JOHN H. STROGER, JR. HOSPITAL
CASE PRESENTATIONS
MARCH 22, 2006

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Case #1

Presented by Warren Piette, MD and Jessie Cheung, MD

History of Present Illness:
This 29 year-old Egyptian man presents with a twelve-year history of a pink rash involving his trunk and legs. The rash is itchy and scaly, and is spreading to involve his arms. He denies any episodes of erythroderma.

Past Medical History
None

Medications/Allergies:
None; No known drug allergies

Family History:
None

Review of Systems:
Patient denies any fatigue, night sweats, or swollen nodes.

Physical Exam:
There are multiple discrete erythematous pink papules, some with fine scale, grouped on the right flank, upper thighs, bilateral arms and lower back. There is no appreciable lymphadenopathy in the inguinal, axillary, or cervical regions.

Laboratory Data:
The following were abnormal or positive:
Peripheral blood smear with 3% Sezary cells.

The following were normal or negative:
Complete blood count, basic metabolic panel, liver function tests.

Histopathology:
8/05 Left thigh: There is a dense lichenoid infiltrate and epidermotropism of atypical lymphocytes

Diagnosis:
Mycosis Fungoides

Treatment and Course:
The patient failed topical steroids, UVB, and PUVA. He began a trial of topical nitrogen mustard in October 2005, and he is currently applying nitrogen mustard to his body from the neck down every night.

Discussion:
Mycosis fungoides accounts for approximately 1% of all non-Hodgkin lymphomas, with a median age of presentation of 57 years and a male:female ratio of 2:1. Its incidence is estimated at 0.36-0.90 per 100,000 person-years. Patients with classic mycosis fungoides, as originally described by Alibert and Bazin two centuries ago, have pink or erythematous scaly patches and plaques that typically appear on sun-protected areas of the skin, such as the proximal extremities, trunk, and buttocks, and have variable degrees of scaling and pruritus.

Kodama et al. recently reported on an early variant of mycosis fungoides characterized by the onset of papules in the absence of more typical patches of the disease, consistent with this patient's

presentation. They concluded that patients with early mycosis fungoides presenting with papules probably do not need aggressive therapy and can be treated with conventional early-stage treatment modalities.

The main prognostic factors identified in mycosis fungoides are the T cell subtype (CD4 or 8), presence of extracutaneous manifestations, patient age, initial response to treatment, high serum level of lactate dehydrogenase, detection of a peripheral blood T cell clone, and histologic large cell transformation. DNA ploidy analysis revealed that circulating aneuploid malignant T cells in patients with Sezary syndrome are associated with large cell transformation. Blood eosinophilia at baseline has been considered to be independently associated with a poor outcome.

A variety of skin-directed and systemic therapies are available to treat mycosis fungoides, and the stage of disease guides the therapeutic choices. In the past, traditional systemic chemotherapy has not resulted in durable remissions in mycosis fungoides. As a consequence, emerging therapeutic efforts have focused on targeted biological agents and manipulation of the host immune response using a multimodality approach. Numerous arms of the immune system must cooperate to generate a sufficient host antitumor response so that the proliferation of the malignant T cell population can be controlled.

Patients with patches or plaques limited to less than 10% of their skin surface area (T1 disease) tend to exhibit normal cellular immune responses. Thus, the use of skin-directed therapy, which targets the tumor burden in the skin by directly inducing apoptosis of malignant T cells, is often sufficient to induce complete clearing of disease. These include superpotent topical steroids, topical chemotherapy, topical imiquimod, topical retinoid application, narrow-band ultraviolet B, psoralen plus ultraviolet A phototherapy (PUVA), and electron beam radiation therapy. Topical steroids and PUVA also decrease the number of resident epidermal Langerhans cells and subsequently interrupt their chronic stimulation of the malignant T cells. If the clearing is not complete, the addition of a single agent systemic immunomodulator, such as IFN-α or bexarotene, may lead to a better clinical response.

References:

1. Kim EJ, Hess S, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. J Clin Invest 2005;115:798-812.
2. Kodama K, Fink-Puches R, et al. Papular mycosis fungoides: a new clinical variant of early mycosis fungoides. J Am Acad Dermatol 2005;52(4):694-8.
3. Querfeld C, Rosen ST, et al. The spectrum of cutaneous T-cell lymphomas: new insights into biology and therapy. Curr Opin Hematol 2005;12:273-278.

Case #2

Case Presented by Jerry Feldman, MD and Jessie Cheung, MD

History of Present Illness:
This 25 year-old Hispanic man presents with a ten-year history of a rash involving his trunk and upper extremities. The rash started as mildly pruritic, red bumps on the chest that initially resolved, only to recur, spread, and persist. He denies any photosensitivity or muscle weakness.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
None

Review of Systems:
Patient denies any arthritis, fatigue, night sweats, or swollen nodes

Physical Exam:
There are diffuse reticulated hyperpigmented plaques with telangiectasias and finely wrinkled hypopigmentated areas interspersed on the trunk, upper extremities, and proximal lower extremities. There is erythema and fine scaling to the right forearm and right abdomen. There is no appreciable lymphadenopathy in the inguinal, axillary, or cervical regions. The nail folds appear clear.

Laboratory Data:
The following were normal or negative:
Complete blood count, basic metabolic panel, liver function tests, ANA, CPK.

Immunohistochemistry and gene rearrangement studies are pending.

Histopathology:
7/05 Arm: There is focal interface dermatitis, vacuolar type. There are no obvious atypical lymphocytes

Diagnosis:
Poikiloderma; precursor to mycosis fungoides?

Treatment and Course:
The patient has been applying triamcinolone ointment 0.1% to the affected areas with some relief of the pruritus but without change in the appearance of the skin.

Discussion:
Mycosis fungoides accounts for approximatedly 1% of all non-Hodgkin lymphomas, with a median age of presentation of 57 years and a male/female ratio of 2:1. Its incidence is estimated at 0.36-0.90 per 100,000 person-years. Patients with classical mycosis fungoides, as originally described by Alibert and Bazin two centuries ago, have pink or erythematous scaly patches and plaques that typically appear on sun-protected areas of the skin, such as the proximal extremities, trunk, and buttocks, and have variable degrees of scaling and pruritus. It has since been noted that mycosis fungoides actually has protean clinical and histopathological presentations and many variants. These include poikiloderma

Case #2 continued

atrophicans vasculare, Sezary syndrome, granulomatous mycosis fungoides, hypopigmented mycosis fungoides, folliculocentric mycosis fungoides, and Woringer-Kolopp disease.

The earliest detectable histologic alteration in patients developing mycosis fungoides is vacuolar interface dermatitis. This is characterized by a variable infiltrate of mononuclear cells at the dermal-epidermal junction, associated with vacuolar degeneration of basal cells and an indistinct or disrupted basement membrane. There is variable migration of mononuclear cells into the epidermis.

Poikiloderma atrophicans vasculare (parapsoriasis variegata or lichenoides) represents a varient of mycosis fungoides that is characterized by generalized poikiloderma, atrophy, mottled dyspigmentation, and telangiectasias. The large plaque lesions are typically round to oval light brown patches with fine scale occurring on the trunk and flexural areas. They may be asymptomatic or mildly pruritic and are usually stable or gradually increase in size. On histology, there is intermittent parakeratosis with mild hyperkeratosis and acanthosis. Poikilodermatous areas show an atrophic epidermis with dilated dermal blood vessels and melanophages. Numerous atypical lymphocytes are observed around dermal blood vessels and some epidermotropism is observed, but Pautrier microabcesses are usually absent. Later lesions show an interface lymphocytic infiltrate with greater epidermotropism and minimal spongiosis. Immunohistologic studies have shown similar phenotypic findings to classic cases of mycosis fungoides – a CD2+, CD3+, CD4+, CD8-, CD45RO+ pattern with a minority of CD7+ cases.

Two studies of juvenile-onset mycosis fungoides have showed an overrepresentation of the poikilodermatous clinical variant, especially in males. The immunohistochemical profile was similar to that observed in classic patch-stage, adult-onset mycosis fungoides. Wain et al. concluded that in children, the poikilodermatous variant of mycosis fungoides is more common, and that this variant may confer a better prognosis than classical mycosis fungoides.

References:

1. Dougherty J. Poikilodermatous atrophicans vasculare. Arch Dermatol 1971;103:550-552.
2. Everett, MA. Early diagnosis of mycosis fungoides: vacuolar interface dermatitis. J of Cutan Pathol 1985;12:271-278.
3. Howard MS, Smoller BR. Mycosis fungoides: classic disease and variant presentations. Semin Cutan Med Surg 2000;19:91-99.
4. Pimpinelli N, Olsen E, et al. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53(6):1053-1063.
5. Querfeld C, Rosen ST, et al. The spectrum of cutaneous T-cell lymphomas: new insights into biology and therapy. Curr Opin Hematol 2005;12:273-278.
6. Wain EM, Orchard GE, et al. Outcome of 34 patients with juvenile-onset mycosis fungoides: a clinical, immunophenotypic, and molecular study. Cancer 2003;98(10):2282-90.

Case #3

Case presented by Warren Piette, M.D. and Meredith Stewart Reimer, M.D.

Patient A:

History of Present Illness:
This previously healthy 59 year-old African-American woman presented with a two month history of pruritic lesions on her trunk, hands, feet, and legs. She incidentally stated that she had progressively developed a generalized distribution of multiple, asymptomatic, hypopigmented patches over the past ten years.

Past Medical History:
None

Medications/Allergies:
None; Allergies to Penicillin and Aspirin

Family History:
Non-contributory. There was no history of similar skin lesions.

Review of Systems:
Negative

Physical Exam:
There were two distinct skin lesions on physical exam. The first lesions were violaceous-brown flat-topped papules and plaques with some fine white scale located on her arms, forearms, dorsal hands, wrists, back, abdomen, legs, and dorsal feet. There were no lesions on the oral or genital mucosa. The second lesions were irregular, hypopigmented, light brown macules and patches located in a generalized distribution sparing her face, neck, palms and soles. These lesions covered >10% of her total body surface area. There was no lymphadenopathy in her neck, axillae, or inguinal areas.

