of action: therapeutic versatility. Poster presented at: 66th Annual Meeting of the American Academy of Dermatology; February 1-5, 2008; San Antonio, TX. **2.** Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. *J Am Acad Dermatol.* 2003;48(6):836-845. FINACEA was only studied in clinical trials for 12 weeks. **3.** Elewski BE, Fleischer AB, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. *Arch Dermatol.* 2003;139:1444-1450. **4.** Thiboutot DM, Fleischer AB, Del Rosso JQ, Rich P. A multicenter study of topical azelaic acid 15% gel in combination with oral doxycycline as initial therapy and azelaic acid 15% gel as maintenance monotherapy. *J Drugs Dermatol.* 2009;8(7):639-648.

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BRIEF SUMMARY
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INDICATIONS AND USAGE

FINACEA Gel, 15%, is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

CONTRAINDICATIONS

FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of animals with papillomas at the treatment site (**see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility**). The clinical relevance of the findings in animal studies to humans is not clear.

Information for Patients: Patients using FINACEA Gel, 15%, should receive the following information and instructions:

• FINACEA Gel, 15%, is to be used only as directed by the physician.
• FINACEA Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
• Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
• Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
• The hands should be washed following application of FINACEA Gel, 15%.
• Cosmetics may be applied after FINACEA Gel, 15%, has dried.
• Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (See **ADVERSE REACTIONS**).
• Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
• Patients should report abnormal changes in skin color to their physician.
• Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro (Ames assay, HGPRT in V79 cells {Chinese hamster lung cells}, and chromosomal aberration assay in human lymphocytes) and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: *Teratogenic Effects: Pregnancy Category B*
There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid

in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers: Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 μg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/ tingling, dryness/tightness/ scaling, itching, and erythema/irritation/ redness, were 19.4% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	FINACEA Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/ stinging/ tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/ irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event. FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety-Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA Gel, 15%, to the eye (see **PRECAUTIONS**).

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Serendipity: Scar Resolution with Laser Hair Removal

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ABSTRACT

A 51-year-old female who previously underwent electrolysis for facial hirsutism, resulting in atrophic scarring on her chin, presented to our office for continued hair-removal treatments. She underwent treatment with the Candela GentleLASE for 20 sessions over a period of 12 years, with a 90% reduction in hair counts and a complete resolution of the scar tissue observed.

Introduction

Historically, electrolysis has generally been regarded as an appropriate but tedious method of delivering permanent hair removal. In addition to being limited to treating individual hair follicles, there are other disadvantages of using this method, including permanent scarring or pitting of the skin. This is a serious potential side effect of using this treatment technique to remove unwanted hair. By contrast, lasers of multiple wavelengths are able to treat large areas of the body quickly, safely and effectively and are now the technology of choice for achieving permanent hair reduction, even amongst many electrologists. Lasers are also widely used for treating numerous other skin conditions, including cutaneous lesions and dyspigmentation, and for wrinkle removal and skin tightening. In this paper, we report the successful treatment of facial hirsutism on a female patient using the GentleLASE laser from Candela and the unexpected resolution of numerous other skin conditions, including post-electrolysis scarring.

Case Report

In 1998, a 51-year-old Caucasian female presented to our office for laser hair removal. She had previously undergone electrolysis for her unwanted facial hair and dermabrasion for irregular pigmentation without success. She was found to have hypotrophic scarring of the chin as a result of electrolysis treatments, as well as epidermal pigmented lesions and continued hirsutism. We treated her with the Candela GentleLASE at the laser's recommended setting for hair removal. She received 20 sessions of laser therapy and showed 90% improvement of her hirsutism. Surprisingly, the patient also demonstrated an almost complete resolution of her scarring as well as a significant improvement in her dyspigmentation. Her facial skin over the previously scarred area also demonstrated visible tissue tightening. The comparison of photos 12 years apart shows the dramatic improvement in the overall appearance of the patient's skin and the noticeable elimination of hair growth.

Discussion

Alexandrite lasers like the GentleLASE laser are well-known for their hair-removal capabilities.   Alexandrite lasers have high melanin-absorption coefficient levels. As a result, they are also excellent at treating a variety of pigmented lesions, including those resulting from sun exposure. While using the GentleLASE laser from Candela for treating unwanted hair or photo-damaged skin, we often notice skin tightening and toning throughout the treatment area.

Non-ablative laser rejuvenation procedures induce a dermal healing response without notable injury to the epidermis. The exact mechanisms of non-ablative dermal remodeling are still debated. Sub-threshold laser-induced injury to the dermis and/or the dermal vasculature theoretically results in a wound-repair response, fibroblast stimulation, and collagen reformation.

Therefore, it should not be surprising to observe multiple, synergistic effects when using the GentleLASE laser, regardless of the primary indication for use. In this case, we were treating for unwanted hair but were also able to improve the patient's dyspigmentation (and through dermal remodeling) resolve a hypotrophic scar. Ironically, the scar itself was an unwanted side-effect of treating for unwanted hair using another means of permanent hair removal.

Conclusion

Lasers of different wavelengths are capable of treating a wide array of dermatologic conditions. Effects of a single wavelength can be multi-faceted, and it is not unusual to see improvement in different areas of the skin even when treating for a singular condition. The results described in this paper using the GentleLASE laser are an example of the possible synergistic results of using a single laser to treat a single patient complaint. As a practitioner, this is an unqualified endorsement of the technology, as it is always better to under-promise and over-deliver on promises made to patients.

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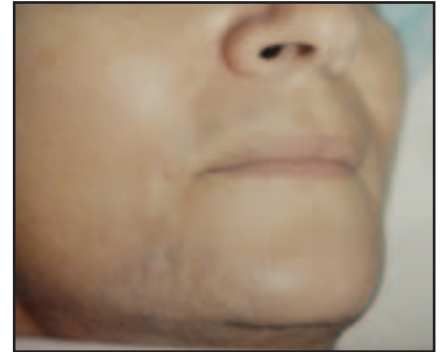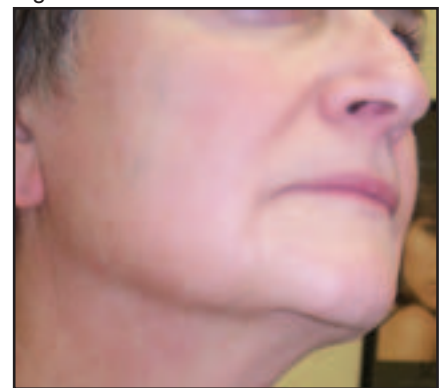
Figure 1

Figure 2

Figure 3

Figure 4

Cutaneous Bronchogenic Cyst:
An Unusual Presentation and Review of the Literature

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ABSTRACT

Cutaneous bronchogenic cysts are rare, congenital malformations of the tracheobronchial system that usually present as cutaneous cysts during childhood due to accompanying airway compromise. We report a case of a congenital cutaneous bronchogenic cyst in a 74-year-old male, present since birth, with enlargement and pruritus as its presenting symptoms, and we review the pertinent clinical and microscopic differential diagnoses.

Introduction

Bronchogenic cysts are malformations of the tracheobronchial system which arise from abnormal ventral budding of the foregut during the third and fourth weeks of gestation. The primitive foregut undergoes infolding both laterally and cephalocaudally to form the foregut proper during this time. The bronchial buds originate from the laryngotracheal groove, which is an outgrowth of the ventral wall of the foregut. If abnormal bronchial budding occurs during this time, a bronchogenic cyst can arise.

Depending on when the abnormal budding occurs, cysts can be located either at the top of the trachea or down into the lung parenchyma. The later the abnormality occurs, the more peripherally the lesion will be located. It is believed that when the malformation occurs at the top of the trachea, a cervical bronchogenic cyst forms. These are rare, however, as most bronchogenic cysts are found within the middle compartment of the mediastinum along the trachea or stem bronchi, or within the posterior compartment adjacent to the esophagus.[1,2] There are five main locations of bronchogenic cysts: paratracheal, carinal, hilar, paraesophageal, and atypical, which includes skin, supraclavicular, and subcutaneous lesions.[3]

Bronchogenic cysts contain clear, serous fluid or mucous, and are lined by respiratory epithelium consisting of pseudostratified columnar ciliated epithelium. Accessory tissues in the cyst wall, such as smooth muscle, seromucinous glands, and cartilage, may also be encountered.

Case Report

A 74-year-old man presented with a slowly enlarging mass on the anterior aspect of the neck that had been present since birth and slowly enlarging. It was accompanied by pruritus. The lesion was excised in toto and was submitted for histologic examination. At low-power examination, a well-circumscribed, epithelial-lined cyst was seen occupying the dermis (Figure 1). At intermediate power of magnification, the cyst wall showed irregular lining with endophytic extension into the cystic lumina. At high-power examination, a pseudostratified ciliated columnar epithelium was seen, with interspersed vacuolated cells consistent with respiratory epithelium (Figure 2). Since removal three months ago, the patient has remained asymptomatic, with no recurrence of the cyst.

Discussion

Given the complications of airway compromise, cervical bronchogenic cysts are usually diagnosed in the pediatric setting. They classically present as a noninflammatory midline neck mass accompanied by symptoms of dyspnea, cough, dysphagia and failure to thrive due to compression of the trachea or esophagus.[4] There are reports, however, of presentations in later adult life that consist of respiratory difficulties and infections.[5,6]

Cervical bronchogenic cysts presenting in the adult population are uncommon. The two most common locations for bronchogenic cysts are the viscera, including the mediastinum and the lung parenchyma.[7] When encountered in the skin, which is rare, they are rarely seen in a midline suprasternal location. Various other locations in the neck have been reported, such as the suprasternal notch,[8] to the left of the thyroid gland,[1,5,9] over the hyoid bone,[10] above the hyoid bone,[11] a supraclavicular right neck mass originating below the clavicle and ending at level III,[6] a right neck mass anterior to the sternocleidomastoid below the angle of the jaw,[12] a left upper neck mass anterior to the sternocleidomastoid muscle at level II,[13] and a cystic mass extending from the inferior pole of right thyroid to the superior mediastinum.[2] Presentations of cervical cysts among the elderly are even more uncommon. In a single similarly reported case, a 70-year-old man presented with a 20-year history of a soft, non-changing, non-tender lump in the suprasternal notch that enlarged in size for two years prior to his visit. His symptoms, however, consisted of difficulty swallowing and neck discomfort. To our knowledge, ours is the first case in which an enlarging midline mass presented with pruritus.

The histological differential diagnoses of bronchogenic cysts include: thyroglossal duct cysts, branchial cleft cysts, thymic cysts, esophageal cysts, and dermoid cysts. Thyroglossal duct cysts (TGDC) consist of secretions from cells that line a localized persistence of the thyroglossal duct. They are lined by either pseudostratified squamous or ciliated epithelium. In the subjacent stroma, there are mucous glands and thyroid follicles, the latter being the distinguishing factor between this entity and bronchogenic cysts. Secondary inflammation is a common finding, especially when a sinus tract is present. Because of this inflammation, the epithelial lining of the cyst may be partially absent.[14] A thyroglossal duct cyst is the most common mass found in the midline of the neck. It usually presents in association with a minor upper respiratory infection, but it can also occur asymptomatically. Although TGDC can be located anywhere from the foramen cecum at the base of the tongue to the level of the thyroid gland, its most common location is at the level of the hyoid bone, where it can be observed moving upwards with protrusion of the tongue. Although most cases occur in childhood, there are reported cases occurring later in life. Inflammation and infection is a common occurrence, and these cysts can enlarge and spontaneously rupture.[14,15]

Branchial cleft cysts represent developmental abnormalities of the 1st through 4th branchial pouches. Those from the 1st pouch can be seen in the preauricular area or near the angle of the mandible, while those from the 2nd pouch are located along the anterior border of the sternocleidomastoid muscle in the midneck. Those related to the 3rd and 4th pouches are usually located in the lower neck, either suprasternally or supraclavicularly. This can often lead to a misdiagnosis of a bronchogenic cyst. They are slow-growing, and they usually don't become apparent until the 2nd or 3rd decade of life. However, they can become suddenly apparent or enlarged in childhood if accompanied by an upper respiratory infection. In neonates, if they become infected, they can rupture or enlarge with resulting respiratory compromise. They typically manifest as nontender, smooth, round masses and can be located at any depth between the skin and the pharynx.[15] Branchial cleft cysts are histologically defined by a squamous or columnar ciliated epithelium, but a characteristic submucosal lymphoid cuff and lack of cartilaginous or smooth muscle elements help to distinguish this

entity from bronchogenic cysts, especially if the cysts are located in the lower neck region. Although not a common finding, glandular elements such as mucinous, seromucinous, and sebaceous glands can also be seen, especially if the cysts are in the lower neck region.[14,15]