Laboratory Data:
The following were normal or negative:
Hepatitis B and C serology, complete blood count, metabolic panel, liver function tests

Histopathology:
7/05 Violaceaous Brown Papule from left forearm: Irregular acanthosis of the epidermis, compact hyperkeratosis, hypergranulosis, and a lichenoid lymphocytic infiltrate in the papillary dermis consistent with lichen planus.
7/05 Hypopigmented patch on right arm: Skin with sparse upper epidermal infiltrate with epidermotropism and exocytosis of large atypical lymphoid cells consistent with early patch stage mycosis fungoides.

Diagnosis:
Lichen Planus and Hypopigmented Mycosis Fungoides (TNM stage II, skin disease only)

Treatment and Course:
Initially, because of its diffuse extent and the degree of pruritus, the lichen planus was treated with a course of prednisone starting at 40mg per day for two weeks, followed by a taper over 4 weeks. She also used clobetasol ointment 0.05% to the lesions twice a day and noted significant improvement in her pruritus and many of the lesions resolved. The hypopigmented lesions have been treated with

triamcinolone 0.1% ointment twice per day. PUVA and UVB treatments were offered to the patient, however, she has declined treatment for the hypopigmented mycosis fungoides.

Patient B:

History of Present Illness:
This 57 year old African American female presents with a two year history of asymptomatic hypopigmented patches which began on her neck and spread to involve her arms, legs, and trunk. No treatments had been attempted.

Past Medical History:
Hypertension, Diabetes Mellitus, Hypercholesterolemia, Hypothyroidism

Medications/Allergies:
Hydrochlorothiazide, Ranitidine, Metformin, Enalapril, Rosiglitazone, Lovastatin, Diltiazem, Levothyroxine, Asprin, Multivitamin
No known drug allergies

Family History:
Non-contributory

Review of Systems:
Patient denies any fevers, chills, or weight loss.

Physical Exam:
There are innumerable small hypopigmented macules and patches are scattered over the arms, legs, and trunk. Findings of epidermal atrophy or telangiectasia are absent. Woods light exam is negative.

Laboratory Data:
The following are normal or negative:
Complete blood count, Liver function tests, Comprehensive metabolic panel, CD4 to CD8 ratio

Histopathology:
9/04 Right arm/Left leg: Sparse superficial lymphocytic infiltrates with exocytosis of occasional lymphocytes. Patchy melanin pigment is present in the basal cell layer. The changes are subtle. The differential diagnosis includes an interface dermatitis such as drug eruption and possibly the earliest stages of Mycosis Fungoides.

7/05 Abdomen: Sections show skin with sparse upper epidermal infiltrate which shows epidermotropism. Some of these cells are atypical and cerebriform. Multiple deeper sections show small collections of these cells in the epidermis. Immunohistochemical stains demonstrate that the infiltrate is composed of CD3+ T cells and is negative for CD 20.

Diagnosis:
Hypopigmented Mycosis Fungoides

Treatment and Course:
After the initial biopsy in September 2004 a trial of topical triamcinolone 0.1% ointment was instituted. The patient did experience some clearing of the lesions on her arms. However, during her visit in July,

2005, new erythematous patches were noted on her trunk and a biopsy was performed. The patient has been offered both light therapy and topical nitrogen mustard but has deferred treatment.

Discussion:

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL), representing approximately 50% of all primary cutaneous lymphomas. The typical cutaneous manifestations of MF consist of patch, plaque, tumor, and erythrodermic stages although a wide range of lesions have been described. Hypopigmented MF is an uncommon, or under-reported, clinical variant, with just over 100 cases described in the literature. Patients can present with only hypopigmented lesions, or there can be a mixture with more classic lesions of MF. Hypopigmented MF is often misdiagnosed for years before the correct diagnosis is made, often being called vitiligo, pityriasis alba, post-inflammatory hypopigmentation, or tinea versicolor.

Case series demonstrate several distinct clinical characteristics of the hypopigmented variant of MF. First, there is a strong predilection for dark-skinned or Asian patients, although it has been rarely described in Caucasian patients. Secondly, hypopigmented MF is more likely to occur in younger patients, with a mean age of onset between 25 and 36 years and a mean age at diagnosis between 32 and 39 years. Typical forms of MF have a mean age of 51.8 years at onset, and 59 years at biopsy diagnosis. Additionally, although MF is rare in children, the hypopigmented variant is more frequent in affected children. Histologically, hypopigmented MF is indistinguishable from the nonhypopigmented variants. However, some authors have described a prevalence of CD8-positive lymphocytes in many cases which may be a distinguishing characteristic of hypopigmented MF. While the mechanism of hypopigmentation is still unclear, it may be due to the cytotoxic effect of T suppressor cells on melanocytes in these CD8 predominant cases.

The natural course and survival rate of the hypopigmented variant of MF seems to be comparable to classic MF. Most cases reported in the literature are of TNM stage I disease generally report good responses to standard treatment methods, especially PUVA, UVB, and topical mechlorethamine. The most successful treatment modality appears to be PUVA, which has been shown to induce rapid and complete repigmentation and histologic clearance of disease in several case series.

References:

1. Akaraphanth R, Douglass MC, Lim MW. Hypopigmented mycosis fungoides: treatment and 6 ½-year follow-up of 9 patients. J Am Acad Dermatol 2000;42(1 pt 1):33-9.
2. Ardigo M, Borroni G, Muscardin L, Kerl H, Cerroni L. Hypopigmented mycosis fungoides in Caucasian patients: a clinicopathologic study of 7 cases. J Am Acad Dermatol 2003;49(2):264-70.
3. El-Shabrawi-Caelen L, Cerroni L, Medieros LJ, McCalmont TH. Hypopigmented mycosis fungoides: frequent expression of a CD8+ T-cell phenotype. Am J Surg Pathol 2002; 26(4):450-7.
4. Lambroza E, Cohen SR, Phelps R, Lebwohl M, Braverman IM, DiCostanzo. Hypopigented variant of mycosis fungoides: demography, histopathology, and treatment of seven cases. J Am Acad Dermatol 1995;32(6):987-93.
5. Werner B, Brown S, Ackerman AB. "Hypopigmented mycosis fungoides" is not always mycosis fungoides! Am J Dermatopathol 2005;27(1):56-57.

Case #4

Case Presented by Warren Piette, MD and Michael Pomroy, MD

History of Present Illness:
This 30 year old male presents with a two year history of a recurring eruption that consists or pruritic, ulcerated lesions. He originally presented to an outside Dermatology clinic in 2003 with a large ulcerated plaque on his left upper chest. This resolved over a period of months without intervention and left some scarring. In 2004, he presented to the same clinic with a complaint of similar lesions that had begun on his chest and legs. This eruption consisted of approximately 100 lesions and he continued to get more.

Past Medical History:
None

Medications/Allergies:
None, including no OTC supplements, no drug allergies

Family History:
Maternal grandmother with breast cancer

Review of Symptoms:
Negative

Physical Exam:
Chest, Back, arms, legs, groin, scalp: innumerable erythematous to red-brown nodules, some of which are hyperkeratotic with central black necrosis as well as ulceration. The patient also had a similar number of erythematous scaly oval and circular patches.

Lab Data:
The following were abnormal or positive:

GGT	62 mg/dl	[nl: 3-60mg/dl]
ALT	75	[nl: 5-35mg/dl]

The following were normal or negative:
Analytic cytometric analysis of peripheral blood; CT of the chest, abdomen and pelvis; CBC, Chem 7AST, LDH, Total and direct bilirubin, Uric Acid, Calcium, Phosphate, Alkanine Phosphatase, cholesterol, triglycerides, TSH, free T4, free T3

Histopathology:
9/05 Right forearm: There is focal parakeratosis. Throughout the epidermis, there are scattered necrotic keratinocytes. There is a lichenoid bandlike infiltrate with large atypical lymphocytes and abundant lymphocytes in the epidermis with convoluted nuclei.
10/05 Right wrist: psoriasiform epidermal hyperplasia with exocytosis of atypical lymphocytes consistent with cutaneous T-Cell Lymphoma (Mycosis Fungoides).
10/05 Right leg: Cutaneous T-Cell Lymphoma with large cell transformation

Diagnosis:
Cutaneous T-Cell Lymphoma (Mycosis Fungoides) with Lymphomatoid Papulosis

Treatment and Course:
When the patient was first seen in our clinic in 10/05 he was on Tetracycline 500mg bid for

lymphomatoid papulosis. At that time he was switched to Minocin 100mg bid. The patient was to start on PUVA in 11/05; however, his lesions started to become increasingly ulcerated and painful. The concern was this did in fact represent a large cell transformation of his CTCL. However, the pain and crusting rapidly resolved following a course of antibiotics. He was started on Targretin (bexarotene) on 11/28/05. Since that time his lesions have decreased dramatically (nearly 50%). The patient's triglycerides have increased since starting Targretin, and he has subsequently been started on Zetia and Lovastatin.

Discussion:

Lymphomatoid papulosis (LyP)is a lymphoproliferative disorder which is characterized by spontaneously resolving papules and nodules with strikingly atypical lymphoid cells. LyP was previously thought to be an inflammatory process, but is now known to be a T cell clonal disorder.

Clinically, lesions of LyP are typically erythematous to red-brown papules and nodules, which are initially smooth and hemorrhagic, and later hyperkeratotic with central, black necrosis, crusting, and ulceration. Individual lesions usually resolve within weeks or months; however, the disease may recur for decades.

Histologically, LyP is classified into 3 groups. Type A, or histiocytic type, shows wedge-shaped lymphocytic infiltrates with abundant Reed-Sternberg-like CD30+ cells mixed with neutrophils and eosinophils. Type B, or lymphocytic type, contains a monomorphous infiltrate of small to medium-sized lymphocytes with cerebriform nuclei similar to those observed in Mycosis Fungoidis (MF). Type C displays cytologic features similar to type A, but the atypical cells form sheets or nodules, simulating anaplastic large cell lymphoma (ALCL). The cells in all forms usually bear the pan-T-cell antigen CD3, and are usually CD30+ even when CD4 and CD8 are not present. It is noteworthy, however, that there are reports of CD30 negative LyP type B.

Numerous studies have reported an association of LyP with other lymphomas including MF, Hodgkin's disease, and ALCL. Association of LyP with MF has been reported to be between 7-39%. It has been suggested that patients with MF and LyP have a favorable prognosis and that lymph node or visceral involvement is uncommon. In one recent study regarding LyP associated with MF, an identical clone was found in lesions of both LyP and MF in all 7 patients in whom analysis was possible. Recent data seems to suggest that LyP and MF are related T-cell lymphoproliferative disorders.

Treatments reported to be beneficial in the treatment of LyP include acyclovir, carmustine, tetracycline, methotrexate, interferon α, and PUVA. Bexarotene (Targretin) has been shown to be safe and effective for cutaneous manifestations of CTCL in clinical trials, and has recently been shown to be effective for LyP as well, both topically and orally. Bexarotene is a rexinoid with selectivity for intracellular retinoid X receptors (RXR) over retinoic acid receptors (RAR). Stimulation of the RARγ-influenced apoptosis pathway can be potentiated by RXR agonists thus increasing the number of T cells undergoing apoptosis. It is important to monitor fasting triglycerides and free thyroxine levels, and patients may require concomitant treatment with statins as well as levothyroxine supplementation.

References:

1. Beljaards, RC et al. The prognosis of patients with lymphomatoid papulosis associated with malignant lymphomas. Br J Dermatol 1992;126:596-602.
2. Bekkenk, MW et al. Primary and secondary cutaneous CD30+ lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood. 2000;95(12):3653-3661.
3. El Shabrawi-Caelen et al. Lymphomatoid Papulosis. Arch Dermatol 2004;140:441-447.
4. Krathen, RA et al. Bexarotene is a New Treatment Option for Lymphomatoid Papulosis. J of Dermatol 2003;206:142-147.
5. Zackheim, HS et al. Lymphomatoid papulosis associated with mycosis fungoides: A study of 21 patients including analyses for clonality. J Am Acad Dermatol 2003;49(4):620-623.

Case #5

Case presented by Sidney Barsky, MD, and Alyssa Nash-Goelitz, MD

History of Present Illness:
This 62 year-old Caucasian male presents with a three to four month history of scattered asymptomatic nodules on the forehead and frontal scalp. The nodules did not respond to a topical antifungal.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory

Review of Systems:
The patient denies any fevers, chills, night sweats, or weight loss.

Physical Exam:
Three erythematous, firm subcutaneous nodules ranging in size from 1 to 2 centimeters are present on the forehead and frontal scalp. No lymphadenopathy is present.

Laboratory Data:
The following were normal or negative:
Basic metabolic panel, liver profile, complete blood count, serum protein electrophoresis

Histopathology

1/04 Forehead: Lymphocytic infiltrate with crush artifact. Immunocytochemistry is performed showing a lymphocytic infiltrate composed of a mixture of T and B cells, suggesting a non neoplastic nature on the infiltrate.
1/04 Forehead: T- and B- cell gene rearrangement study: negative for monoclonality.
9/05 Forehead: Dense deep dermal atypical lymphocytic infiltrate
12/05 Forehead: A diffuse monomorphous proliferation of large atypical lymphocytes is present in the dermis wiith a clear grenz zone. The cells have large vesicular nuclei with prominent nucleoli and basophilic cytoplasm. The cells stain positively for CD 20.

Radiology:
CT chest (with and without contrast): No gross lymphadenopathy or abnormality.

Diagnosis:
Large B-cell Cutaneous Lymphoma

Treatment and Course:
Initially clobetasol ointment was given to treat the affected area and resultant moderate improvement of the lesions was noted. Treatment was tapered to triamcinolone ointment 0.025%. In August, 2004, the patient noticed new lesions. Subsequent biopsies noted a progressive malignant change. He was then referred to hematology oncology for further care. CT scan of the chest, abdomen and pelvis is pending, and if negative, plan is for radiation therapy to affected areas.

Case #5 continued

Discussion:

Cutaneous B-cell lymphomas can present as primary cutaneous tumors or secondary to systemic lymphomas. Classification of primary cutaneous B-cell lymphomas is controversial and is organized according to the World Health Organization into follicular lymphoma, large B-cell lymphoma, extra nodal marginal zone B-cell (MALT) lymphoma, and mantle cell lymphoma.

Lesions of primary cutaneous B-cell lymphoma generally present as pink to violaceous papules, plaques, and nodules most commonly on the head and neck. Large B-cell cutaneous lymphomas (LBCLs) are high-grade lymphomas histologically, but histologic grade does not appear to correlate with prognosis in primary cutaneous disease. Primary cutaneous lesions of LBCL that arise on the head and neck are indistinguishable from follicular lymphoma and may be managed with equal success. The EORTC recognizes a distinctive subset arising on the leg associated with an "intermediate" prognosis and a 5-year survival of 58%.

Histopathologically, LBCL exhibits a diffuse monomorphous dermal and/or subcutaneous proliferation of large atypical lymphocytes. Rarely, epidermotropism has been described. The cells have large vesicular nuclei with prominent nucleoli and abundant indistinct or basophilic cytoplasm. Ulceration, epithelial necrosis, and numerous mitotic figures are usually present. The cells usually express CD19, CD20, CD79α, and variably monotypic sIg or cIg. Clonal rearrangement of immunoglobulin genes is present.

Most cases of LBCL are managed successfully with local radiation therapy or complete surgical removal. Treatment of BCL associated with extracutaneous or widespread cutaneous involvement usually requires multiple-agent chemotherapy and should be coordinated with an oncologist.

Large B-cell lymphomas are usually fatal, but appear to have a better prognosis in the rare case limited to the skin. Factors potentially associated with a poor prognosis include B symptoms (ie, fever, chills, night sweats), generalized distribution of skin lesions, and elevated serum lactate dehydrogenase levels.

Our patient initially carried the diagnosis of pseudolymphoma as initial biopsies revealed an infiltrate composed of T and B cells, lacked clonality, and contained polytypic B cells. It is often difficult to differentiate cutaneous B cell lymphoma (CBCL) from pseudolymphoma on the basis of clinical evaluation alone. The histopathologic findings are usually helpful. The histologic features that favor pseudolymphoma over CBCL include (1) acanthosis, (2) a top-heavy infiltrate, (3) a mixed cellular infiltrate, (4) presence of germinal centers, (5) a presence of tingible bodies (fragmented basophilic nuclear debris of degenerated lymphoid cells), (6) vascular proliferation, (7) preservation of the adnexal structures, and (8) the appearance of the germinal centers. In questionable cases, immunohistochemical studies are very helpful and show a monotypic light-chain restriction of the surface immunoglobulins in primary cutaneous B-cell lymphoma but not in pseudolymphoma.

In the past many of the cases diagnosed as pseudolyphoma would now very likely be classified as being indolent varieties of primary cutaneous B cell lymphoma. Early recognition of the lymphoma potential of these kinds of infiltrates remains a challenging clinical and pathologic problem.

References:

1. Bogle MA, Riddle CC, Triana EM, et al. Primary cutaneous B-cell lymphoma. J of Am Acad Dermatol. 2005;53(3):479-84.
2. Fung MA, Murphy MJ, Hoss DM, et al. Practical evaluation and management of cutaneous lymphoma. J Am Acad Dermatol 2002;46(3):325-57.
3. Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. J Am Acad Dermatol. 1998;38(6):877-905.
4. Pandolfino T, Siegel R, Kuzel T, et al. Primary cutaneous B-cell lymphoma: review and current concepts. J Clin Oncol 2000;18:2152-68.
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Case #6

Case Presented by Jerry Feldman, MD and Sari Weinstein, MD

History of Present Illness:
This 19 year-old African American woman initially presented with a four-month history of an enlarging new "mole" on her left preauricular area and a two-month history of non-tender left cervical lymphadenopathy. She felt well otherwise and could not recall any preceding illnesses.

Past Medical History:
None

Medications/Allergies:
None; Penicillin (rash)

Family History:
Non-contributory

Review of Systems:
No fevers, chills, joint pains, chest pains, shortness of breath, gastro-intestinal complaints, oral ulcers, or other rashes.

Physical Exam:
She is a well-appearing young woman with a 2.5 x 2.0 centimeter irregular brown indurated plaque on her left preauricular area; in addition, there is a 1 centimeter firm subcutaneous swelling in her left posterior neck.

Laboratory Data:
The following were abnormal or positive:

Monocytes	10.6%	[nl: 2.0-9.0]
Eosinophil	5.5%	[nl: 1.0-4.0]
Neutrophil	46%	[nl: 50-75]
ESR	60mm/hr	[nl: 0-15]

The following were normal or negative:
Complete blood count, ANA, Anti-centromere antibody, basic metabolic panel, monospot

Histopathology:
1/05 Left cervical lymph node: necrotizing histiocytic lymphadenitis; multinodular necrotic areas with numerous foamy histiocytes containing cell debris and aggregates of non-phagocytic monocytes detected on the edge of necrotic foci; neutrophils are notably absent; cytometric analysis did not detect a clonal population of lymphocytes
9/05 Left preauricular area: skin with dense dermal lymphohistiocytic infiltrates with apoptosis compatible with Kikuchi's Disease involving the skin; immunohistochemical stains show mainly CD3+ lymphoid cells and CD68 highlights the numerous histiocytes

Diagnosis:
Kikuchi's Disease

Treatment and Course:
Adenopathy has not recurred after her lymph node biopsy, however the plaque on her face has not significantly softened or regressed despite trials of hydrocortisone, triamcinolone, fluocinonide and tacrolimus 0.1% ointments, and multiple intralesional injections of triamcinolone up to 10 mg/cc.

Case #6 continued

Discussion:

Kikuchi's Disease (KD), or histiocytic necrotizing lymphadenitis, was first reported in Japan in 1972 by Kikuchi and Fujimoto et al but has since been recognized worldwide in persons of all races and ethnicities. It is characterized by benign painful or painless unilateral cervical lymphadenopathy in young adults. Up to 80% of cases occur in women, usually under age 40. Because it can clinically and histologically mimic lymphoma or lupus, it is important to consider KD as a rare cause of lymph node enlargement with fever in young female patients. Its specific incidence is unknown.

The clinical symptoms of KD are nonspecific but generally include cervical adenopathy and fever and rarely a combination of other associated symptoms. Posterior cervical lymph nodes are most commonly involved, and the lymphadenopathy is usually rubbery or firm, discrete, and smaller than two centimeters. Cutaneous manifestations may be common in the pediatric population.