Thymic cysts are developmental cysts comprised of ectopic thymic tissues lined by one or more of the following epithelium: flattened, cuboidal, squamous (single or stratified) or columnar (single, ciliated or pseudostratified). Sometimes, the lining can consist simply of fibrous tissue without epithelium. The wall usually possesses Hassall's corpuscles and can have additional lymphoid, parathyroid or thymic tissue, as well as cholesterol granulomas. Uniloculated cysts are usually devoid of any inflammation, while multiloculated cysts are always accompanied by inflammation and fibrosis. Sometimes, this thymic tissue connects to the epithelial lining of the cyst itself. Thymic cysts usually present as painless swellings in children or adolescents, and those of the unilocular type are thought to originate from the third branchial pouch. They are commonly found in the neck, anywhere along a line from the angle of the mandible to the manubrium sternum. The most common location is posterior to the left lateral lobe of the thyroid. They can be unilocular or multilocular and filled with fluid that is yellow-brown to cloudy. Their sizes range from 1-15 cm. Inflammation is usually absent.[14,15]

Esophageal cysts represent faulty closure of endodermal structures and can be lined by squamous, ciliated, or columnar epithelium. The most common location for these cysts is in the lower half of the esophagus. A double layer of smooth muscle in the wall of the cysts differentiates them from bronchogenic cysts.[14,15] Epidermal cysts are slow-growing, solitary developmental cysts that derive from the follicular infundibulum and often possess a surface punctum. The walls of the cyst are typically devoid of cutaneous adnexa and contain a stratified keratinizing squamous epithelium that is filled with desquamated keratinous debris. These cysts affect patients of all ages, and they usually present in early adulthood or middle age. These cysts may be encountered anywhere on the neck, but are more commonly seen on the trunk.[15]

Dermoid cysts can be characterized as developmental anomalies in which lack of epithelial approximation at the midline leads to cysts that are microscopically similar to epidermal cysts, except that they contain skin appendages including pilosebaceous units, eccrine glands and apocrine glands. Like epidermal cysts, dermoid cysts can contain keratinaceous debris. Additionally, they can possess greasy material admixed with hairs as well as mural adipose tissue. Dermoid cysts usually present in childhood or adolescence. Although most commonly found in lines of embryonic closure in the faces of children, they can occur in the neck and therefore constitute an important differential diagnosis to consider.[14]

In summary, cutaneous bronchogenic cysts are rarely seen in adults and are particularly uncommon among the elderly. This case, however, underscores the importance of considering this entity in the differential diagnosis of any midline neck anomaly at any age.

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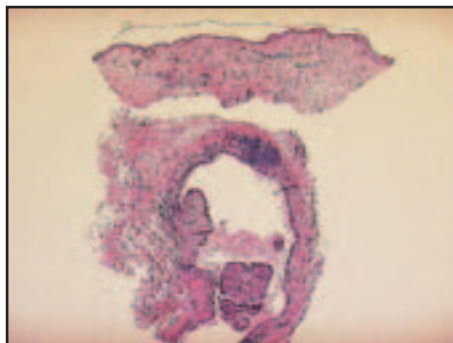15. Weedon D. Skin Pathology 2nd ed. Churchill Livingston 2002. PP. 504, 511, 512.

Figure 1: Low-power photomicrograph depicting epithelial-lined dermal cysts.
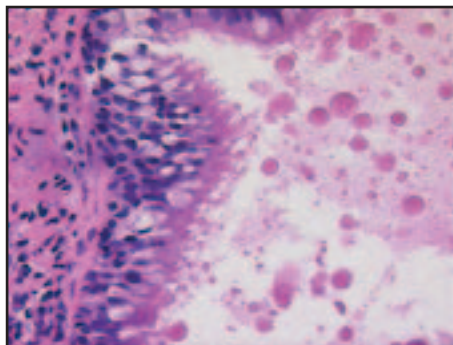

Figure 2: High-power photomicrograph depicting pseudostratified ciliated respiratory epithelium with mucous vacuoles.

An Unusual Presentation of Elastosis Perforans Serpiginosa

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ABSTRACT

Perforating diseases are a group of disorders in which there is a transepidermal elimination of collagen, elastic tissue or necrotic connective tissue. These include reactive perforating collagenosis, acquired perforating dermatosis, perforating periumbilical calcific elastosis, perforating folliculitis, and elastosis perforans serpiginosa (EPS). We report a case of an 18-year-old female who presented to our clinic with multiple red papules and plaques with scale on her abdomen, back, and bilateral lower extremities. A biopsy of one of the lesions was consistent with EPS. Only a few cases of EPS have been reported in the literature that presented with discrete or grouped papular lesions without clinically significant serpiginous configuration. Only five reported cases of disseminated EPS have been reported with Down syndrome patients. We report the first case in the literature of EPS that is disseminated and presented with grouped papular lesions without underlying systemic/connective tissue conditions.

Introduction

Perforating diseases are a group of disorders in which there is a transepidermal elimination of collagen, elastic tissue or necrotic connective tissue. The etiology for these disorders is largely unknown.[1]

Reactive perforating collagenosis (RPC) is a rare familial disorder which begins during childhood. Patients develop keratotic papules induced by superficial trauma. The Koebner phenomenon may occur, in which injury to the skin results in the formation of new lesions. The arms and hands are mainly involved. The papules tend to spontaneously heal in 6-8 weeks. Pathology shows transepidermal elimination of collagen fibers.[1]

Acquired perforating dermatosis (APD) is mainly associated with diabetes mellitus or the pruritus of renal failure. It presents as numerous keratotic papules and nodules. It favors the lower extremities of adults, although it can be generalized. The pathology reveals transepidermal elimination of necrotic material, collagen or, rarely, elastic tissue.[1]

Perforating periumbilical calcific elastosis presents clinically as keratotic plaques on the abdomen, especially in the periumbilical area of multiparous black women. Pathology reveals transepidermal elimination of calcified elastic fibers.[1] Some hypothesize that this condition is a result of local cutaneous trauma from factors such as obesity, multiple pregnancies, or multiple abdominal surgeries.[2] However, similar transepidermal elimination has been observed in patients who treated their dermatitis with commercially available calcium salt water.[1]

Perforating folliculitis usually presents in the second or third decade of life. The disease is characterized by the development of discrete, erythematous follicular papules with a central white keratotic core. Lesions most often affect the extremities, with a predilection for the hairy portions of the arms, forearms and thighs.[3] Duration of lesions is variable, ranging from several months to years. The exact etiology is unknown, although it is speculated to be the end result of abnormal follicular keratinization that most likely is caused by irritation, either chemical or physical, and even chronic rubbing.[2]

And finally, there is elastosis perforans serpiginosa (EPS), which will be reviewed in the discussion section.

Case report

An 18-year-old female was referred to our clinic by a pediatrician complaining of an itchy rash on her bilateral upper extremities, lower extremities, back and abdomen for about a week. Prior to the start of the rash, she did not use any new medications or any new products. Patient did not have any fever, chills, or any constitutional symptoms. She did not have any significant past medical history. She also had no prior surgical history or known drug allergies, and she was taking multivitamins.

On physical examination, the patient had multiple red papules and plaques with slight scale on her abdomen, back, and bilateral lower extremities (Fig. 1-3).

At the initial visit, a 3 mm punch biopsy was performed on one of the lesions on the back. Histopathology revealed a ruptured follicular unit surrounded by mixed cell infiltrate including neutrophils and histiocytes. Also, there was a narrow channel through which elastic tissue fibers had penetrated. Orcein stain for elastin was positive (Fig. 4-7). The diagnosis was EPS.

Patient was prescribed Locoid Lipocream (hydrocortisone butyrate) to be applied twice daily to the affected area. The lesions on the back and abdomen were resolved after two weeks of treatment with Locoid Lipocream. A two-month follow-up revealed the remaining lesions on the lower extremities had resolved on their own.

Discussion

EPS begins during adolescence or early adulthood, with a male to female ratio of 4:1.[4] Lesions of EPS are keratotic papules that tend to be arranged in a serpiginous or annular pattern, mainly on the lateral neck but also on the face and arms.[1] Most patients experience only mild pruritus or no symptoms. Lesions often spontaneously resolve within months or a few years.[4] Pathology reveals elastic fibers being eliminated through a narrow channel through the epidermis.

The molecular mechanism of transepidermal elimination of the elastic material is poorly understood. It has been postulated that the interaction between elastic material and keratinocytes plays an important part in this extrusion mechanism. It has been hypothesized that altered elastic fibers bind via the elastin receptor to the keratinocytes. This induces a rapid terminal differentiation with the formation of an epidermal channel.[5]

According to Fujimoto et al., in vitro elastin peptides induce migration and terminal differentiation of cultured keratinocytes via 67 kDa elastin receptor. In the lesional skin of patients with EPS, the 67 kDa elastin receptor was specifically expressed in the epidermis immediately surrounding the elastic material that was being eliminated. Thus, the authors of this article concluded that the 67 kDa elastin receptor might be involved in the interaction between keratinocytes and altered elastin in EPS, resulting in extrusion of elastic material.[5]

EPS occurs most frequently as an isolated finding (idiopathic EPS). About 25-33% of cases have been associated with genetically determined connective tissue disorders including Down syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, Marfan syndrome, pseudoxanthoma elasticum, Rothmund-Thomson syndrome and acrogeria.[6] A minority of EPS cases have been associated with penicillamine.

There are currently no well-established protocols for the investigation of possible associated connective tissue disorders in patients who present with EPS. In a paper by Vearrier et al.,[7] the authors surveyed 31 pediatric dermatologists who had cared for EPS patients within the previous two years. They concluded that most pediatric dermatologists limit their evaluation of EPS patients to a thorough patient history and physical examination without any additional diagnostic testing. This limited approach may be sufficient evaluation to screen for associated connective tissue disorders for the affected patients.[7]

The exact mechanism for penicillamine-induced EPS is unknown. Penicillamine therapy is used mainly for the treatment of Wilson's disease. Penicillamine chelates and depletes tissue copper. The possible explanation for penicillamine-induced EPS could be that the final step in the elastin biosynthesis pathway involves desmosine cross-links between elastin chains. The cross-links are produced by the action of lysyl oxidase (three allysine and one lysine constitute one desmosine), which uses copper as its co-factor. Due to the long-term

penicillamine use, the copper is depleted, and therefore lysyl oxidase is incapable of forming cross-links between elastic fibers, resulting in fragmented elastic fibers.[8]

Price et al.[8] report a patient with Wilson's disease who was treated with penicillamine for 14 years. She developed EPS, and histological examination of the skin revealed the characteristic penicillamine-induced "lumpy-bumpy" elastic fibers in the dermis. This "lumpy-bumpy" configuration of elastic fibers is pathognomonic for penicillamine-induced elastosis.

More important, at the time of the biopsy, a non-lesional skin also showed the same elastic fiber changes. Of greatest significance was the finding of identical elastic fiber alterations in an artery. Three years before EPS lesions appeared, the patient underwent a surgical procedure in which a small piece of skeletal muscle was removed from the left hand during the surgical release of a flexion contracture. Elastic-stain sections of the accompanying small artery demonstrated the presence of "lumpy-bumpy" elastic fibers. This finding indicates that if penicillamine is taken in high doses for a long period of time, not only will it damage skin elastic fibers, but systemic elastic fiber alterations, including alteration of elastic fibers in arteries, is also a possibility.[8] Therefore, some authors have proposed periodic biopsies of clinically normal flexural skin (before EPS skin lesions appear) in order to assess the status of elastic fibers and avoid serious complications.[8]

There have been no well-designed studies of therapeutic interventions for EPS. Some therapies reported to be successful include local cryotherapy, systemic or local retinoids, tangential excision, electrosurgical destruction, imiquimod cream and laser ablation. However, most lesions will resolve spontaneously within months or a few years.[4]

So why is our case unique? Few reported cases of discrete or grouped papular lesions without clinically significant circular or serpiginous configurations have been reported. Therefore, in an article titled "The Perforating Disorders" (JAAD vol.10 1984), authors proposed that a more accurate name for the condition might be simply "elastosis perforans."[9]

Most EPS patients present with the localized form of this condition. Only five cases of disseminated EPS have been reported previously with Down syndrome patients. The reason for this is unclear, but premature aging of the skin, joint hyperlaxity and acrocyanosis have been associated with Down syndrome, suggesting a subtle disorder of connective tissue.[10]

Therefore, we report the first case in the literature of EPS that is disseminated and presented with grouped papular lesions without any underlying systemic/connective tissue conditions.

In conclusion, a thorough history and physical examination of our patient did not find any associations with any systemic connective tissue conditions. We report another case of idiopathic EPS, which, contrary to popular belief, comprises the majority of EPS presentations. Our case is consistent with the self-limiting nature of this condition.

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Figure 1

Figure 2

Figure 3

Figures 1-3 Multiple red papules and plaques with slight scale on bilateral lower extremities
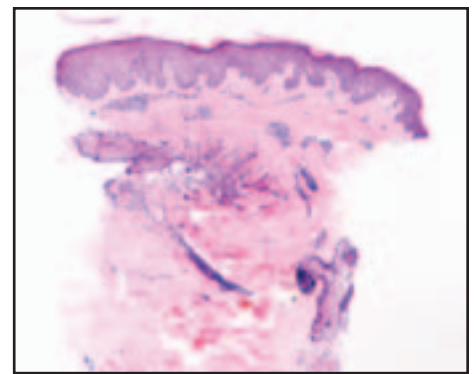

Figure 4

Ruptured follicular unit surrounded by mixed cell infiltrate (hematoxylin-eosin stain)
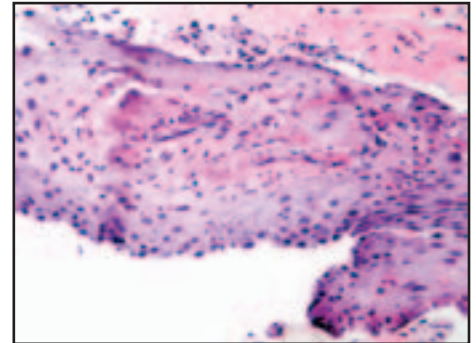

Figure 5

Higher magnification showing narrow channel through which elastic fibers have penetrated (hematoxylin-eosin stain)
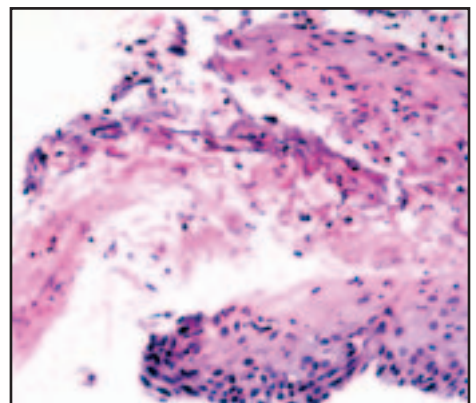

Figure 6

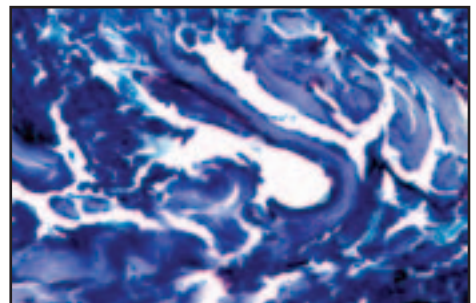Higher magnification showing eosinophilic elastic fibers (hematoxylin-eosin stain)

Figure 7

Orcein stain positive for elastin fibers

NAIL MATRIX MELANOMA
A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

We report the case of a 16-year-old female presenting with dystrophic nail of her right fourth finger. A biopsy was scheduled and performed a week after initial consult, which confirmed a diagnosis of nail matrix melanoma. This case is presented to help increase the awareness of atypical presentations of nail matrix melanoma. Delayed detection of nail matrix melanoma often results in disease progression with poorer prognosis. We also give a brief overview on management and prognosis.

Case Report

A 16-year-old, white female with no significant past medical history presented with abnormal nail growth of her right fourth finger that had evolved over three years. The abnormal nail growth was associated with intermittent bleeding. Prior family practice treatment consisted of avulsion of the nail without improvement. The mother stated that there was a pigmented streak in the nail prior to the avulsions. There was no family history of melanoma. Physical examination of her right fourth finger showed no pigmentation proximal to the nail or in the nail itself. The area of the nail was noted to grow in an abnormal fashion and also appeared to have a lesion underneath. No pigment was visible on dermoscopy. The rest of her fingernails appeared normal.

A nail matrix biopsy of her right fourth finger with nail avulsion was scheduled and performed a week after initial consult. After the proximal nail fold was reflected, pigment was visualized and excised. No abnormality was seen on the nail bed after nail avulsion. Pathology report revealed a 0.5 mm thick melanoma, level III invasion, with ulceration. Tumor-infiltrating lymphocytes and mitotic index of 1/mm^{2} were observed (Figures 1-5).

After diagnosis of nail matrix melanoma was established, she was referred to an oncology surgeon, where a sentinel node biopsy revealed one of two lymph nodes positive for metastatic malignant melanoma. Whole body PET scan was negative. She underwent amputation of her right fourth finger at the distal interphalangeal joint and lymphadectomy of the right axillary sentinel lymph node. At the time of submission, she is to undergo interferon treatment for her metastatic melanoma.

Background

Subungual melanoma, a variant of acral lentiginous melanoma (ALM), arises from the nail bed and accounts for 0.7% to 3.5% of cutaneous melanomas.[1] Subungual melanoma generally arises from the nail matrix, but may involve other components of the nail unit including the proximal nail fold, nail bed, and hyponychium. The incidence of ALM is similar for all ethnicities, but the proportion of ALM is higher in darker-skinned individuals.[1,2] Subungual melanoma is often misdiagnosed, and the delay can be considerable, as was evident in this case.[1,3] Early diagnosis of subungual melanoma is still a challenge for dermatologists in part due to several benign conditions presenting with melanonychia striata, a pigmented, longitudinal nail streak.[4] Differential diagnosis includes longitudinal melanonychia, subungual hematoma, pyogenic granuloma, trauma, or onychomycosis.[4] Varied clinical presentation along with high incidence of amelanosis add to the delay in diagnosis. [5]

Diagnostic approach

General nail-specific ABCDEF guidelines for assessment of subungual melanoma are outlined in Table 1.[6] Chronic unexplained monodactylic nail dystrophy should also be investigated.[5] Clinical evaluation may include dermoscopy, a technique to view pigmented skin lesions through a hand-held lens, or a dermatoscope, after previously applying a fluid (oil, alcohol, or water) on the lesion.[7,3] Dermatoscopy allows for the visualization of morphologic structures of the epidermis and dermoepidermal junction.[7] Diagnosis is made by biopsy, which should include part of the nail bed, nail plate, and nail matrix.[1] The American Joint Commission on Cancer (AJCC) recommends that staging, level of invasion, ulceration, mitotic rate, and Breslow and Clark's levels be determined.[8] The AJCC pathologic staging for cutaneous melanoma is outlined in Table 2.

Management

Treatment of nail matrix melanoma is primarily surgical, with wide local excision and digit amputation as primary modalities of therapy.[1,2] Despite the fact that the most significant factor influencing prognosis is presence of lymph node involvement, the role of sentinel node biopsy remains controversial in the literature. AJCC recommends sentinel lymph node biopsy as standard of care in patients for whom the information will be useful in planning subsequent treatment and follow-up regimens.[8] In contrast, a recent prospective, randomized trial reported no significant increase in survival in those undergoing wide lesion excision and sentinel lymph node biopsy compared to those undergoing wide lesion excision alone.[10]

Prognosis

Prognosis for subungual melanoma is poor, often due to late detection and subsequent advanced stage at time of diagnosis. Results of 5-year survival rates based on Breslow depth in 49 patients with subungual melanoma at the Memorial Sloan-Kettering Cancer Center database from 1992 to 2004 are shown in Table 3.[9] Overall 5-year survival for the 49 patients with subungual melanoma was 58%,[9] which is similar to the figures in other reported studies. Takematsu et al. reported a 5-year survival of 40% in 16 patients with subungual melanoma.[11] Of the 93 cases of subungual melanoma reported by O'Leary et al., 46% survived 5 years.[2]

Survival rates from the 2008 AJCC melanoma staging database are also outlined in Table 4.[8] Delay in diagnosis and presence of advanced disease contribute to the poor prognosis, as was present in this case. An ulcerated, <1.0 mm thick melanoma with no lymph node metastasis has a 5-year survival rate of 94%. Unfortunately, because our patient has an ulcerated, <1.0 mm thick melanoma with lymph node metastasis, her 5-year survival rate is reduced significantly to 55%.

Conclusion

Nail matrix melanoma is often a challenge to diagnose early due its rarity and resemblance to other disorders of the nail. Delay in diagnosis often results in disease progression, with poorer prognosis and treatment options. Early excision and pathologic examination of all lesions with suspicious clinical features is presently the only modality to avoid misdiagnosis.

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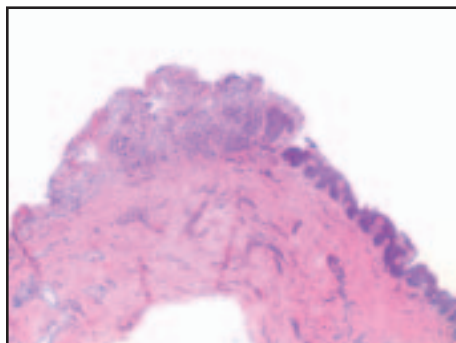
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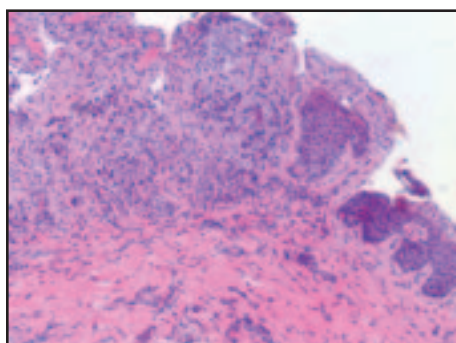
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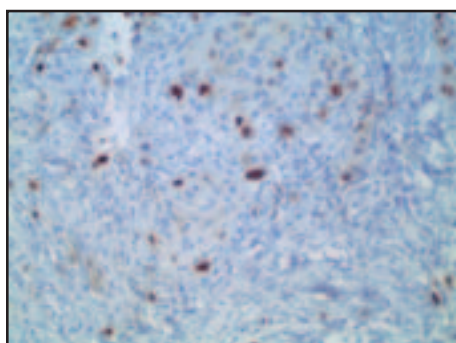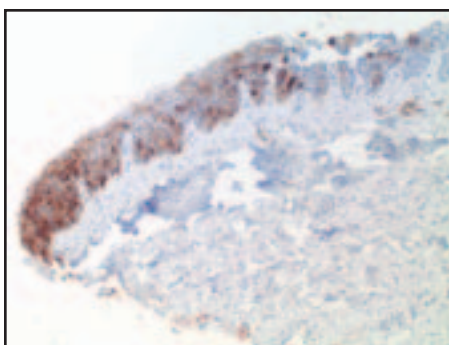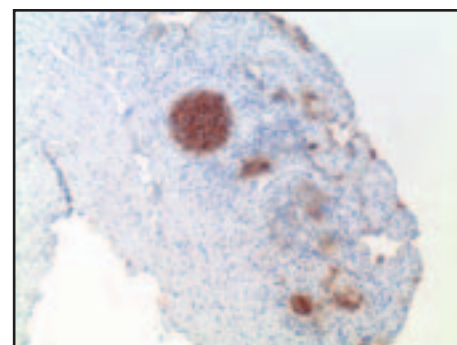
Figure 3

Figure 4

Figure 5

Table 1: ABCDEF guidelines for assessment of subungual melanoma

A	Age – peak incidence in 50 to 70 years of age and African Americans, Asians, and Native Americans
B	Brown to black band > 3mm and variegated borders
C	Change in nail band or lack of change despite treatment
D	Digit most commonly involved – thumb > hallux > index finger; dominant hand; single digit
E	Extension of pigment around proximal and/or lateral nail (Hutchinson's sign)
F	Family or personal history of melanoma

Table 2: AJCC TNM classification for melanoma

T Classification

T1	≤1.0 mm	a: without ulceration and mitosis <1/mm^2
		b: with ulceration or mitosis ≥1/mm^2
T2	1.01–2.0 mm	a: w/o ulceration
		b: with ulceration
T3	2.01–4.0 mm	a: w/o ulceration
		b: with ulceration
T4	>4.0 mm	a: w/o ulceration
		b: with ulceration

N Classification

N1	One lymph node	a: micrometastasis
		b: macrometastasis
N2	2–3 lymph nodes	a: micrometastasis
		b: macrometastasis
		c: in-transit met(s)/satellite(s) without metastatic nodes

N3 4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with
    metastatic node(s)

M Classification

M1	Distant skin, subcutaneous, or lymph node mets	Normal LDH
M2	Lung mets	Normal LDH
M3	All other visceral or any distant mets	Elevated LDH

Mets = metastases
a Micrometastases are diagnosed after sentinel or completion lymphadenectomy.
b Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

Table 3: 5-year survival rates in 49 patients with subungual melanoma

Breslow depth	5-year survival
≤1 mm	100%
>1 to <4 mm	67%
≥4 mm	19%

Table 4: 5-year survival rates based on 2008 AJCC melanoma staging database

	IA	IB	IIA	IIB	IIC	IIIA	IIIB	IIIC
Ta: non-ulcerated	T1a	T2a	T3a	T4a		N1a	N1b	N3
	97%	91%	79%	71%		N2a	N2b	47%
						78%	48%	
Tb: ulcerated		T1b	T2b	T3b	T4b		N1a	N1b N2b
		94%	82%	68%	53%		N2a	N3
							55%	38%

SOLODYN is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older. SOLODYN did not demonstrate any effect on non-inflammatory acne lesions. Safety of SOLODYN has not been established beyond 12 weeks of use. This formulation of minocycline has not been evaluated in the treatment of infections. To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, SOLODYN should be used only as indicated.