The diagnosis of KD is usually based on excisional lymph node biopsy. The characteristic histopathology includes architecture distortion by mostly well-circumscribed nodular aggregates of histiocytes, with coagulative necrosis and karyorrhectic debris. Many histiocytes within necrotic foci display phagocytosis of karyorrrhectic nuclear fragments. The immunophenotype includes a predominance of polyclonal T cells; the histiocytes express histiocyte-associated antigens such as lysozyme, CD68, and myeloperoxidase. Plasma cells and neutrophils are scarce. SLE may resemble KD histologically, but large numbers of plasma cells or hematoxylin bodies favors the diagnosis of SLE. The condition most serious and most commonly confused with KD is malignant lymphoma; the cellular histiocytic and immunoblastic proliferations may be mistaken for the atypical lymphocytes of lymphoma. KD also lacks the monoclonal lymphocyte population on flow cytometry studies seen in lymphoma.

The cause of KD remains unknown. Bacteria, viruses, and parasites have been implicated but not confirmed as associations. Others postulate that the disease may be a hyperimmune response to various microbial, chemical, physical or neoplastic agents. No statistics describing the potential association with these specific causes have been reported.

Most patients have a benign, self-limited course ranging from 1 to 4 months, although the subsequent or simultaneous development of systemic lupus erythematosus has also been described. No specific treatment has been universally reported to be effective, although nonsteroidal anti-inflammatory agents, hydroxychloroquine, and glucocorticoids have been used. Rapid improvement has been noted after excisional biopsy, suggesting that removal of the abnormal tissue contributes to the recovery. Three to four percent of KD patients experience 1 or more recurrent episodes, and recurrences have occurred up to 18 years after initial presentation. Because a possible association between Kikuchi's syndrome and the eventual development of SLE has been suggested, patients require long-term monitoring.

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Case #7

Case Presented by Warren Piette, MD and Samantha Golden, MD

History of Present Illness:
This 23 year-old African American female presents with reticulated hyperpigmentation of her upper and lower extremities associated with both pain and weakness. She was seen at an outside hospital 6 months prior with fevers, myalgias, headaches, arthralgias and erythema and swelling of her lower extremities. She had hyperpigmented, palpable nodules with pain to palpation. She was admitted to the hospital twice. The nodules in her skin were improving on prednisone and colchicine when she presented to Cook County Hospital, but she was still having pain and weakness in her lower extremities.

Past Medical History:
None

Medications/Allergies:
None, No known drug allergies

Family History:
Non-contributory

Review of Systems:
Negative for change in bowel habits or urine color. No shortness of breath, chest pain, nausea or vomiting.

Physical Exam:
The patient had mottled, reticulated, hyperpigmentation on her upper and lower extremities with some well-demarcated round, hyperpigmented plaques. There was pain on palpation to her legs and she had some weakness, left worse than right.

Laboratory data:
The following were abnormal or positive:

Hemoglobin	8.9 GM/DL	[nl: 12.0-16.0]
White blood cells	11.44 TH/UL	[nl: 4.00-10.00]
Neutrophils	78%	[nl: 46.0-78.0]
ESR	>140	[nl: 0-15]

The following were normal or negative:
Metabolic panel, G6PD, Total protein, Albumin, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, AST, ALT, SSA, SSB, Scl-70, ASMA, p-ANCA, Cryoglobulins, Anticardiolipins, β2Glycoprotein antibodies, RPR, Rheumatoid factor, C3, C4, CKMB, Hepatitis B, Hepatitis C, ANA

Histopathology:
7/05 (Outside Hospital) Leg: Within the subcutaneous fat there are at least two medium sized blood vessels with fibrinoid change and acute inflammation. Mild neutrophilic inflammation is also present in the adjacent fat. There are no granulomas seen. If this biopsy represents lesions localized to the leg, erythema induratum is the most likely diagnosis. However, an underlying systemic vasculitis such as polyarteritis must be considered.
(Cook County Hospital): At the dermal fat junction, there are medium sized arterteries with fibrinoid degeneration and infiltration of the vessel wall consistent with Benign Cutaneous Polyarteritis Nodosa.

Case #7 continued

Diagnosis:
Benign Cutaneous Polyarteritis Nodosa

Treatment and Course:
Her skin disease improved on prednisone and colchicine for 3 months prior to her presentation at Cook County Hospital. Dapsone was added for residual pain. She is currently off prednisone.

Discussion:
Polyarteritis Nodosa (PAN) is a term applied to multiple vascultic syndromes. Benign cutaneous PAN (BCPAN) is limited to the skin, muscles, and articulations, sparing the internal organs. It is chronic and has a benign prognosis. Erythematous tender subcutaneous nodules and livedo reticularis are common manifestations of BCPAN. Less commonly, peripheral gangrene can be present. The extra-cutaneous manifestations of BCPAN are frequent and include fever, fatigue, anorexia, myalgia, arthralgia, and possibly non-destructive arthritis. Neuropathies of the lower extremities can be observed, but are usually localized to the areas of skin involvement. Histologically, BCPAN is characterized by damage to the medium and small arteries of the deep dermis and hypodermis. There is usually a panarteritis with fibrinoid necrosis and a polymorphous inflammatory granuloma, predominantly neutrophils and occasionally eosinophils, which infiltrates the whole of the arterial wall. Patients exhibit an inflammatory syndrome and moderate hyperleukocytosis, without hypereosinophilia. Usually other laboratory examinations are normal, or negative including ANCA screening. There is an association of BCPAN in children with streptococcal infection, with cutaneous signs preceded by infections of the upper respiratory tract and increased anti-streptolysin O antibodies. Benign Cutaneous PAN usually has a good prognosis. Non-steroidal anti-inflammatory drugs, colchicines, and especially dapsone are usually successful. Oral corticosteroid therapy may be useful for sever disease or for initial treatment failure

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Case #8

Presented By Sidney Barsky, MD and Michael Pomroy, MD

UNKNOWN

Case #9

Case presented by Jerry Feldman, MD and Jane Kwan, MD

History of Present Illness:
This 39-year-old Filipino woman presented with a six-year history of brown macules on both her cheeks. According to the patient, the lesions seemed to appear all at once, and have progressively darkened over time. The only treatment she has ever tried is an unknown "bleaching" product she bought in the Philippines two years ago. She noted neither improvement nor worsening of her lesions with this product.

Past Medical History:
Hypertension

Medications/Allergies:
Atenolol; No known drug allergies

Family History:
Grandmother is of Chinese origin.

Physical Exam:
There are 2-3mm dark brown agminated macules clustered bilaterally on the lateral malar areas of the cheeks. There is no pigmentation of the sclerae. In addition, she has a larger area of agminated light brown macules on her right shoulder.

Histopathology:
2/05 Left cheek: There are dendritic melanocytes concentrated in the upper dermis positive for S-100.

Diagnosis:
Hori's nevus (acquired bilateral nevus of Ota-like macules)

Treatment and Course:
The patient was started on a combination of 3% hydroquinone and tretinoin 0.025% cream daily. After three months of treatment, there was no improvement in the lesions and the medications were discontinued. She is currently scheduled for Q-switched Nd:YAG laser treatment.

Discussion:
Acquired bilateral nevus of Ota-like macules (ABNOM) is a form of acquired, circumscribed dermal melanocytosis that was first described by Hori et al in 1984. Subsequently termed Hori's nevus, this entity is characterized by the appearance of pigmented macules on the face bilaterally. Lesions tend to appear in the third to fifth decades of life, predominantly in females of Asian origin. Men are only rarely affected.

Classically, blue-brown or slate-gray macules can develop bilaterally on the forehead, temples, eyelids, malar areas, alae of the nose, and root of the nose. In contrast to nevus of Ota, pigmentation is not found on the ocular, oral, and nasal mucous membranes. On pathology, dendritic melanocytes are found in the upper and middle portions of the dermis. There is no fibrosis or disruption of normal skin architecture.

The exact pathogenesis of ABNOM is not known, however, several hypotheses have been considered. It is thought that the lesions may be due to epidermal melanocytes dropping down into the dermis or the migration of melanocytes from the hair bulb to the dermis over time. Other theories include melanocytes with slowed melanin synthesis, or the latent activation of immature melanocytes lying dormant in the dermis. This delayed stimulation of melanocytosis might be triggered by dermal inflammation, the atrophy or degeneration of the epidermis or dermis that occurs with aging, or some unknown cause. Since lesions tend to develop in sun-exposed areas, UV radiation might play a role. The preponderance of female patients and onset in the reproductive years suggests that estrogen or progesterone may contribute as well.

Case #9 continued

The differential diagnosis of ABNOM includes nevus of Ota, female facial melanosis (Riehl's melanosis), or melasma. Clinically, it can be distinguished from nevus of Ota in several ways. Nevus of Ota most often appears at birth, perinatally, or around puberty; ABNOM develops later in life. The lack of mucosal pigmentation also distinguishes ABNOM from nevus of Ota. Histologically, both entities exhibit dendritic dermal melanocytes, however, while these cells are diffusely distributed throughout the entire dermis in nevus of Ota, they are concentrated in the upper and mid-dermis in ABNOM.

Several modalities have been shown to be successful in the treatment of ABNOM. Dermabrasion has shown favorable results, however it may be difficult to control the depth of ablation. Good outcomes have been achieved with the carbon dioxide laser as well as the Q-switched ruby, alexandrite, and Nd:YAG lasers. Chemical peels and bleaching agents have been disappointing in the treatment of ABNOM, although they can be a helpful adjunct to laser therapy and the post-inflammatory hyperpigmentation that may result from it.

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Case #10

Case presented by Jerry Feldman, MD, Gina Dillig, MD, Candice Thrash, MD

History of Present Illness:
This 44 year old Filipino woman presented with a three year history of an enlarging lesion on her left thigh. Over the past couple months, the lesion has showed areas of numbness and ulceration. She travels to the Philippines often and was most recently there about a year ago. She was seen at an outside hospital where her PPD was positive and a biopsy of the lesion showed a granulomatous infiltrate.

Past Medical History:
BCG vaccine as a child

Medications/ Allergies:
None; No known drug allergies

Family History:
No family members with tuberculosis

Review of Systems:
Dry cough and 4 lb weight loss over the past year. Denies fever, chills, night sweats, nausea, emesis or bloody sputum.