Important Safety Information for SOLODYN Tablets

- The most commonly observed adverse reactions are headache, fatigue, dizziness, and pruritus.
- Minocycline like other tetracycline-class drugs can cause fetal harm when administered to a pregnant woman.

- Tetracycline drugs should not be used during tooth development (last half of pregnancy and up to 8 years of age) as they may cause permanent discoloration of teeth.
- 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.
- Central nervous system side effects, including light-headedness, dizziness, and vertigo, have been reported with minocycline therapy.
- In rare cases, photosensitivity has been reported.
- Should not be used during pregnancy or by individuals of either gender who are attempting to conceive a child; concurrent use of tetracyclines with oral contraceptives may render oral contraceptives less effective.

- This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.
- Safety beyond 12 weeks of use has not been established.
- Cases of anaphylaxis, serious skin reactions, erythema multiforme, and drug rash with eosinophilia and systemic symptoms have been reported postmarketing with minocycline use. Discontinue SOLODYN immediately if symptoms occur.

Reference: 1. IMS Health. National Prescription Audit (NPA). Data through March 2011. Data on file, Medicis Pharmaceutical Corporation.

See following pages for Brief Summary of Full Prescribing Information.
SOLODYN is a registered trademark of Medicis Pharmaceutical Corporation.
SOL 10-038R1 01/31/12

SOLODYN®
(MINOCYCLINE HCl, USP)
EXTENDED RELEASE TABLETS
Benefits built in™

**BRIEF SUMMARY
(see package insert for full
prescribing information)**

SOLODYN®
(minocycline HCl, USP) Extended Release
Tablets

Rx Only
KEEP OUT OF REACH OF CHILDREN

INDICATIONS AND USAGE
Indication
SOLODYN is indicated to treat only
inflammatory lesions of non-nodular
moderate to severe acne vulgaris in
patients 12 years of age and older.

Limitations of Use
SOLODYN did not demonstrate any effect
on non-inflammatory acne lesions. Safety
of SOLODYN has not been established
beyond 12 weeks of use. This formulation
of minocycline has not been evaluated in
the treatment of infections.

To reduce the development of drug-
resistant bacteria as well as to maintain the
effectiveness of other antibacterial drugs,
SOLODYN should be used only as indicated
(see Warnings and Precautions).

CONTRAINDICATIONS
This drug is contraindicated in persons
who have shown hypersensitivity to any of
the tetracyclines.

WARNINGS AND PRECAUTIONS
Teratogenic Effects

A. MINOCYCLINE, LIKE OTHER
   TETRACYCLINE-CLASS DRUGS,
   CAN CAUSE FETAL HARM WHEN
   ADMINISTERED TO A PREGNANT
   WOMAN. IF ANY TETRACYCLINE IS USED
   DURING PREGNANCY OR IF THE PATIENT
   BECOMES PREGNANT WHILE TAKING
   THESE DRUGS, THE PATIENT SHOULD
   BE APPRISED OF THE POTENTIAL
   HAZARD TO THE FETUS.

   SOLODYN should not be used during
   pregnancy or by individuals of either
   gender who are attempting to conceive
   a child *(see Nonclinical Toxicology & Use
   in Specific Populations)*.

B. THE USE OF DRUGS OF THE
   TETRACYCLINE CLASS DURING TOOTH
   DEVELOPMENT (LAST HALF OF
   PREGNANCY, INFANCY, AND CHILDHOOD
   UP TO THE AGE OF 8 YEARS) MAY
   CAUSE PERMANENT DISCOLORATION
   OF THE TEETH (YELLOW-GRAY-BROWN).

   This adverse reaction is more common
   during long-term use of the drug but
   has been observed following repeated
   short-term courses. Enamel hypoplasia
   has also been reported. TETRACYCLINE
   DRUGS, THEREFORE, SHOULD NOT BE
   USED DURING TOOTH DEVELOPMENT.

C. All tetracyclines form a stable calcium
   complex in any bone-forming tissue. A
   decrease in fibula growth rate has been
   observed in premature human infants
   given oral tetracycline in doses of 25
   mg/kg every 6 hours. This reaction was
   shown to be reversible 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 Use in Specific Populations).

Pseudomembranous Colitis

**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 a primary cause of
"antibiotic-associated colitis".

After the diagnosis of pseudomembranous
colitis has been established, therapeutic
measures should be initiated. Mild
cases of pseudomembranous colitis
usually respond to discontinuation of
the drug alone. In moderate to severe
cases, consideration should be given to
management with fluids and electrolytes,
protein supplementation, and treatment
with an antibacterial drug clinically effective
against Clostridium difficile colitis.

Hepatotoxicity
Post-marketing cases of serious liver injury,
including irreversible drug-induced hepatitis
and fulminant hepatic failure (sometimes
fatal) have been reported with minocycline
use in the treatment of acne.

Metabolic Effects
The anti-anabolic action of the tetracyclines
may cause an increase in BUN. While
this is not a problem in those with normal
renal function, in patients with significantly
impaired function, higher serum levels
of tetracycline-class drugs may lead to
azotemia, hyperphosphatemia, and acidosis.
If renal impairment exists, even usual oral
or parenteral doses may lead to excessive
systemic accumulations of the drug
and possible liver toxicity. Under such
conditions, lower than usual total doses
are indicated, and if therapy is prolonged,
serum level determinations of the drug
may be advisable.

Central Nervous System Effects
Central nervous system side effects
including light-headedness, dizziness or
vertigo have been reported with minocycline
therapy. Patients who experience these
symptoms should be cautioned about
driving vehicles or using hazardous
machinery while on minocycline therapy.
These symptoms may disappear during
therapy and usually rapidly disappear
when the drug is discontinued.

Benign Intracranial Hypertension
Pseudotumor cerebri (benign intracranial
hypertension) in adults and adolescents
has been associated with the use
of tetracyclines. Minocycline has
been reported to cause or precipitate
pseudotumor cerebri, the hallmark
of which is papilledema. Clinical
manifestations include headache and
blurred vision. Bulging fontanels have been
associated with the use of tetracyclines
in infants. Although signs and symptoms
of pseudotumor cerebri resolve after
discontinuation of treatment, the possibility
for permanent sequelae such as visual loss
that may be permanent or severe exists.
Patients should be questioned for visual
disturbances prior to initiation of treatment
with tetracyclines. If visual disturbance
occurs during treatment, patients should
be checked for papilledema. Concomitant
use of isotretinoin and minocycline
should be avoided because isotretinoin, a
systemic retinoid, is also known to cause
pseudotumor cerebri.

Autoimmune Syndromes
Tetracyclines have been associated with the
development of autoimmune syndromes.
The long-term use of minocycline in the
treatment of acne has been associated
with drug-induced lupus-like syndrome,
autoimmune hepatitis and vasculitis.
Sporadic cases of serum sickness have
presented shortly after minocycline
use. Symptoms may be manifested by
fever, rash, arthralgia, and malaise. In
symptomatic patients, liver function tests,
ANA, CBC, and other appropriate tests
should be performed to evaluate the
patients. Use of all tetracycline-class drugs
should be discontinued immediately.

Photosensitivity
Photosensitivity manifested by an
exaggerated sunburn reaction has been
observed in some individuals taking
tetracyclines. This has been reported
rarely with minocycline. Patients should
minimize or avoid exposure to natural or
artificial sunlight (tanning beds or UVA/B
treatment) while using minocycline. If
patients need to be outdoors while using
minocycline, they should wear loose-fitting
clothes that protect skin from sun exposure
and discuss other sun protection measures
with their physician.

**Serious Skin/Hypersensitivity
Reaction**
Cases of anaphylaxis, serious skin reactions
(e.g. Stevens Johnson syndrome), erythema
multiforme, and drug rash with eosinophilia
and systemic symptoms (DRESS) syndrome
have been reported postmarketing with
minocycline use in patients with acne.
DRESS syndrome consists of cutaneous
reaction (such as rash or exfoliative
dermatitis), eosinophilia, and one or more
of the following visceral complications
such as: hepatitis, pneumonitis, nephritis,
myocarditis, and pericarditis. Fever and
lymphadenopathy may be present. In some
cases, death has been reported. If this
syndrome is recognized, the drug should be
discontinued immediately.

Tissue Hyperpigmentation
Tetracycline-class antibiotics are known
to cause hyperpigmentation. Tetracycline
therapy may induce hyperpigmentation in
many organs, including nails, bone, skin,
eyes, thyroid, visceral tissue, oral cavity
(teeth, mucosa, alveolar bone), sclerae and
heart valves. Skin and oral pigmentation
has been reported to occur independently
of time or amount of drug administration,
whereas other tissue pigmentation has
been reported to occur upon prolonged
administration. Skin pigmentation includes
diffuse pigmentation as well as over sites
of scars or injury.

**Development of Drug Resistant
Bacteria**
Bacterial resistance to the tetracyclines
may develop in patients using SOLODYN,
therefore, the susceptibility of bacteria
associated with infection should be
considered in selecting antimicrobial
therapy. Because of the potential for
drug-resistant bacteria to develop during
the use of SOLODYN, it should be used only
as indicated.

Superinfection
As with other antibiotic preparations,
use of SOLODYN may result in overgrowth
of nonsusceptible organisms, including
fungi. If superinfection occurs, SOLODYN
should be discontinued and appropriate
therapy instituted.

Laboratory Monitoring
Periodic laboratory evaluations of organ
systems, including hematopoetic renal
and hepatic studies should be performed.
Appropriate tests for autoimmune syndromes
should be performed as indicated.

ADVERSE REACTIONS
Clinical Trial 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 following table summarizes selected
adverse reactions reported in clinical trials
at a rate of ≥1% for SOLODYN.

**Selected Treatment-Emergent Adverse
Reactions in at least 1% of Clinical
Trial Subjects**

Adverse Reactions	SOLODYN (1 mg/kg) N=674 (%)	PLACEBO N=364 (%)
At least one treatment-emergent event	379 (56)	197 (54)
Headache	152 (23)	83 (23)
Fatigue	62 (9)	24 (7)
Dizziness	59 (9)	17 (5)
Pruritus	31 (5)	16 (4)
Malaise	26 (4)	9 (3)
Mood alteration	17 (3)	9 (3)
Somnolence	13 (2)	3 (1)
Urticaria	10 (2)	1 (0)
Tinnitus	10 (2)	5 (1)
Arthralgia	9 (1)	2 (0)
Vertigo	8 (1)	3 (1)
Dry mouth	7 (1)	5 (1)
Myalgia	7 (1)	4 (1)

Postmarketing Experience
Adverse reactions that have been reported
with minocycline hydrochloride use in a
variety of indications include:

Skin and hypersensitivity reactions:
fixed drug eruptions, balanitis, erythema
multiforme, Stevens-Johnson syndrome,
anaphylactoid purpura, photosensitivity,
pigmentation of skin and mucous
membranes, hypersensitivity reactions,
angioneurotic edema, anaphylaxis, DRESS
syndrome *(see Warnings and Precautions)*.

Autoimmune conditions: polyarthralgia,
pericarditis, exacerbation of systemic lupus,
pulmonary infiltrates with eosinophilia,
transient lupus-like syndrome.

Central nervous system: pseudotumor
cerebri, bulging fontanels in infants,
decreased hearing.

Endocrine: brown-black microscopic thyroid
discoloration, abnormal thyroid function.

Oncology: thyroid cancer.

Oral: glossitis, dysphagia, tooth
discoloration.

Gastrointestinal: enterocolitis, pancreatitis,
hepatitis, liver failure.

Renal: reversible acute renal failure.

Hematology: hemolytic anemia,
thrombocytopenia, eosinophilia.

Preliminary studies suggest that use of minocycline may have deleterious effects on human spermatogenesis (see Nonclinical Toxicology).

DRUG INTERACTIONS
Anticoagulants
Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Penicillin
Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.

Methoxyflurane
The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.

Antacids and Iron Preparations
Absorption of tetracyclines is impaired by antacids containing aluminum, calcium or magnesium and iron-containing preparations.

Low Dose Oral Contraceptives
In a multi-center study to evaluate the effect of SOLODYN on low dose oral contraceptives, hormone levels over one menstrual cycle with and without SOLODYN 1 mg/kg once-daily were measured. Based on the results of this trial, minocycline-related changes in estradiol, progestin hormone, FSH and LH plasma levels, of breakthrough bleeding, or of contraceptive failure, can not be ruled out. To avoid contraceptive failure, female patients are advised to use a second form of contraceptive during treatment with minocycline.

Drug/Laboratory Test Interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects: Pregnancy category D (see Warnings and Precautions)

SOLODYN should not be used during pregnancy. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and stop treatment immediately.

There are no adequate and well-controlled studies on the use of minocycline in pregnant women. Minocycline, like other tetracycline-class drugs, crosses the placenta and may cause fetal harm when administered to a pregnant woman.

Rare spontaneous reports of congenital anomalies including limb reduction have been reported with minocycline use in pregnancy in post-marketing experience. Only limited information is available regarding these reports; therefore, no conclusion on causal association can be established.

Minocycline induced skeletal malformations (bent limb bones) in fetuses when administered to pregnant rats and rabbits in doses of 30 mg/kg/day and 100 mg/kg/day, respectively, (resulting in approximately 3 times and 2 times, respectively, the

systemic exposure to minocycline observed in patients as a result of use of SOLODYN). Reduced mean fetal body weight was observed in studies in which minocycline was administered to pregnant rats at a dose of 10 mg/kg/day (which resulted in approximately the same level of systemic exposure to minocycline as that observed in patients who use SOLODYN).

Minocycline was assessed for effects on peri- and post-natal development of rats in a study that involved oral administration to pregnant rats from day 6 of gestation through the period of lactation (postpartum day 20), at dosages of 5, 10, or 50 mg/kg/day. In this study, body weight gain was significantly reduced in pregnant females that received 50 mg/kg/day (resulting in approximately 2.5 times the systemic exposure to minocycline observed in patients as a result of use of SOLODYN). No effects of treatment on the duration of the gestation period or the number of live pups born per litter were observed. Gross external anomalies observed in F1 pups (offspring of animals that received minocycline) included reduced body size, improperly rotated forelimbs, and reduced size of extremities. No effects were observed on the physical development, behavior, learning ability, or reproduction of F1 pups, and there was no effect on gross appearance of F2 pups (offspring of F1 animals).

Nursing Mothers
Tetracycline-class antibiotics are excreted in human milk. Because of the potential for serious adverse effects on bone and tooth development in nursing infants from the tetracycline-class antibiotics, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see Warnings and Precautions).

Pediatric Use
SOLODYN is indicated to treat only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years and older. Safety and effectiveness in pediatric patients below the age of 12 has not been established.

Use of tetracycline-class antibiotics below the age of 8 is not recommended due to the potential for tooth discoloration (see Warnings and Precautions).

Geriatric Use
Clinical studies of SOLODYN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

OVERDOSAGE
In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Long-term animal studies have not been performed to evaluate the carcinogenic potential of minocycline. A structurally related compound, oxytetracycline, was found to produce adrenal and pituitary tumors in rats.

Mutagenesis—Minocycline was not mutagenic *in vitro* in a bacterial reverse mutation assay (Ames test) or CHO/HGPRT mammalian cell assay in the presence or absence of metabolic activation. Minocycline was not clastogenic *in vitro* using human peripheral blood lymphocytes or *in vivo* in a mouse micronucleus test.

Impairment of Fertility—Male and female reproductive performance in rats was unaffected by oral doses of minocycline of up to 300 mg/kg/day (which resulted in up to approximately 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN). However, oral administration of 100 or 300 mg/kg/day of minocycline to male rats (resulting in approximately 15 to 40 times the level of systemic exposure to minocycline observed in patients as a result of use of SOLODYN) adversely affected spermatogenesis. Effects observed at 300 mg/kg/day included a reduced number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile, and (at 100 and 300 mg/kg/day) increased numbers of morphologically abnormal sperm cells. Morphological abnormalities observed in sperm samples included absent heads, misshapen heads, and abnormal flagella.

Limited human studies suggest that minocycline may have a deleterious effect on spermatogenesis.

SOLODYN should not be used by individuals of either gender who are attempting to conceive a child.

HOW SUPPLIED/STORAGE AND HANDLING
How Supplied
SOLODYN (minocycline HCl, USP) Extended Release Tablets are supplied as aqueous film coated tablets containing minocycline hydrochloride equivalent to 45 mg, 55 mg, 65 mg, 80 mg, 90 mg, 105 mg, 115 mg or 135 mg minocycline, are supplied as follows.

The 45 mg extended release tablets are gray, unscored, coated, and debossed with "DYN-045" on one side. Each tablet contains minocycline hydrochloride equivalent to 45 mg minocycline, supplied as follows:

| NDC 99207-460-30 | Bottle of 30 |
| NDC 99207-460-10 | Bottle of 100 |

The 55 mg extended release tablets are pink, unscored, coated, and debossed with "DYN-055" on one side. Each tablet contains minocycline hydrochloride equivalent to 55 mg minocycline, supplied as follows:

| NDC 99207-465-30 | Bottle of 30 |

The 65 mg extended release tablets are blue, unscored, coated, and debossed with "DYN-065" on one side. Each tablet contains minocycline hydrochloride equivalent to 65 mg minocycline, supplied as follows:

| NDC 99207-463-30 | Bottle of 30 |

The 80 mg extended release tablets are gray, unscored, coated, and debossed with "DYN-080" on one side. Each tablet contains minocycline hydrochloride equivalent to 80 mg minocycline, supplied as follows:

| NDC 99207-466-30 | Bottle of 30 |

The 90 mg extended release tablets are yellow, unscored, coated, and debossed with "DYN-090" on one side. Each tablet contains minocycline hydrochloride equivalent to 90 mg minocycline, supplied as follows:

| NDC 99207-461-30 | Bottle of 30 |
| NDC 99207-461-10 | Bottle of 100 |

The 105 mg extended release tablets are purple, unscored, coated, and debossed with "DYN-105" on one side. Each tablet contains minocycline hydrochloride equivalent to 105 mg minocycline, supplied as follows:

| NDC 99207-467-30 | Bottle of 30 |

The 115 mg extended release tablets are green, unscored, coated, and debossed with "DYN-115" on one side. Each tablet contains minocycline hydrochloride equivalent to 115 mg minocycline, supplied as follows:

| NDC 99207-464-30 | Bottle of 30 |

The 135 mg extended release tablets are pink (orange-brown), unscored, coated, and debossed with "DYN-135" on one side. Each tablet contains minocycline hydrochloride equivalent to 135 mg minocycline, supplied as follows:

| NDC 99207-462-30 | Bottle of 30 |
| NDC 99207-462-10 | Bottle of 100 |

Storage
Store at 25ºC (77ºF); excursions are permitted to 15º-30ºC (59º-86ºF) [See USP Controlled Room Temperature].

Handling
Keep out of reach of children

Protect from light, moisture, and excessive heat.

Dispense in tight, light-resistant container with child-resistant closure.

U.S. Patent 5,908,838, U.S. Patent 7,790,705 and Patents Pending*
*90 mg is also covered by U.S. Patents 7,541,347 and 7,544,373

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85256

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Erythema Gyratum Repens-like Psoriasis

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ABSTRACT

Psoriasis is a very common disease with essentially pathoneumonic physical examination findings. This being said, it is a polygenic disorder with the potential for significant interindividual variability. Our case of erythema gyratum repens-like psoriasis represents a unique case of psoriasis that mimics this important group of diseases. Classic findings upon physical examination include a figurate erythema that is migratory and composed of concentric rings with a wood-grain appearance. Pruritis and scale are also appreciated, as well as areas of extensive post-inflammatory hyperpigmentation. Important when considering this disorder is excluding erythema gyratum repens, as this disease has a close association with internal malignancy.

Case Report

An otherwise-healthy, 26-year-old African American male presented with a two-year history of multiple scaly-red plaques to his trunk, face, and extremities. The patient stated that this rash initially presented on his scalp as a solitary lesion, but progressed following a motorcycle accident from which he suffered extensive skin trauma. New lesions were presenting as old ones resolved, and he noted darkening that persisted once lesions were gone. At the time of presentation, he was was asymptomatic and otherwise without complaint, denying any pruritus, joint pain, or mucosal involvement. Personal and family histories were unremarkable, and the patient was not taking any medication.

Physical examination revealed multiple scaling annular plaques on erythematous bases (Fig. 1 & 2). These lesions, which were quite pronounced upon inspection, formed concentric rings in a serpiginous fashion (Fig. 3). There was central clearing without a leading or trailing scale, and areas of secondary hyperpigmentation (Fig. 4) were also appreciated. Examination of his fingernails revealed pitting, as well as subungual thickening and discoloration (Fig. 5).

Pathologic examination (via punch biopsy taken from the edge of a plaque on the left thigh) demonstrated an epidermal acanthosis with elongated, club-shaped epidermal ridges, as well as thinning of the suprapapillary plates and a diminished granular layer (Fig. 6). Additionally, there was prominent, confluent parakeratosis with collections of neutrophils.

Based on the clinical presentation described above, as well as the findings appreciated on frozen section, a diagnosis of psoriasis was made. Empirical therapy with topical triamcinolone was initiated and resulted in modest improvement. Because of the extensive and pronounced nature of the disease, however, biologic therapy was ultimately prescribed – resulting in almost complete resolution of this impressive case of psoriasis.

Discussion

The figurate erythemas are a unique group of dermatoses that represent the cutaneous manifestation of various underlying diseases. Although appearing similar in its clinical presentation, the pathogenesis of erythema gyratum repens is oftentimes much more serious in nature and thus requires significant consideration when evaluating a patient with this disease. Radiographic, laboratory, and histologic modalities are all part of this comprehensive evaluation, as internal malignancy has been found in approximately 80% of the cases identified.

Our case of erythema gyratum repens-like psoriasis represents a unique presentation of an extremely common disease. This disease has been reported previously during resolution of pustular psoriasis, following treatment with acitretin, and now following trauma. Although a direct correlation cannot be proven, the onset of this rash, along with the koebnerization, makes this a likely association. Additionally, this case exemplifies the mathematical modeling of pattern formation that appears due, at least in part, to the perturbation of the predisposed genetic regulatory network, as well as to external factors and other entities not yet fully understood.

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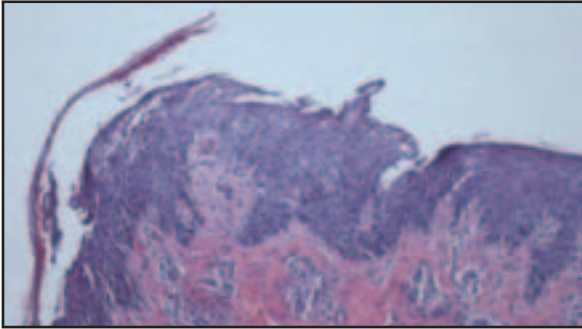
Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

FACIAL LINEAR MORPHEA IN CHILDHOOD A CASE REPORT AND DISCUSSION

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ABSTRACT

This is a case report of 13-year-old black female with unilateral facial linear morphea. This condition, en coup de sabre, can be disfiguring and disabling. Of the various types of morphea, the linear form is the most common subtype among pediatric patients. At the time of presentation, the patient's condition was notably disfiguring, although not disabling. Treatment was immediately instituted, and her progress has been followed.

Case Report

A 13-year-old black female presented to our clinic with a two-year history of non-healing, scarring and bruising on the right side of her face. She had not had treatment for these lesions. She had been applying Dermablend cosmetics to disguise these lesions.

Her past medical history was unremarkable, and there were no prior related medical problems. The patient denied any other symptoms such as headaches, jaw and tooth pain, eating difficulties, joint pain, seizures or learning disabilities. She had never been hospitalized nor had any surgeries. There were no family members with similar dermatologic manifestations.

Physical examination revealed a moderately well-demarcated, tan-yellow, bound-down, linear plaque with brown hyperpigmented borders encompassing the entire right forehead and involving the right upper eyelid and the right side of the nose (Figure 1). On the right cheek extending to the right jaw line and the chin, there was a moderately well-demarcated, tan-yellow, bound down, atrophic plaque with brown hyperpigmented and violaceous borders (Figure 2).

Based on the history and physical exam, the diagnosis of facial morphea, en coup de sabre, was established. In an attempt to attenuate any further disfigurement, our patient was started on a regimen of oral prednisone 60 mg daily, oral methotrexate 15 mg weekly, and folic acid 1 mg daily.