Physical Exam:
There was a 13 x 17 cm brown to pink plaque with few areas of necrosis and hemorrhagic crust on the left thigh. The center of the lesion demonstrated loss of sensation. There were a few pink papules on the right wrist and left forearm.

Laboratory Data:
The following were abnormal or positive:
PPD: positive
Sputum culture: positive for Mycobacterium Tuberculosis Complex

The following were normal or negative:
Sputum stain for AFB:negative x 2

Radiology:
Chest X-ray: Left upper lobe mass like opacity with interspersed lucencies
Chest CT: Fibrosis is present in the left apex. Reticulonodular opacities are seen in both apices, the posterior segments of upper lobes, and both lower lobe superior segments. These raise concern for possible active or old tuberculosis. No definite cavitation.

Histopathology:
6/05 Left thigh (National Hansen's Disease Center in Baton Rouge, Lousiana): well formed granulomas fill the dermis and extend into the subcutis. In some foci, these involve small cutaneous nerves. In other rare foci, early tissue necrosis is associated with the granulomas.
Fite-Farraco stain revealed rare acid fast organisms within histiocytes and small cutaneous nerves.
PCR (National Hansen's Center): negative, however when bacilli are very rare, PCR is often negative. It is speculated that the rare bacilli are actually long dead and DNA has been degraded.

Case #10 continued

Diagnosis:
Hansen's disease, tuberculoid type with concurrent pulmonary tuberculosis

Treatment and Course:
The patient was started on daily Isoniazid 300mg, Rifampin 600 mg, Pyrazinamide 1 g, Ethambutol 800 mg and vitamin B6 50 mg under directly observed therapy for her pulmonary TB. Dapsone 100 mg daily was added for coverage of Mycobacterium leprae. The patient is doing well and her thigh plaque is resolving. Her paucibacillary disease requires both Dapsone 100mg and Rifampin 600mg daily for 1 year according to the USA Public Health Service.

Discussion:
The presentation of leprosy, Hansen disease (HD) with concurrent pulmonary tuberculosis (TB) is a rare occurrence with incidence ranging from 2.5% to 7.7% in India to as high as 13.4% in South Africa. In the United States, the first report of this occurrence was in Portland, Oregon by Lee and colleagues in 2003. This case represents the second known patient with concurrent leprosy and pulmonary tuberculosis in the United States.

The diagnostic criteria for HD is based on patients having one or more of three cardinal signs: 1) hypopigmented or reddish patches with loss of sensation; 2) involvement of the peripheral nerves as demonstrated by thickening and associated loss of sensation; and 3) detection of AFB on skin smears or biopsy material. Detection of anti-PGL antibodies and PCR analysis are relatively new technologies, that so far, have not played a significant role in the diagnosis of leprosy.

The relationship between HD and TB is complex and controversial. They are both gram-positive acid-fast mycobacteria that are characterized by chronic granulomatous diseases manifesting a spectrum of clinical and histopathologic features that reflect the host's immune response to the infective agents. They share common antigens as evidenced by conversion of tuberculin and lepromin intradermal tests after the administration of BCG vaccine. Even though infection with one mycobacterium does not confer immunity to the other, there is some degree of cross-immunity. Reports suggest that infection with TB allows infection with HD to occur at a reduced rate. Interestingly, cross-immunity is not symmetric and infection with HD offers little protection, if any, against TB.

The capacity to mount a robust and specific cell-mediated immune response is highly host specific and required to contain and combat HD and TB. Both the innate and acquired immune systems must be utilized. Toll-like receptor 2 (TLR2) is an integral player in the innate immune system. It is found on dendritic cells and when bound by mycobacteria will activate the transcription of IL-12 and TNF-a. IL-12 inturn activates CD4 T cells to produce INF-y and IL-2. Mutations in TLR2 have been shown to impart increased susceptibility to TB and lepromatous HD. Patients at risk for coinfection with M. leprae and M. tuberculosis, including our patient, may have difficulty producing IFN-y in response to IL-12 stimulation.

It is important to recognize the concomitant occurrence of leprosy and TB to prevent selection of resistant M. tuberculosis strains, to ensure appropriate management, and to prevent neurologic and cosmetic disabilities associated with HD.

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Case #11

Case presented by Warren Piette, MD, and Carin Litani, MD

History of Present Illness:
This 12 year-old boy and 8 year-old girl both present with a history of easy bruising on the lower extremities since early childhood. The lesions heal slowly but are not tender. The 8 year-old girl also has a history of hyperextensible joints in her hands. The mother of these children presents similarly with an 18 year history of easy bruising on the lower extremities. She states she forms large wounds after minor trauma that heal slowly.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
Mother has two siblings with similar findings

Review of Systems:
Negative

Physical Exam:
Both children display 4-8 cm yellow-brown and violaceous nontender patches on the anterior shins. The 8 year-old girl demonstrates joint hypermobility of her hands. Mother displays large violaceous to brown patches with areas of atrophy around old wounds on the anterior shins.

Laboratory Data:
None

Histopathology:
None

Diagnosis:
Ehlers-Danlos Syndrome, likely Type II.

Treatment and Course:
Both children were advised to avoid contact sports. Mother and children were sent for genetic counseling.

Discussion:
Ehlers-Danlos Syndrome consists of a clinically and genetically heterogeneous group of inherited connective tissue disorders characterized by varying degrees of skin hyperextensibility, joint hypermobility, and skin fragility. Patients exhibit easy bruising, atrophic scars following superficial injury, delayed wound healing and wound dehiscence. EDS has been classified into six clinically distinct syndromes: Classical (Type I/II), Hypermobility (Type III), Vascular (Type IV), Kyphoscoliosis (Type VI), Arthrochalasia (Type VIIa,b), and Dermatosparaxis (Type VIIc).
The molecular pathogenesis of Ehlers-Danlos Syndrome involves three fundamental mechanisms affecting the biosynthetic pathways of collagen fibril formation: 1. Deficiency of collagen processing enzymes; 2. Dominant negative effects of mutant collagen α-chains; and 3. haploinsufficiency. These three mechanisms are demonstrated in different EDS subtypes. For example, Type VI (Kyphoscoliosis EDS) and Type VIIc (Dermatosparaxis EDS) are examples of deficient enzyme activity, lysyl-

hydroxylase deficiency and procollagen peptidase deficiency respectively. Both these conditions are inherited in an autosomal recessive fashion. Studies have shown that the classical and vascular types of EDS can be attributed to the two other mechanisms.

Dominant negative mutations and haploinsufficiency, which is a loss of function mutation, affecting type III collagen or COL3A1 has been shown to cause the vascular type of EDS (Type IV). Dominant negative mutations in the genes encoding type I collagen (COL1A1, COL1A2), type III collagen (COL3A1), and type V collagen (COL5A1, COL5A2) along with haploinsufficiency of type V collagen cause the classical type of EDS. Recent studies concerning the molecular basis of EDS have expanded beyond the collagen family to include tenascin-X, a large matricellular protein of unknown function which has been shown to be highly expressed during development and also around tendons, ligaments, and in skin. The exact mechanism by which TNX mutations cause EDS has yet to be clarified.

The classical and hypermobile EDS share many clinical features and all are inherited in an autosomal dominant pattern. Type I and Type III are more easily diagnosed than Type II as Type I displays more severe skin findings while Type III features increased joint pathology, including recurrent joint dislocations and osteoarthritic changes. Type II, which this patient likely demonstrates, is a milder form of classical EDS and may be overlooked. Although Type II EDS has a subtle clinical presentation, it is important to diagnose the syndrome early and educate the patient regarding reducing the risks associated with certain careers and sports and prevent potential complications associated with pregnancy and surgery.

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Case #12

Case presented by Warren Piette, M.D. and Meredith Stewart Reimer, M.D.

History of Present Illness:
This 33 year-old male presented to the emergency room at Cook County hospital with complaints of fatigue, low-grade fevers, bilateral hand swelling and pain, skin rash and nausea with vomiting for the past 2 weeks. At that time, he was diagnosed with systemic lupus erythematosus (SLE) and started on prednisone therapy. He was followed in the rheumatology clinic and managed with prednisone and hydroxychloroquine for the SLE. He was then referred to the dermatology clinic for management of his worsening skin rash that involved his scalp, face, trunk, and arms.

Past Medical History:
SLE

Medications/Allergies:
Prednisone 20mg per day, hydroxychloroquine 200mg twice a day; No known drug allergies

Family History:
Non-contributory. There was no history of similar skin lesions or SLE

Review of Systems:
Positive for fever, fatique, hand swelling, arthralgias in hands and wrists, nausea, vomiting, and intermittent perineal and perianal painful ulcerations.

Physical Exam:
There are large erythematous, atrophic plaques with surrounding hyperpigmentation to his scalp, ears and conchae, face, neck, chest, back, arms, and forearms. The plaques on his scalp are associated with scarring alopecia. There are no oral or genital ulcers.

Laboratory Data:
The following were normal or negative:
RF, Sm Ab, SSA Ab, SSB Ab, UA, PT, PTT, LFTs, Hepatitis B/C serologies, HIV screen
The following were abnormal or positive:

ANA	>1:160	[<1:160]
dsDNA antibody	461.38 IU/ml	[<50]
C3	54 mg/dl	[88-208]
C4	6 mg/dl	[16-47]
Lupus anticoagulant	positive	[negative]
WBC	2.9 k/µl	[3.7-10.5]
Platelets	118 k/µl	[167-400]

Histopathology:
5/04 Arm: Epidermis with hyperkeratosis and interface dermatitis with lymphocytes and vacuolar changes, compatible with lupus erythematosus. A PAS stain is negative.

Diagnosis:
Systemic lupus erythematosus, widespread discoid lupus erythematosus and subacute cutaneous lupus erythematosus.

Treatment and Course:
After his diagnosis with SLE in November, 2004, the patient was started on hydroxychloroquine 200 mg twice per day and prednisone 20mg per day. He was started on methotrexate 10mg per week in May,

2005. Due to low white blood cell counts, methotrexate was discontinued in September, 2005 and azathioprine was started at a dose of 100mg per day. In November, 2005, his white blood cell count fell again to 2,800 cells/μL, so azathioprine was discontinued. In December, 2005, the patient required hospital admission for superinfection of his skin lesions with MSSA, bacteremia, and sepsis and was treated with intravenous antibiotics. During his admission, methotrexate was discontinued, the prednisone dose was increased to 60mg per day, and mycophenolate mofetil (MMF, CellCept) was started. He left the hospital on a dose of MMF 1000mg twice per day. Since commencing treatment with MMF, he has noted moderate improvement of his skin lesions.

Discussion:

The cutaneous manifestations of lupus erythematosus (LE) can be divided into 3 general categories: acute cutaneous LE (ACLE), subacute cutaneous LE (SCLE), and chronic cutaneous LE (CCLE). Others subdivide the subtypes into two broad categories based on the histologic finding of interface dermatitis. The skin lesions that demonstrate an interface dermatitis include discoid LE (DLE), SCLE, and ACLE, which are the most common cutaneous lesions in patients with LE. CCLE can have several clinical variants including DLE, hypertrophic or verrucous DLE, lupus tumidus, lupus panniculitis, palmar/plantar DLE, as well as other rare variants. The most common subset is DLE. DLE can be classified as localized, when it involves only the head and neck, or widespread. In addition, there exists of group of patients in whom the DLE lesion is only one manifestation of SLE (DLE-SLE subset)

The lesions of DLE are characterized by erythema, telangiectasia, adherent scale, follicular plugging, dyspigmentation, atrophy and scarring. The lesions are usually sharply demarcated and round or 'disc-like' (discoid). The presence of scarring and atrophy are characteristic and distinguish these lesions from SCLE. There are several important differences between patients with localized DLE and those with widespread DLE. Patients with localized DLE are rarely in the DLE-SLE subset and less commonly have a positive antinuclear antibody (ANA) titer or leukopenia. Additionally, approximately 50% of patients with localized DLE will have remission of their disease, whereas patients with widespread DLE will rarely have remissions (<10%). The DLE-SLE subset includes patients that have scarring DLE skin lesions as one manifestations of their systemic disease. In addition to widespread DLE, these patients are also more likely to have periungual telangiectasias, persistant elevated sedimentation rates, leukopenia, and positive ANA. When these patients present with purely cutaneous disease, most will fulfill the American College for Rheumatology (ACR) criteria for the diagnosis of SLE within 1-3 years. Generally, patients in the DLE-SLE subset are said to have a more benign course than SLE patients without DLE, and the risk of serious systemic involvement, including renal disease or involvement of the nervous system is rare.

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Case #13

Case Presented by Sidney Barsky, MD, and Alyssa Nash-Goelitz, MD

History of Present Illness:
This 18 year-old Hispanic male presents with hypertrophy of the right upper and lower extremities and trunk since age eight, which has gradually increased in size over the past 10 years. He also complains of redness over the right arm, right knee, and right thigh for the past year.

Past Medical History:
Hypertension

Medications/Allergies:
None; No drug allergies

Family History:
No family history of hypertrophies

Review of Systems:
Patient complains of decreased right arm mobility.

Physical Exam:
The right upper and lower extremities are significantly larger than the left upper and lower extremities. In addition large, non-tender, soft, subcutaneous masses can be palpated over the right shoulder, right chest, and right arm. Erythema and increased hair growth is noted over the dorsum of the right hand and forearm. Lastly, scattered petechiae are noted over the right knee and right thigh.

Laboratory Data:
The following are normal or negative:
Complete blood count, AST, ALT, Coagulation studies, Comprehensive metabolic panel

Radiology:
CT scan of the chest, abdomen, and pelvis notes a uniform increase in the subcutaneous adipose tissue. No soft tissue masses or bone abnormalities are noted. Plain X-Rays of the right foot and hand show soft tissue hypertrophy. No bone abnormalities are present.

Histopathology:
2/05 Right Knee: The upper dermis contains dilated blood vessels.

Diagnosis:
Hemihyperplasia-Multiple Lipomatosis Syndrome

Treatment and Course:
The patient is currently being evaluated for possible liposuction of the lipomas.

Discussion:
Hemihyperplasia is known to be a heterogeneous disorder often associated with a large number of various malformations and complications. Proteus syndrome is frequently confused with hemihyperplasia; however, certain characteristics can help differentiate between the two. First patients with proteus syndrome present with mild to moderate hyperplasia at birth that rapidly progresses throughout childhood. In contrast patients with hemihyperplasia present at birth with significant hyperplastic asymmetry evidencing little change throughout life. Patients with proteus syndrome may have a wide variety of cutaneous lesions including verrucous epidermal nevi, connective tissue nevi,

Case #13 continued

lipomas, vascular malformations, and exostoses. Patients with hemihypertrophy do not have these findings except for lipomas, and capillary vascular malformations. The vascular malformations seen in hemihyperplasia are flat or only slightly raised in contrast to the compressible nodules and large subcutaneous masses observed in proteus syndrome. Some patients with Proteus syndrome may present with craniofacial abnormalities, hyperostoses, mental retardation, and splenic hyperplasia. These findings are absent in hemihyperplasia.

Although our patient states that the asymmetrical limb growth appeared only after 8 years of age, we believe that hemihyperplasia-multiple lipomatosis syndrome is still the most likely diagnosis. The manifestations of hemihypertrophy are usually relatively stable from infancy through adolescence. It has been postulated that hemihyperplasia-multiple lipomatosis syndrome may be a forme fruste or a milder form of proteus syndrome. This provisional designation may prove to be a useful description for a group of patients that show moderate abnormalities of asymmetry and overgrowth with subcutaneous lipomata.

Hemihyperplasia with multiple lipomas is a distinct subset of hemihyperplasia. Cutaneous capillary malformations may occur in some instances. Mild-to-moderate signs are usually present at birth. Progressive overgrowth does not occur, but tends to be commensurate with growth of the child

References:

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Case # 14

Case presented by Jerry Feldman, M.D. and Meredith Stewart Reimer, M.D.

History of Present Illness:
This 45 year-old African American man presented with a 15 year history of blisters and "poor healing" on his hands, fingers, wrists, anterior legs, and dorsal feet, sparing the mucosa. He noted that blisters usually form after not only trauma and friction, but also form spontaneously. Several biopsies in the past failed to provide a definitive diagnosis. He had tried various topical corticosteroids, including clobetasol ointment, with minimal improvement. He has used protective measures, such as a cloth wrist band under his watch strap, which does prevent blister formation.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory. There was no history of similar skin lesions.

Review of Systems:
Negative

Physical Exam:
There are several 1-2cm intact, tense bullae, some hemorrhagic, and erosions on his dorsal hands and fingers. There are extensive areas of atrophic and sclerotic, hypopigmented plaques on the dorsal hands, fingers, anterior legs, and dorsal feet accompanied by several 1mm yellow-white milia on the dorsal hands.

Laboratory Data:
The following were normal or negative:
Complete blood count, AST, ALT, Hepatitis B and C serologies, 24-hour urine porphyrin levels, ferritin, glucose-6-phosphate-dehydrogenase (G6PD)

Histopathology:
9/04 Hand: Punch biopsy from the edge of an intact blister revealed a non-inflammatory subepidermal blister.
Direct immunofluorescence reveals a linear deposition of IgG and C3 at the dermoepidermal junction.
Salt split skin in process of submission.

Diagnosis:
Epidermolysis Bullosa Acquisita

Treatment and Course:
The patient was started on Dapsone at 50mg per day. His dose was increased to 100mg per day after one month. After 3 months of therapy, the patient has noted mild to moderate improvement in his symptoms with less frequent blister formation.

Discussion:
Epidermolysis bullosa acquisita (EBA) is rare, chronic, subepidermal blistering disease of the skin and mucous membranes. EBA is classically characterized by skin fragility, spontaneous and trauma-

induced blisters that heal with scar formation and milia. There is no racial or gender predilection, and there is an estimated incidence of 0.17 to 0.26 per million people in Western Europe. Most patients present in adulthood, although childhood cases of EBA have been reported. There are at least 5 clinical presentations of EBA. The most common type, as seen in our patient, is the "classical" type or mechanobullous non-inflammatory disease with an acral distribution. Other types include the bullous pemphigoid-like presentation, cicatrical pemphigoid-like presentation, Brunsting-Perry pemphigoid-like presentation, and linear IgA bullous dermatosis-like disease. Patients with the dermolytic, or nonimflammatory, variant of EBA have trauma-induced blisters and erosions on noninflamed skin, atrophic scars, milia, nail dystrophy, and/or oral erosions.

The etiology of EBA is unclear. However, EBA is characterized by IgG autoantibodies directed against the NC1 domain of type VII collagen, and because these antibodies have recently been shown to induce blistering in mice models, an autoimmune mechanism is strongly suggested. EBA has been associated with many other diseases and autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, chronic thyroiditis, diabetes mellitus, inflammatory bowel disease, especially Crohn's disease, cryoglobulinemia, multiple endocrinopathy syndrome, multiple myeloma, amyloidosis, and relapsing polychondritis. Autoimmunitiy to collagen type VII is also seen with bullous systemic lupus erythematosus, and there have been several case reports of patients with both EBA and bullous SLE. Both EBA and bullous SLE patients are strongly associated with the HLA-DR2 allele, which has been associated with hyperimmunity.

Histologically, EBA is classically described as a non-inflammatory subepidermal blister. However, bullous pemphigoid-like disease can demonstrate variable degrees of dermal infiltrates of neutrophils, eosinophils, and mononuclear cells. Direct immunofluorescence (DIF) demonstrates linear immune deposits along the DEJ comprised mostly of IgG. In most cases, indirect immunofluorescence (IIF) performed on salt slit skin helps to distinguish bullous pemphigoid (BP) from EBA. There is epidermal roof staining in BP and dermal floor staining in EBA.

EBA is a chronic disease which is classically refractory to many treatments. The inflammatory form of EBA responds more readily to therapy than the classical form. For mild to moderate disease, many patients respond to dapsone, because of the neutrophil predominance in the inflammatory form. There have also been several case reports of successful treatment with colchicine. If these modalities fail, prednisone in a dose of 0.5 to 1.0 mg/kg/day, cyclosporine, IVIg, plasmapharesis, extracorporeal photochemotherapy, and mycophenolate mofetil have all been reported to be successful in case reports.