Discussion

Morphea is an inflammatory disease primarily of the dermis and subcutaneous fat, which ultimately leads to a scar-like sclerosis.[1] It is generally thought to be an autoimmune disorder affecting a single organ, the skin.[13] Current classification schemes divide morphea into categories based solely on cutaneous morphology, without reference to systemic disease or autoimmune phenomena.[13] There are three major childhood entities, which are plaque, linear, and generalized morphea.

Classic features of morphea include asymmetric, linear, sclerotic plaques, usually 2-15 cm in diameter.[1] Skin structures such as hair and sweat glands are frequently damaged. Active lesions can have a lilac border, and inactive lesions often become hyperpigmented.[1] Morphea is not associated with systemic disease. It often progresses for several years and then regresses.[1]

The pathogenesis is still not fully understood, but it is thought to involve three major, closely connected components – vascular damage, activated T cells, and altered connective-tissue production by fibroblasts. An increased prevalence of anti-single strand (ss) DNA, anti-topoisomerase IIα, anti-phospholipid, anti-fibrillin 1 and anti-histone antibodies can be seen. Antinuclear antibodies (ANA) are seen in the majority of juvenile patients with linear morphea.[9]

Approximately 20% of the patients with morphea are children and teenagers.[11] Linear morphea is the most common type of morphea seen in childhood. The prevalence ratio of female to male is about 2:1, and two-thirds of the patients with linear morphea are younger than 18 years.[1]

This subtype may involve the underlying fascia, muscle and tendons. As a consequence of this, muscle weakness may occur, due to the shortening of the muscles and fascia, which may lead to impairment of joint motility.[1] Patients may be significantly affected psychologically, because the lesions are typically disfiguring and disabling.

Linear morphea may present initially as a linear, erythematous, inflammatory plaque. More frequently it begins as asymptomatic lesions of plaque-type morphea that coalesce to form a scar-like band.

En coup de sabre is a type of linear morphea involving the forehead.[1] This form of morphea earned its name because of the appearance that the "strike of a blade" has caused a sharp, deep, vertical line on the face.[14] It is normally unilateral and extends from the forehead into the frontal scalp. It may start as a linear streak or as a row of small plaques that coalesce. A paramedian location is more common than a median location. Like plaque morphea, it may initially be surrounded by a discrete lilac ring that extends longitudinally and may reach the eyebrows, nose and even the cheeks. The waning inflammation leaves a linear, hairless crevice that in some patients is more sclerotic, while in others is more atrophic.[1] En coup de sabre can also involve the underlying muscles and osseous structures. Rarely, inflammation and sclerosis progress to involve the meninges or even the brain, creating a potential focus for seizures. Typically, en coup de sabre causes a progressive inflammation which is indistinguishable from the inflammatory process of linear morphea. It often leads to gradual involution of the skin, fatty tissues and underlying bones.

Treatment of morphea is dependent on the severity of the symptoms. There are currently various treatments that have proven to be effective for asymptomatic patients. These include topical corticosteroids, topical calcineurin inhibitors, and derivatives of vitamin D and vitamin A. For symptomatic patients, oral corticosteroids may be helpful in the inflammatory stages of morphea,[1] and methotrexate seems to be helpful in the maintenance treatment.[15] Since the oral corticosteroids do not improve established sclerosis,[1] sometimes physical therapies, such as stretching exercises or even reconstructive surgery, are necessary when joint motility is impaired.

Surgical interventions such as autologous fat transplantation have been reported anecdotally,[16] while other reports have shown PUVA to be effective.[17]

Conclusion

Because our patient presented with quite progressive features on the right side of her forehead and cheek, treatment was initiated with 60mg/day of prednisone, 15mg/week of methotrexate, and 1mg/day of folic acid. The patient was seen back in 30 days for follow-up. At that time, the lesions appeared to be mildly softened as compared to presentation. The patient was seen monthly twice more for subsequent follow-up visits, and the lesions appeared to be slowly softening and decreasing in size.

The patient was lost to follow-up due to health insurance issues and was not seen back for several months. At this time she had been without prednisone and methotrexate for approximately 14 months.

The previous treatment plan was reinstituted, and the medicines are slowly being tapered. The patient will continue with quarterly follow-up visits to monitor her progress and adjust the treatment regimen based upon clinical improvement or failure.

To date, Dermablend cosmetics have proven to be the most effective treatment in the cosmetic appearance of this patient's lesions.

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Questions

1. What is a common serologic finding in children with linear morphea?
   a. Elevated IgE
   b. Elevated IgA
   c. ANA
   d. Elevated LDH

2. What is the most common type of morphea seen in childhood?
   a. Plaque
   b. Guttate
   c. Generalized
   d. Linear

Answers Below

Figure 1

Figure 2

Brooke-Spiegler Syndrome Presenting with Multiple Trichoepitheliomas: A Case Report

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ABSTRACT

Brooke-Spiegler syndrome (BSS) is an uncommon, autosomal dominant disease characterized by multiple adnexal tumors, in particular, cylindromas, trichoepitheliomas, and occasionally spiradenomas.[1] The disease can present as only cylindromas, trichoepitheliomas, or a combination of both.[1] These variations can occur between members of the same family. This article presents a case of a 43 year old male who presented with numerous lesions on his face and back. Histopathology was consistent with trichoepitheliomas.

Introduction

Brooke-Spiegler syndrome (BSS) was first described by Brooke[2] and Fordyce[3] separately as trichoepithelioma papulosum multiplex (TPM) in 1892, while Spiegler was credited in 1899 for describing cylindromatosis.[4] It is thought that both presentations occur due to defective tumor-suppressor genes.[5,6]

Case

We present a case of a 43-year-old Caucasian male who presented with numerous lesions on his face and back. He stated that they had been present for many years, and there appeared to be a family history of the lesions as well. There were multiple, flesh-colored, elevated, papular lesions along his nasal labial folds that were consistent with trichoepitheliomas. There were also several cystic lesions diffusely distributed along the body that were infectious in nature, and therefore the patient was placed on doxycycline twice a day. Patient claimed Accutane had been ineffective in the past. Also, the patient presented with a leonine facies, having glabellar lines accentuated, causing slight disfigurement. Included in the differential was leprosy, so a punch biopsy was performed.

On follow-up, the patient was still developing a few new cysts despite doxycycline treatment, and there was continued presentation of leonine facies. The pathology report of a biopsy of his right ear was read as a basal-cell carcinoma. Given the unusual presentation, biopsies of other sites were performed to rule out the presence of basal-cell carcinoma and also to rule out any other underlying condition. The pathology of these lesions came back as trichoepitheliomas. Brooke-Spiegler syndrome was diagnosed, and the patient was scheduled for dermabrasion but failed to follow up.

Discussion

Brooke-Spiegler syndrome (BSS) is an uncommon, autosomal-dominant disease characterized by multiple adnexal tumors, in particular, cylindromas, trichoepitheliomas, and occasionally spiradenomas.[1] Cylindromas and trichoepitheliomas may also present together on the same patient or occur separately on different patients of the same family. They were once thought to originate from a single genetic entity.[1,7] Most families and individual patients will demonstrate both types of lesions.[11] Both cylindromatosis and TPM are uncommon disorders that present as autosomal dominant in their inheritance pattern.[1] Basal-cell carcinomas, trichoblastomas, and follicular cysts may be associated with or occasionally present within pre-existing lesions of BSS.[8,9] It is rare that cylindromas are found to undergo malignant degeneration.[10] Any of the previously mentioned adnexal tumors may be found alone or in any combination. BSS appears more commonly in women, as there seems to be a decrease with male penetrance and expressivity.[1,8] There does not appear to be any ethnic or racial predisposition.[1,8] Cylindromatosis has a rate of penetrance of around 60% to 75%, with some studies suggesting it may be close to 100%.[7]

While the origin of BSS is unknown, it has been theorized that both cylindromas and trichoepitheliomas are derived from the hair follicle bulge.[4] The gene in which familial cylindromatosis has been localized is on chromosome 16q12-q13, and it is also thought to be a tumor suppressor gene caused by missense mutations in the CYLD gene.[5,12] Families with identical germline mutation in the CYLD gene have been shown to produce both trichoepitheliomas and cylindromas.[12] TPM appears to be more genetically heterogeneous due to a study that mapped a gene relating to TPM to the 9p21 locus, most likely p15.[6] CYLD has been demonstrated to regulate signal transduction pathways whose activity reacts to levels of ubiquitination of component proteins in the JNK and NF-kB signaling pathways.[13,14]

Typically, TPM is seen with numerous, firm, skin-colored, well-demarcated papules that are often distributed on the face symmetrically, with heavier concentrations along the central face and nose. The papule may have an umbilicated or depressed center. They most commonly appear in childhood or adolescence.[12] These patients often have disfigurement since trichoepitheliomas tend to grow in number and size over time, which usually can contribute to psychosocial problems.[12]

Through histology, classical trichoepithelioma (non-desmoplastic) can be diagnosed based on established criteria. Keratinizing cystic spaces surrounded by keratinocytes and papillary mesenchymal bodies are surrounded by an adherent fibrocystic stroma.[12] The specimen should show relative symmetry overall. Difficulties may arise in distinguishing trichoepithelioma from less typical keratotic variants of basal-cell carcinoma.[12] Distinguishing these neoplasms can be done through staining with lymphoid markers, cell membrane glycoproteins, cytokeratin expression, and cell-cycle regulatory proteins.[15,16]

TPM can be treated by a variety of ablative techniques. Several treatments using high-energy, pulsed or continuous-wave carbon dioxide lasers have been shown effective in reducing the appearance of the lesions.[12] Other therapies include dermabrasion, cryotherapy, electrodesiccation and curettage, and radiation.[17,18]

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Figure 4

Figure 1

Figure 2

Figure 3

Newborn with Nonblanchable Rash

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ABSTRACT

We present a case report of a 17-hour old female presenting at birth with a "hematoma" on the entire arm and mid-portion of her back. There was no evidence of peri-natal trauma nor infection. Family medical history was non-contributory. The lesions were non-blanchable and no ulcerations or limb length discrepancies were noted.

History

We were consulted on the case of a 17-hour-old female presenting at birth with a "hematoma" on the entire arm and mid-portion of her back.

Birth history

The patient was born appropriate for gestational age at 39 1/7-week gestation to a 33-year-old, gravida 2, para 1, miscarriage 1 (G2,P1,A1) mother with an uncomplicated pre-, peri- and post-natal course. The patent's birth weight was 6 pounds 4 ounces with a head circumference of 12.25 cm. There were no maternal fetal infections. Upon discharge, the patient received the hepatitis B vaccination, recorded a 24-hour total bilirubin level of 6.5 (reference 0.3-8.0) and weighed 5 pounds 13 ounces.

Family history

Non-contributory. There is no family history of any congenital abnormalities.

Examination

The examination revealed a red to purplish, reticulated vascular network with a segmental distribution along both the anterior and posterior right arm and forearm and extending to the mid upper back with an abrupt demarcation at midline (Figures 1 and 2). A violaceous plaque on the dorsal right hand was noted (Figure 3). No ulcerations, scalp defects, other vascular lesions or heart murmurs were present. Upon emotional stress or change in temperature, mottling of the lesion was more pronounced. No limb length discrepancies were noted. Vital signs were within normal limits. Echocardiogram and EKG were normal.

Diagnosis

Cutis marmorata telangiectatica congenita

Discussion

Cutis marmorata telangiectatica congenita (CMTC), also known as van Lohuizen disease, was first described in 1922 by Dutch pediatrician Cato van Lohuizen. CMTC is commonly described as a violaceous to reddish, diffuse, reticulated, vascular pattern commonly located on the extremities of newborns. Some patients may present with ulcerations overlying the joints, leading to significant scarring. Lesions often improve over time, with stabilization of the lesion's growth by two years of age.[1]

Although the pathophysiology remains elusive, some authors have proposed theories such as the failure of the mesodermal vessels to grow properly during embryogenesis, peripheral neural dysfunction and even external factors such as teratogenic agents.[1,2,3]

Histopathologically, CMTC does not have a hallmark characteristic, making this disorder a clinical diagnosis. However, the biopsy can demonstrate capillary, venous and, rarely, lymphatic dilation and increased microvascularization.[4]

The incidence of anomalies associated with CMTC ranges from 27-80% according to three reports, with the most common being limb asymmetry.[5,6,7] In a study of 85 patients, 65% had unilateral cutaneous lesions, and 69% of patients had limb abnormalities, with the lower limb primarily being involved.[6] Devillers et al. identified 9% of CMTC patients having ocular anomalies, and cutaneous atrophy was present in 9% of patients.[7] Repeated limb measurements throughout development and regular ophthalmology visits are important early on in the child's developmental process. Depending on the limb length discrepancy and gait disturbance, treatment options include shoe lifts or surgical options such as epiphysiodesis (premature closing of the growth plates) and lengthening reconstruction surgery. Neurological abnormalities including frontal bossing, dilated ventricles, and mental retardation were identified in 14% of participants in a study involving 35 patients.[7] Routine follow-up with a pediatrician at the recommended ages is essential in order to screen for these developmental delays. Even less commonly, skin ulceration can be present. The affected area can worsen with cold temperatures, so keeping the skin warm is important in preventing ulceration. Antibiotics and wound care can be used to treat the ulcerations if needed.