References:

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2. Engineer L, Ahmed AR. Emerging treatment for epidermolysis bullosa acquisita. J Am Acad Dermatol 2001; 44(5):818-28.
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Case #15

Case presented by Jerry Feldman, MD and Jane Kwan, MD

History of Present Illness:
This 44-year-old Hispanic woman presented with a 5-year history of firm nodules on her buttocks bilaterally. About a decade ago in Mexico, she had received injections of an unknown substance into her buttocks in the hopes of enlarging the treated area and enhancing its aesthetic appearance. She subsequently developed inflamed, tender nodules with areas of focal ulceration. Over the years, the ulcerations have healed and the nodules have become firm and less painful. The patient also gave a history of intermittent lower leg swelling and pain. She had been treated in the emergency room for cellulitis, however these findings have never been seen in our clinic.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory

Physical Exam:
There are firm, indurated, lumpy nodules and plaques on the bilateral buttocks. The skin overlying these thickened areas is erythematous and hyperpigmented. Scattered amongst the lesions are several hypopigmented, depressed, atrophic scars. There is no inguinal lymphadenopathy.

Laboratory Data:
The following tests were negative or within normal limits:
Antinuclear antibody
Complete blood count

Histopathology:
7/05 Buttock: There are vacuoles throughout the reticular dermis surrounded by granulomatous inflammation.

Diagnosis:
Sclerosing lipogranuloma (paraffinoma)

Treatment and Course:
The patient is awaiting further treatment recommendations.

Discussion:
Injection of mineral oils into the skin was reported as early as 1899, when a physician injected paraffin into the scrotum of a boy who had undergone bilateral orchiectomy. The introduction of various liquid oils, such as paraffin or lanolin, into the subcutaneous tissue has mainly been performed for cosmetic or reconstructive purposes. Areas that are commonly treated include the penis, scrotum, breasts, gluteal region, cheeks, nose, eyelids, calves, and scalp. Although few physicians provide oil injection therapy anymore, the practice still exists in many foreign countries. Often, it is administered by non-medical personnel, and there have been numerous reports of patients who have self-administered substances such as mineral oil or even transmission oil.

The injected substances are long-chain saturated acyl hydrocarbons for which humans lack the necessary enzymes to dissolve. The exogenous oils act as a foreign body, inciting an inflammatory response. Histologically, early lesions contain many multinucleated foreign body giant cells surrounding cystic spaces that were once occupied by the injected oils. Usually the material is not seen since it is washed out during the

processing of the tissue. If present, the vacuoles will stain with Oil Red-O or Sudan. This can help distinguish paraffinoma from silicone granuloma, which can look identical histologically but will not stain positively. Over time, interstital fibrosis develops with prominent hyalinization of the collagen and the classic "Swiss cheese" vacuoles. Foci of calcification may be seen in older lesions.

Skin lesions are usually localized to the area of injection, although migration and even distant metastasis of the foreign substance to the lymphoreticular system or lungs has been reported. The findings consist of firm and indurated nodules and plaques with a lumpy appearance and feel. The overlying skin is often erythematous or hyperpigmented depending on the age of the lesion. Often, there is focal ulceration or even drainage of an oily or purulent substance. Lesions may appear within months of the injections, but may take as long as 30 years to manifest.

Mineral oil injections have been associated with the development of autoimmune findings; up to 10% of patients may eventually meet the criteria for a connective tissue disease. In specific, patients may develop fever, arthralgias, arthritis, Raynaud's phenomenon, and autoantibodies. It is thought that activated macrophages in sclerosing lipogranuloma may release interleukin-1, resulting in immune system activation and autoantibody formation.

Complete surgical excision remains the treatment of choice for sclerosing lipogranuloma. Often, debriding all of the fibrosed subcutaneous tissue results in a defect that requires split thickness skin grafts or flaps for closure.

References:

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Case #16

Case Presented by Lisette Ortiz-Ferrer, MD and Sari Weinstein, MD

History of Present Illness:
This 8 year-old African American girl presented to us with a history of eczema on the face and extremities, as well as recurrent boils on her eyelids, scalp, back and legs since age 2. She has been brought to an outside institution multiple times for management of these boils with incision and drainage as well as systemic antibiotics, but it is not known which antibiotics were given or culture results. Her eczema has been treated with hydrocortisone 1% ointment with minimal response.

Past Medical History:
Recurrent tonsillitis; no asthma, allergic rhinitis or pneumonia. No history of bone fractures. No dental problems to date; first decidual tooth was lost at age 7.

Medications/Allergies:
Hydrocortisone 1% ointment, diphenhydramine, bacitracin; No known drug allergies

Family History:
Mother's family without any eczema, asthma or allergic rhinitis; father's history unknown

Review of Systems:
No headaches, shortness of breath, stomach upset, fever, chills, or joint pains

Physical Exam:
Multiple papules and lichenified plaques with mild erythema and scaling were seen on the cheeks, antecubital and popliteal fossae, as well as the anterior ankles. A 1 cm diameter skin-colored, non-tender nodule was found on the right lower eyelid. On the scalp, 1-2 mm diameter skin skin-colored papules and pustules were observed. Several 2-3 cm linear scars on the flank and posterior legs from previous incision and drainage were seen. No lymphadenopathy was appreciated. Oral mucosa and teeth appear normal and there is a suggestion of a broadened nasal bridge. No nail abnormality was seen. No hyperextensible joints were appreciated.

Laboratory Data:
The following were abnormal or positive:

IgE Quantitation	5,447 IU/mL	[normal ≤ 280]

The following were normal or negative:
Complete blood count with differential (5% eosinophils), chemistry, serum protein electrophoresis, fungal and bacterial culture of scalp

Histopathology:
None

Diagnosis:
Hyperimmunoglobulin E Syndrome

Treatment and Course:
Protopic 0.1% ointment twice a day and emollients were given for the lichenified plaques. Erythromycin 2% topical solution and PhisoHex to her scalp, as well as bacitracin ointment and warm compresses at the first sign of new skin abscesses, were added.

Case #16 continued

Discussion:

The hyperimmunoglobulin E syndrome (HIES) is a rare, idiopathic, multisystem immunodeficiency disorder. Inspired by the biblical character besotted with boils, it was first referred to as *Job's Syndrome* by Davis et al. in their 1966 description of two girls with red hair, chronic dermatitis, and recurrent staphylococcal abscesses and pneumonias. In 1972, *Buckley's syndrome* was described in two boys with similar symptoms as well as coarse facies, peripheral blood eosinophilia, and elevated serum IgE levels. Since that time, over 200 cases have been reported in the literature; this syndrome is now often referred to as hyper-IgE recurrent infection syndrome.

The classic triad of HIES includes recurrent cutaneous and sinopulmonary infections, chronic dermatitis from birth or early childhood, and elevated serum IgE levels. The cutaneous infections are frequent, start in infancy, and are almost always due to *Staphylococcus aureus*. Cold abscesses, which are fluctuant, nontender, nonerythematous, and not associated with fever or systemic symptoms, are pathognomonic for HIES but not essential to the diagnosis. Mucocutaneous candidiasis and dermatophytoses are also common. Sinopulmonary infections, usually caused by *S. aureus,* may be recurrent and severe. The pruritic dermatitis in HIES may be confused with atopic dermatitis (AD) although its distribution is often atypical for true AD. Also, the patients lack a history of asthma, allergic rhinitis, or a family history of atopy. Skin biopsy reveals an eosinophilic infiltrate similar to that seen in eosinophilic pustular folliculitis. Other associated features include characteristic coarse faces with a prominent forehead, wide alar base to the nose, and a wide outer canthal distance, retained primary teeth, scoliosis, joint hyperextensibility, long bone fractures and osteopenia.

Serum IgE levels in HIES are elevated over ten times the normal limit or greater than an arbitrary cut-off of 2000 IU/mL, but there is no correlation between the IgE levels and the severity of the disease. There is often also eosinophilia of blood and sputum. While IgE levels are elevated in other disorders such as atopic dermatitis, the presence of abscesses, coarse facies, infections and skeletal abnormalities may enable differentiation.

Although first noted in red-haired Caucasians, HIES has also been observed in those of Asian and African descent. While its incidence is unknown, it is found equally in males and females. There is an autosomal dominant pattern of inheritance with variable penetrance. As the phenotype is variable it is likely that mutations in several different genes may cause HIES; a defect in regulation could occur anywhere along the path of IgE synthesis, from T-cell stimulation, appropriate cytokine production, receptor signaling events and the ability of B cells to class-switch into IgE manufacture. There appears to be a 10-30-fold reduction in the Th1 cytokine IFN-γ compared to normal controls when stimulated by *S. aureus* or *C. albicans* leading to a severe dysbalance towards the Th2 phenotype through a defective IL-12/IL-18/IFN-γ axis. Other cytokines such as IL-6 and IL-8 may potentiate or block the production of IgE and also pose new targets for future therapeutic intervention.

Meanwhile, treatment of the dermatitis in HIES is similar to that of AD and is accomplished with topical glucocorticoids and emollients, and the cutaneous infections are treated with oral antibiotics, wound care, and incision and drainage of abscesses. Some authors recommend anti-staphylococal and antifungal antibiotic prophylaxis. Other therapies, which include cimetidine, ascorbic acid, cromoglycate, cyclosporine A, isotretinoin, intravenous immunoglobulin, plasmapheresis, and IFN-γ, have been described only in case reports.

References:

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3. Netea MG, Kullberg BJ, van der Meer JWM. Severely impaired IL-12/IL-18/IFN-γ axis in patients with hyper IgE syndrome. Eur J Clin Invest 2005;35:718-721.
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Case #17

Case presented by Sidney Barsky, MD, and Gina Dillig, MD

History of Present Illness:

The patient is a 9 year old girl who presented with dark streaks on her skin that have been increasing in extent over the last 8 years. Most concerning are some thicker areas on her neck that extended onto her face. Her mother noted that the entire right side of her daughter's body was larger than the left side, present since birth.

Past Medical History:

None

Medications/ Allergies:

None; No known drug allergies

Family History:

No other family members with skin problems including brother and sister

Review of symptoms:

No seizures or changes in vision.

Social History:

The patient is currently attending 3rd grade for a second time and has difficulty in school.