Kienast et al. proposed formal diagnostic criteria, including major and minor criteria.[5] The presence of all three major criteria and at least two out of five minor criteria are significant for diagnosis of CMTC.

Major criteria consisted of:
1. congenital reticulate erythema
2. absence of venectasia
3. unresponsiveness to local warming (characteristic of physiologic cutis marmorata)

Minor criteria included:
1. fading of erythema within two years
2. telangiectasias
3. port-wine stain outside of area affected by CMTC
4. ulceration
5. atrophy

The differential diagnosis for CMTC includes vascular lesions from neonatal lupus erythematosus, nevus flammeus, Klippel-Trenaunay syndrome, and Sturge-Weber syndrome.

Most infants with neonatal lupus are females who are born to mothers carrying the Ro/SSA (Smith surface antigen) antibody. Typically, the annular or polycyclic erythematous macules are not present at birth. Infants develop these lesions during the first few weeks of life. Although these skin lesions are transient in nature, the most permanent association is congenital 3rd degree heart block, occurring in over one-half of the infants.[8] Those infants who only carry the U1RNP (U1-ribonucleoprotein) antibodies do not develop the heart block.[8] In this case, our patient had the lesions present at birth, the mother was Ro/SSA and ANA (anti-nuclear antibody) negative, and the echocardiogram was negative, ruling out this disorder.

Nevus flammeus, or port-wine stain, is a relatively common, benign,

congenital capillary malformation occurring in 25% percent of newborns.[9] Typically, these lesions present as a non-blanchable, pink-to-red macule or patch located along the posterior midline neck to the occipital scalp. Some individuals present with a reticulated pattern and often times are misdiagnosed with CMTC. However, CMTC lesions tend to ulcerate and are very course on palpation as opposed to lesions seen in nevus flammeus.[10] Though there are no underlying associated anomalies with nevus flammeus, about 5% of these lesions are permanent.[9] The lesions can also enlarge with the growth of the child, but most involute and fade during childhood. Pulse dye lasers can be effective in treating port-wine stains but can lead to scarring and even recurrence.[9]

In Klippel-Trenaunay syndrome, the cutaneous finding appears more like a capillary stain than a reticulated pattern and is characterized by hyperplasia of the affected limb. The pathophysiology behind this condition is increased venous congestion and lymphatic malformation. The enlarging of the affected limb is due to soft-tissue swelling and bone hypertrophy. Close orthopedic and vascular surgery follow-up is suggested in this syndrome. In this case, our patient had a reticulated pattern with no underlying hemihypertrophy as seen in Klippel-Trenaunay syndrome.

Sturge-Weber syndrome is a condition characterized classically by a unilateral vascular malformation involving the trigeminal nerve distribution V1 and at times the V2 and V3 dermatome.[10] This sporadic inherited condition is associated with neurological abnormalities including seizures, mental retardation, and paralysis. Often the eye may be involved, leading to glaucoma and possible blindness, and the incidence of ocular pathology is increased if bilateral lesions are present.[11] MRI evaluation of the head may reveal tram track calcifications beneath leptomeningeal malformations. Our patient's lesions did not involve the V1-V3 dermatomal distribution, and neurological evaluation was negative, thus ruling out this condition.

Since this disease is usually self-limiting, treatment is not required. In most cases, the lesions dramatically improve and many have complete resolution within the first two years of life. However, when there are associated anomalies present, prognosis is good with early intervention. Close follow-up is recommended by a multi-disciplinary team consisting of dermatologists, orthopedists, cardiologists and ophthalmologists to address any potential concern. Patients should have yearly eye exams evaluating for glaucoma and extremity measurements performed by the patient's pediatrician. Developmental delay should be screened by the pediatrician in order for timely intervention. CMTC has not been well studied or documented in the literature. There are support groups such as the Vascular Birthmark Foundation (www.birthmark.org) on the Internet for patients affected by the disease, which does appear to help families cope with this condition and give access to leaders within this medical field.

Since birth, the infant is being followed by a multi-disciplinary team consisting of dermatologists, an ophthalmologist and her pediatrician. We instructed the family of the possibility of limb length discrepancies, ulcerations, heart defects and potential eye lesions. The parents chose a local university setting for a second opinion. At this time, the second opinion confirmed our diagnosis. The infant is scheduled for an ophthalmology appointment to rule out glaucoma and is being followed by the multidisciplinary team to monitor for limb length issues and ulcerations.

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Figure 1. Red to purplish reticulated vascular network on the anterior right forearm

Figure 2. Red to purplish reticulated vascular network on the posterior right arm extending to the mid upper back

Figure 3. Violaceous plaque on right hand

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Painful Subcutaneous Nodules: An Initial, Abrupt Presentation of a Metastatic Carcinoma of Unknown Primary Origin

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ABSTRACT

Cutaneous metastases from an unknown primary malignancy are infrequent and are indicative of a bad prognosis. We present the case of a patient with multiple, painful and rapidly appearing subcutaneous nodules with no other constitutional symptoms. The histopathology showed a poorly differentiated carcinoma in the deep dermis and the subcutis. The immunohistochemical studies were only positive for cytokeratins, and negative for P63, TTF-1, leukocyte common antigen, renal cell antigen, S-100 protein and HMB-45. The contrast CT scans demonstrated a metastatic, diffuse, nodular process involving the soft tissues and lymph nodes associated also with lytic lesions of the bone. Nevertheless, the primary tumor site was never entified. This is a rare and acute presentation of subcutaneous nodules as the first manifestation of internal malignancy of unknown origin where the first service consulted was dermatology.

Introduction

The cutaneous manifestations of internal malignances are infrequent and usually appear after the diagnosis of the primary tumor has been made. However, they may also be the first clinical sign of a tumor of unknown origin, or the first sign of disease progression in an established oncology patient.[1]

Nowadays, the metastatic carcinoma of unknown origin is known as a condition characterized by generalized metastases affecting several organs without clinical evidence of the primary tumor, with an overall deterioration of the state of health, bad response to chemotherapy treatment and a survival rate between three and four months. These tumors of aggressive behavior present as early tumoral dissemination and represent 5% to 10% of all oncology cases.[1,2] In some cases, it is very difficult for the pathologist to establish the origin of the primary tumor, and the medical history is not helpful. Currently, immunohistochemical stains have helped establish a classification of undifferentiated tumors into four categories: carcinomas, melanomas, sarcomas and lymphomas.

The immunohistochemical stains most often used are cytokeratins (CKs) to identify carcinomas, S-100 protein for melanoma, and the common leukocyte antigen (CD45) for lymphoma. If a sarcoma is suspected, a battery of stains geared toward identifying cell lineage, such as desmin for smooth muscle, CD34 for vascular lesions, and myogenin for skeletal muscle, should be performed. Nevertheless, even with all the immunohistochemical stains, advanced radiologic tests and other modern diagnostic tools available, the origin of an unknown primary tumor is identified in 27% of cases before the patient dies, in 57% when the autopsy is done, and in 16% it is not possible to find the primary tumor even after post mortem tests.[3,4]

Case report

A 63-year-old African-American man presented in July 2010 with a three-week history of abrupt appearance of two painful nodules, one on the back and the other on the right groin area. The patient noticed that after a few weeks, more nodules had appeared rapidly all over his body, sparing the face and head. His past medical history was remarkable for hypertension, benign prostatic hypertrophy, and seizures secondary to a craniotomy due to a gunshot wound he had had years before. At the time the nodules appeared, the patient denied any fever or other major constitutional symptoms, and aside from the loss of 10 pounds of weight in the last month his major complaint was pain.

On physical exam, there were numerous, firm, 2-3 cm skin-colored nodules, very painful to the touch (Figure 1). A biopsy of a nodule from the abdomen was performed for routine histopathology and immunohistochemical stains. The H&E stain showed a poorly differentiated carcinoma involving the deep dermis (Figure 2). The immunohistochemical stains were positive for cytokeratin and negative for P63, TTF-1, common leukocyte antigen, renal cell antigen, S100 protein, and HMB-45. Contrast CT scans of the chest and abdomen showed extensive metastatic disease with diffuse nodular process involving the soft tissues and lymph nodes to the lower neck, anterior and posterior chest wall, mediastinal region and lung masses, hepatomegaly with several hypodense nodular lesions, and mesenteric and retroperitoneal adenopathy. The bone CT scan showed numerous lytic lesions and increased size of the right lower extremity, suggesting lymphedema. The final diagnosis was cutaneous metastases from a carcinoma with unknown primary tumor. The patient was referred to oncology and started chemotherapy with cisplatinum and paclitaxel.

Discussion

A diagnosis of carcinoma of unknown primary tumor is diagnosed in cases where, after taking a detailed medical history and performing physical exam (with rectal and pelvic examination), CBC, CMP, urinalysis, occult blood in stools, histopathology, immunohistochemical stains, chest X-ray, and CT scan of chest, abdomen and pelvis (including a mammography in female patients), the detection of the primary tumor is still not possible.[2,3,5] In these cases, the immunohistopathology and electron microscopy may aid in evaluation of the patient and guide in choosing the best treatment.[1]

The tumors of unknown origin can be classified into four histopathologic subtypes: 1) well-to-moderately differentiated adenocarcinomas (50%); 2) undifferentiated or poorly differentiated adenocarcinomas (30%); 3) squamous cell carcinomas (15%); and 4) undifferentiated neoplasms (5%), including poorly differentiated carcinomas, neuroendocrine tumors, lymphomas, germ cell tumors, melanomas and sarcomas. Our case was a poorly differentiated carcinoma, and as with other cases of unknown primary tumors, it disseminated early, exhibiting an aggressive behavior with multiple sites of involvement as described in the literature in more than 50% of these patients.[3]

Our case was positive for cytokeratins, supporting the diagnosis of carcinoma, and negative for S-100 and HMB 45, ruling out the possibility of melanoma. On the other hand, TTF-1, a tissue transcription factor expressed in epithelial cells of the thyroid, lungs and their neoplastic counterparts, was negative in our case. The renal cell antigen was negative, so no renal origin was possible, and P-63 was also negative for a possible SCC.[3]

This patient represents one of those cases where the primary tumor is never found and there is an unusually abrupt initial presentation, with the rapid appearance of numerous painful subcutaneous metastases with no major constitutional symptoms.

It is important to bear in mind that metastases of a tumor with unknown primary origin could be located in the superficial layers of the skin or the subcutaneous tissue and can be clinically similar to lipomas or cutaneous cysts, with the dermatologist being the first specialist consulted.

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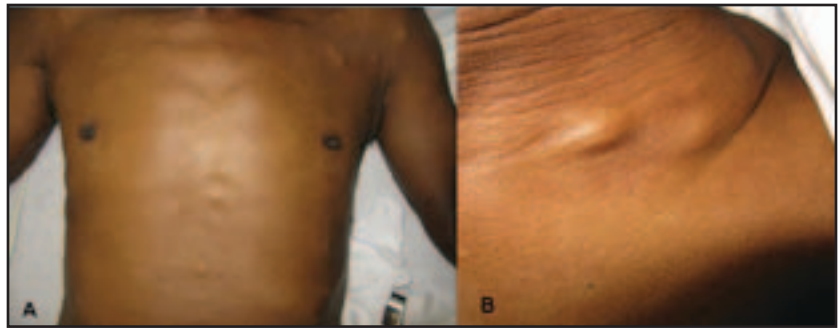
Figure 1: A: Multiple skin-colored, subcutaneous nodules over chest and abdomen. **B:** subcutaneous nodules close up.
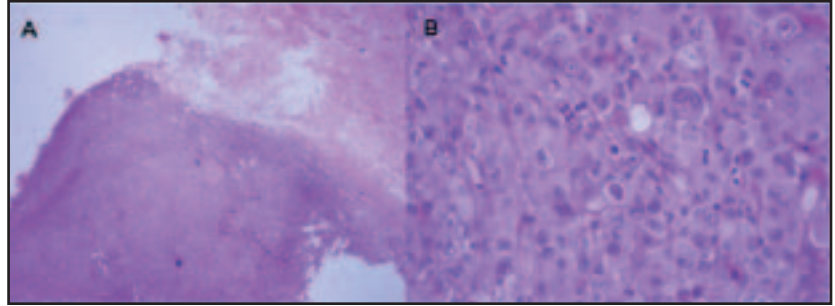
Figure 2: A: Microscopic detail of a nodule. **B:** H&E, poorly differentiated carcinoma involving the deep dermis.