Physical Exam:

The right side of the body is noticeable larger than the left, most prominent in the hands and feet. Her skin shows hyperpigmented velvety whorled plaques along Blaschko lines greater on the right side of the body but extending onto the left side as well. On the neck lichenified plaques are seen.

Laboratory Data:

Ophthalmology exam- normal

Histopathology:

8/05 Forearm: Papillated epidermal hyperplasia with a slight increase in basal melanin pigment.

Diagnosis:

Epidermal Nevus Syndrome

Treatment and Course:

The patient has been using vaseline and 10% urea cream to thick areas with some softening noted.

Discussion:

Epidermal nevi (EN) are hamartomatous lesions derived from ectodermal mutations during early embryonic stages. Their location and extension, following Blaschko lines, reflect embryonic migration patterns of the skin and mosaicism. Epidermal nevi appear at birth or within the first year of life. In the newborn, the nevi are linear or ovoid, flat velvety plaques. During adolescence, the lesions become more raised, verrucous, and hyperpigmented. The incidence of EN is approximately 1 in 1000 live newborns. Of those, 10-18% of patients have mosaicism in the mesodermal layers as well, causing associated disorders of the eye, nervous and musculoskeletal systems and are labeled epidermal nevus syndrome (ENS).

In addition to nevi, other cutaneous lesions in ENS include hyperpigmentation and hypopigmentation, cafe au lait macules, hemangiomas, acanthosis nigricans and melanocytic nevi.

Case #17 continued

Ocular defects are frequent findings and can include colobomas, subconjunctival lipodermoids and corneal opacities. CNS involvement in ENS is estimated to occur in 50-70% of patients where head and neck EN may serve as a marker. Seizures and mental retardation are the most common abnormalities. When present, seizures typically commence by the end of the first year of life. Mental retardation ranges from none to severe. Other neurologic manifestations can include hypotonia, hemiparesis, hydrocephalus, hemimegalencephaly, cortical atrophy, and intracerebral calcifications. Skeletal manifestations are seen in 50-66% of patients and can include hypertrophy or hypoplasia of bones, bone cysts, facial hemihypertrophy, limb hypertrophy and vitamin D-resistant rickets from massive phosphate excretion.

There are at least 6 different types of ENS including sebaceous nevus syndrome, nevus comedonicus syndrome, Becker nevus syndrome, phakomatosis pigmentokeratotica, Proteus syndrome, and congenital hemidysplasia with ichthyosiform nevus and limb defects syndrome (CHILD). There is the proposed addition of a 7th type of ENS, keratinocytic nevus or verrucous epidermal nevus in association with central nervous system structural disorder with or without a musculoskeletal disorder. Vidaurri-de la Cruz H, et al., reported the clinical findings in 13 patients with keratinocytic nevi and systemic involvement, 66% of the female patients had neurologic disorders, 25% had eye disorders and 87% had musculoskeletal disorders, including hemihypertorphy. They also found an increased risk of hypophosphatemic rickets and mesodermal tumors including rhabdomyosarcomas in this group of patients. Although, rickets and rhabdomyosarcoma were not present, our patient would fit into this category of ENS presenting with keratinocytic nevi, acanthosis nigricans, hemihypertrophy and mild mental retardation.

Management of ENS requires a multidisciplinary approach. Neurologic, ophthalmologic and orthopedic referrals are often required. Small EN can be excised. For larger lesions, excision is problematic. Liquid nitrogen, topical and systemic retinoids, deep shave excision, carbon dioxide or other laser therapies and dermabrasion have been reported as potential alternatives with variable success.

References:

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Case #18

Case Presented by Lissette Ortiz-Ferrer, Warren Piette, MD and Samantha Golden, MD

History of Present Illness:
This 10 year-old African American boy presents with a lifelong history of symmetric, thickened and dark plaques on his hands, thighs, knees, shins, and ankles. The patient's mother denies that these lesions change in size or move away from the affected areas. There is no pain or pruritus associated with them.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
No one in the family has similar lesions

Review of Systems:
Negative. The patient has no physical or developmental abnormalities.

Physical Exam:
The patient has large, well-demarcated, thickened, hyperpigmented plaques distributed bilaterally and symmetrically on his hands, thighs, knees, shins, and ankles. There is minimal scale and slight surrounding erythema.
Nails, scalp, and mouth are all normal.

Laboratory data:
None

Histopathology:
6/00 Knee: The lesion is surrounded by a thick stratum corneum with loosely arranged keratin lamelli. The stratum lucidum is compact and markedly thickened, and the granular layer is also thickened. The epidermis shows mild elongation and blunting of the rete ridges with a well organized cellular pattern. The basal layer is intact. The upper dermis shows a mild perivascular infiltrate of lymphocytes, and the capillaries show a normal pattern without significant dilatation. These findings are non-specific for a keratoderma.

Diagnosis:
Progressive Symmetric Erythrokeratoderma

Treatment and Course:
The patient has been treated with Dovonex and Psorcon without improvement.

Discussion:
Progressive symmetrical erythrokeratoderma (PSEK) was first presented and named by Gottron in 1922, but had been described earlier. The condition is not congenital but has its onset during early childhood. Clinically this disease is manifested as symmetrically distributed, fixed, or very slowly progressive erythematous, scaly plaques. There is considerable similarity to the clinical picture of Erythrokeratoderma variabilis (EKV), however PSEK has more palmoplantar keratoderma and an absence of migratory lesions. The symmetry of PSEK is also more striking than EKV. The main areas affected are the palms and soles, extensor aspects of the extremities, buttocks and head. The abdomen

Case #18 continued

and chest are often spared. The plaques may progress during childhood and then are usually stable. There are no physical or developmental associations and patients are otherwise entirely normal.

The histopathology is non-specific, usually demonstrating a loose hyperkeratotic stratum corneum and wide plugged hyperkeratotic follicular openings. There may be some acanthosis and papillomatosis and occasional dyskeratotic epidermal cells can occur.

Progressive symmetric erythrokeratoderma is inherited as an autosomal dominant trait with incomplete penetrance and variable expressivity.

In 1997 Ishida-Yamamoto and colleagues demonstrated a frameshift mutation in the loricrin gene on chromosome 1q21 in a family with PSEK. Loricrin is the major structural component of the cornified cell envelope. Loricrin mutations have also been found in an icthyotic variant of mutilating keratoderma (Vohwinkel syndrome) and in a congenital in a congenital icthyosiform erythroderma presenting as a collodion baby and later developing palmoplantar keratoderma and pseudoainhum.

Various keratolytics, urea, ammonium lactate, tars, topical corticosteroids and topical retinoids have been used with limited or no success. There are reports of success with the use of oral retinoids but recurrence is to be expected on cessation of therapy.

References:

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Case #19

Case Presented by Lissette Ortiz-Ferrer, MD, and Carin Litani, MD

History of Present Illness:
This 40 year-old African American man presented to us with multiple thickened lesions on the bottom of his feet, which were tender and bled easily. He also complained of thickened and disfigured finger and toenails, as well as white lesions inside his mouth. He stated that his symptoms have waxed and waned for many years and have been controlled with topical and long-term systemic antifungals. He denies receiving any treatment since 1995.

Past Medical History:
Chronic mucocutaneous candidiasis diagnosed at age 14
Acne vulgaris since age 15

Medications/Allergies:
None; No known drug allergies

Family History:
No other family members with the same condition. Positive family history of diabetes and hypertension

Review of Systems:
Patient denied fever or chills, intolerance to heat or cold, weight gain or weight loss, or gastrointestinal upset

Physical Exam:
Brown to yellow hyperkeratotic and friable plaques were found on the medial and plantar aspects of both feet. Dystrophic and thickened fingernails and toenails with a yellowish discoloration were seen. Thick white plaques were seen inside the mouth on the tongue and mucosa. Some open and closed comedones, as well as erythematous papules and nodules were found on the face.

Laboratory Data:
The following were normal or negative:
Complete Blood Count, Metabolic Panel, Liver Panel, Thyroid Functions, Urinalysis.
The following were abnormal or positive:
Fungal culture from the nail grew *Phoma* species.
KOH from the mouth showed pseudohyphae.

Histopathology:
11/05 Nail: PAS stain of nail clippings were positive for fungal elements.

Diagnosis:
Chronic Mucocutaneous Candidiasis

Treatment and Course:
This patient was given Mycelex troches 10 mg 5 times a days as needed for oral thrush and Loprox 1% cream, as well as urea cream 10% twice a day under occlusion for his nails and feet. His acne is treated with benzoyl peroxide 10% gel daily and doxycycline 100 mg twice a day. He is currently managed by Infectious Disease who is treating him with Sporanox 100 mg daily and who will repeat immunologic studies.

Case #19 continued

Discussion:

Chronic mucocutaneous candidiasis (CMC) is a heterogeneous clinical syndrome in which the patient suffers persistent and recurrent infections of the skin, nails and mucous membranes with *C. albicans,* as well as other pathogens like dermatophytes and bacteria. Classification of this syndrome includes a form with associated endocrinopathy, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), which demonstrates autosomal recessive inheritance and has been linked to a mutation in the AIRE gene. The mechanisms behind this gene and the inability to clear candida still remain elusive. No gene has yet been linked to CMC without endocrinopathy although studies have shown that the pathogenesis includes an altered cytokine response. Data demonstrates that CMC patients produce decreased amounts of IL-2 and Il-12 and increased amounts of IL-6 and IL-10 along with high titers of IgG1 and IgA candida specific antibodies which corresponds with a low Th1 and high Th2 cytokine production pattern. More specifically, these alterations were more clearly pronounced in response to stimulation with purified carbohydrate *Candida* fractions as opposed to protein fractions. Overall, these recent studies suggest that CMC patients may overproduce inflammatory cytokines in response to *Candida* which in turn trigger a feedback loop to overproduce IL-10, resulting in the downregulation of the protective Th1 response thus inhibiting proper clearance of *Candida*. The location of the exact defect remains unknown.

Current management of CMC depends on the therapeutic and prophylactic liberal use of systemic antifungals. The problem with this regime besides systemic side effects remains emerging resistance and frequent relapses upon cessation of treatment. The data mentioned above suggest a role for the exogenous administration of cytokines or cytokine antagonists which have shown to be successful in animal models. Hopeful future therapies include a candidiasis vaccine and transfer factors to confer a donor's cell mediated immunity to the CMC recipient.

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