Sweet's Syndrome: A Case Presentation and Literature Review

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ABSTRACT

Sweet's syndrome is an acute febrile neutrophilic dermatosis with unknown pathoetiology. Its association with infections, autoimmune diseases, inflammatory bowel disorders, malignancies, and adverse drug reactions implicates immune system dysregulation as an attractive mechanism of action. Drug-induced cutaneous reactions are idiosyncratic and thus unpredictable manifestations of immune system mediated hypersensitivities. Skin lesions usually resolve upon discontinuation of the sensitizing medication, but may lead to permanent pigmentary changes.

Case Presentation

History and Clinical Presentation

A 44-year-old Caucasian female presented for initial evaluation of a widespread eruption of one-week duration, worsening over time, accompanied by fever and general malaise. Our patient admitted to a history of gastroenteritis and diarrhea a few weeks prior, for which she was prescribed Bactrim DS (trimethoprim - sulfamethoxazole) by her primary care physician. After three days of taking Bactrim DS, the patient started breaking out first in hives, then in a generalized painful rash on her upper and lower extremities as well as the truncal area. She denied oral, ocular, vaginal or rectal lesions of any kind. She gave a history of kiwi fruit allergy, but no known drug or other allergies. Upon further questioning she disclosed her son's sensitivity to sulfa-containing medications and ensuing drug-associated skin eruption that occurred in his early childhood.

Physical Examination

Her skin inspection revealed scattered erythematous papules and nodules, some with discrete distribution, others coalescing into violaceous plaques, distributed predominantly over the limbs and trunk. Selected lesions began as firm, raised, and painful pustules, but subsequently evolved into edematous vesicles according to the patient's account. Lesions to the upper back, chest, and extremities were well demarcated, annular but with irregular borders, erythematous centers, and targetoid appearance (Figures 1-4).

Histopathology

Upper back tangential shave biopsy sample was obtained and demonstrated a neutrophilic dermatosis with interface involvement. The presence of lichenoid interface change and dermal neutrophilic infiltrates raised a possibility of a hypersensitivity reaction, especially a drug reaction or Sweet's syndrome. No fungal organisms were detected using periodic acid-Schiff (PAS) stain.

Diagnosis

Sweet's syndrome (acute febrile neutrophilic dermatosis)

Differential Diagnoses

Inflammatory dermatoses:

1. *Non-infectious dermatoses*
   - Behçet's disease
   - Bowel-associated dermatosis
   - Bullous dermatoses
     - ○ Dermatitis herpetiformis, linear IgA bullous dermatosis
   - Collagen vascular diseases
   - Cutaneous small vessel vasculitis
   - Dermatomyositis
   - Discoid lupus erythematosus (DLE)
   - Erythema elevatum diutinum
   - Erythema multiforme
   - Erythema nodosum
   - Granulomatous disorders
     - ○ Sarcoidosis, granuloma faciale, inflammatory granuloma annulare
   - Halogenoderma
   - Lichenoid hypersensitivity reaction
   - Lymphocytic infiltrate of Jessner
   - Lymphocytoma cutis (Spiegler-Fendt sarcoid)
   - Neutrophilic eccrine hidradenitis
   - Neutrophilic urticaria
   - Other neutrophilic dermatoses
   - Papular mucinosis (lichen myxedematosus)
   - Polymorphous light eruption (PMLE)
   - Pseudolymphoma
   - Pyoderma gangrenosum
   - Rheumatoid neutrophilic dermatosis
   - Vasculitis
     - ○ Small vessel vasculitis, urticarial vasculitis
   - Wegener's granulomatosis
2. *Infectious dermatoses*
   - Cellulitis
   - Deep fungal infections
     - ○ Blastomycosis, coccidiomycosis, cryptococcosis, histoplasmosis
   - Erysipelas
   - Leishmaniasis
   - Mycobacterial infections
     - ○ Tuberculosis, Mycobacterium marinum, leprosy
   - Pyoderma
   - Secondary syphilis
   - Septic vasculitis

Neoplastic Dermatoses:

1. Lymphoma cutis
   - Cutaneous angiocentric lymphoma
   - Cutaneous T-cell lymphoma
   - Large T- or B-cell lymphoma
   - Mycosis fungoides
2. Metastatic visceral carcinomas with paraneoplastic skin manifestations

Course and Treatment

Following a discussion of the diagnosis and possible treatment options, the patient was given an intramuscular triamcinolone (Kenalog) injection. She was also started on levocetirizine dihydrochloride (Xyzal), triamcinolone 0.025% cream, and prednisone oral regimen. Patient returned to the office in two weeks for the follow-up visit, with much skin improvement noted after the prescribed treatment. She was counseled on the diagnosis and prognosis, the importance of finishing all given medications, and the probable reasons for the skin eruption. Moreover, she was informed of the likelihood of the same reaction occurring with any future administrations of Bactrim DS (trimethoprim - sulfamethoxazole), as well as any other drugs containing sulfa chemical groups.

Discussion

Clinical Features of Sweet's Syndrome

Sweet's syndrome (SS)—synonymous with acute febrile neutrophilic dermatosis—belongs to a class of non-infectious neutrophilic skin diseases all sharing similar histopathological features. Notably, there is a characteristic presence of a dense perivascular neutrophilic infiltrate, but no demonstrable vasculitis or infectious etiology.[1] Cutaneous presentations of SS encompass lesions of erythematous, tender, inflammatory papular or plaque-forming distribution, frequently accompanied by fever,

malaise, and peripheral leukocytosis. Extracutaneous extensions of the disease may involve arthralgia, myalgia, and arthritis in approximately one-third of the patients, mainly affecting the knees and wrists. Ocular abnormalities occur in 20-50% of patients, and range from conjunctivitis and episcleritis to iridocyclitis. Other systemic expressions of SS include headache, dyspnea, pleurisy, hematuria, proteinuria, renal insufficiency, and acute renal failure.[2] ESR, C-reactive protein, and globulins are often elevated. Patients with associated internal malignancy may exhibit complicated hematological profile, with increased or decreased white cell count, lymphocytosis or lymphopenia, and thrombocytosis or thrombocytopenia.[1] Skin eruptions typically resolve completely over time; nevertheless, some residual post-inflammatory hyperpigmentation cannot be ruled out.

Epidemiologically, SS affects women more often than men (female predominance of 4 to 1), with typical patients between 30 and 60 years of age. SS has worldwide distribution, but curiously is encountered more frequently in Japan.[2] Prodromal upper respiratory tract infection, diarrhea, and constitutional symptoms resembling influenza often precede the evolution of skin lesions. Eruption is comprised of painful papules, pustules, or nodules forming sharply demarcated inflammatory plaques with intense edematous reaction reminiscent of vesiculation. Cutaneous manifestations may resemble pyoderma gangrenosum in cases of bulla formation. They tend to be multiple, asymmetrical, and affect the face, neck, and both upper and lower extremities, with less common truncal involvement.[3]

Pathoetiology

The pathogenesis of acute febrile neutrophilic dermatosis appears multifaceted, and etiology is frequently idiopathic. Some theorists pose hypersensitivity reaction as a possible explanation for the onset of the syndrome.[3] The differential diagnosis of SS incorporates inflammatory dermatoses of infectious and non-infectious origin. Skin-derived neoplastic processes as well as metastatic visceral carcinomas can also account for SS-mirroring lesions and should be considered among the differential diagnoses.[2]

Classical SS associations and triggers have been described, including gastrointestinal infections (mostly yersiniosis) and upper respiratory tract illnesses (due to Streptococcus or Staphylococcus).[4] Atypical mycobacteria, cytomegalovirus, hepatitis, HIV virus, Behçet's disease, sarcoidosis, and BCG vaccination have all been proposed as inducers of the syndrome.[2] SS has also been observed in autoimmune diseases (e.g., dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome),[5,6] inflammatory bowel diseases,[7] pregnancy,[8] myeloproliferative disorders or hematologic dysplasias,[9,10] melanomas,[11] and internal malignancies or solid tumors.[12,13] In fact, this syndrome should be considered an important cutaneous marker of occult systemic malignancy and a very first manifestation of an underlying paraneoplastic process.

Unusual correlation of a post-myocardial-infarction Dressler's syndrome with SS has been delineated in scientific literature.[14] Why such ostensibly diverse clinical and pathophysiological entities as acute renal failure,[15] hypothyroidism,[16] and kidney transplantation[17] have all reportedly induced cases of acute febrile neutrophilic dermatosis remains a medical mystery for now. Perhaps there are multiple intercepting immunogenetic factors that account for the differing etiological pathways yet converging end results.

Sweet's Syndrome as a Manifestation of Adverse Drug Reactions

A host of drug-induced SS cases have been reported in literature, distinctively exhibiting a temporal relationship between the ingestion of the offending drug and the onset of cutaneous outbreaks. Conversely, there is an expected remediation of symptoms and skin lesions upon cessation of the presumed chemical elicitor. Sulfonamides (trimethoprim-sulfamethoxazole in particular, accounting for 63.8% of cases18), barbiturates, tetracyclines, NSAIDs, and carbamazepine are the commonest causes of fixed drug eruptions.[19,20] Trimethoprim-sulfamethoxazole has been previously associated with the inception of SS,[21] and systemic sulfa has been proposed to induce the dermatosis as well.[22] This case study described the incidence of the syndrome secondary to Bactrim DS (trimethoprim-sulfamethoxazole) administration, further confirming anecdotal and literature accounts of this adverse drug reaction attributable to trimethoprim-sulfamethoxazole sensitivity. In patients suddenly developing characteristic cutaneous eruptions accompanied by pyrexia, SS ought to be excluded, and involvement of prescription medications (such as Bactrim DS) suspected.

Similarly, oral contraceptive Triphasil has been connected to SS, with an impressive clinical resolution of dermatosis upon its withdrawal from the patient's medication routine.[23] Hydralazine,[24] minocycline,[25] and clindamycin[26] have all been linked to SS as causative agents. Other described associations include pegfilgrastim (a pegylated form of granulocyte colony-stimulating factor), which induced bullous form of the syndrome in congenital neutropenia patients,[27] granulocyte colony-stimulating factor,[28,29] sargramostim (granulocyte-macrophage colony-stimulating factor),[30] quinupristin/dalfopristin,[31] all-trans retinoic acid,[32] and celecoxib.[33] Prudent clinicians should develop a high index of suspicion and always consider adverse drug reactions in differential diagnosis of acute febrile neutrophilic dermatoses.

Course, Treatment, and Prognosis

Immediate administration of oral and intramuscular glucocorticoid therapy seems to be the treatment of choice in the clinical management of the SS. Systemic antihistamines with topical steroids may also be of some value as well as yield symptomatic resolution. Relief of both cutaneous and extracutaneous manifestations is expected, but recurrences are common.[1] Antibiotic therapy is the preferred management route in Yersinia-associated infections resulting in SS.[3] Off-label use of biologics, including T-cell inhibitors (alefacept and efaluzimab) and TNF antagonists (receptor decoy etanercept, monoclonal antibodies adalimumab and infliximab), has provided some preliminary efficacy.[34,35]

Anecdotal alternative treatments exist, with select case reports pointing to their effectiveness. Potassium iodide,[36] oral metronidazole,[37] dapsone,[38] colchicine,[39] indomethacin,[40,41] cyclosporine,[42] thalidomide,[43] and systemic interferon-α44 may all have a role as steroid-sparing novel pharmacotherapeutic options. Their evidence-based potential is yet to be elucidated with double-blind placebo-controlled trials.

Cconclusion

In patients presenting with sudden painful skin eruptions morphologically resembling characteristic SS pattern, comprehensive medical and prescription-drug history needs to be obtained. Internal and/or hematologic malignancies as part of paraneoplastic phenomena should be ruled out as possible causes of the SS. Concealed autoimmune disorders and inflammatory bowel diseases can be investigated in cases of elusive etiology.

Treatment of choice for the SS includes systemic corticosteroids (prednisone) for several weeks, with excellent response and relief of both cutaneous and extracutaneous symptoms. Myriad alternative therapeutic approaches exist or have been attempted with variable clinical success. Further basic science research and randomized clinical trials testing the efficacy of these agents could lead to the development of superior treatment modalities, as well as shed more light on the pathogenesis of this condition.

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Figure 1.
An abrupt and painful skin eruption of edematous and erythematous papules coalescing into firm plaques on the patient's upper extremity

Figure 2.
Erythematous, tender nodules resembling vesicles (pseudovesiculation) on the patient's upper chest

Figure 3.
Multiple, firm, sharply bordered, confluent lesions on the patient's shoulder

Figure 4.
Erythematous papules displaying pseudovesiculation on the patient's palm

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