## *Case #1*

***PRESENTED BY:*** *Lissette Ortiz-Ferrer, M.D. and Gina Dillig, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 57-year-old African-American woman presented in September 2003 with a two-month history of extensive cutaneous and oral blisters. She was diagnosed elsewhere with bullous pemphigoid and was treated with nicotinamide and minocycline without improvement. Her condition continued to worsen to the point of developing new and painful blisters everyday and having difficulty taking meals. She reports a 10-pound weight loss in the past 3 months. The patient denies epistaxis, cough, hoarseness, dysuria or rectal bleeding.

### PAST MEDICAL HISTORY:

Non-contributory

### MEDICATIONS:

None

### ALLERGIES:

Penicillin (facial angioedema)

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Twenty-pack year of cigarettes; quit in November 2003.
Occasional alcohol; no use of illicit drugs.

### PHYSICAL EXAMINATION:

The patient was found with multiple erythematous bullae and erosions over her chest, back and legs, as well as the posterior pharynx. Conjunctival erythema was seen but there was no ocular ulceration or scarring.

## LABORATORY EXAMINATION:

The following laboratory studies were normal or negative:

Purified Protein Derivative
General chemistry
Aspartate aminotransferase
Alanine aminotransferase
DEXA scan (11/03)- normal bone mineral content of the femoral necks
Hemaglobin
Hematocrit
Platelets (297)

The following laboratory studies were abnormal or positive:

LDL 176 (0-130)
Cholesterol 247 (130-240)
Trigylcerides 152 (30-150)
LDH- 229-315 (85-210)
DEXA scan (11/03)- osteopenia of the lumbar spine
Thiopurine methyl transferase (TPMT) - level does not allow reliable designation of this patient as either a carrier or non-carrier
White blood count 11.4 (3.7-10.5)

## BIOPSY:

CSP-03-11666 Hematoxylin & Eosin (Back- lesional skin): There is an intraepidermal vesicle with suprabasal separation and acantholysis. A sparse inflammatory infiltrate shows lymphocytes and occasional eosinophils.

Direct immunofluorescence (Back- perilesional skin): Intercellular deposition of IgG

Indirect immunofluorescence: pending

## DIAGNOSIS:

Pemphigus Vulgaris

## TREATMENT AND COURSE:

The patient was started on prednisone 60 mg by mouth daily, Aluminum subacetate (Domeboro) soaks, and 1% silver sulfadiazide cream (Silvadene). After 2 weeks, she was tapered to 40 mg daily of prednisone which was maintained for 2 more weeks, until she started to develop new blisters on her skin and mouth accompanied by a foul odor. Prednisone was then increased to 60 mg daily, in addition to clindamycin 300 mg three times daily for 14 days, clotrimazole

(Mycelex) troches five times daily, lidocaine/benedryl/maalox swish before meals, calcium 1500 mg daily, vitamin D 800 U daily and Zantac 150 mg by mouth twice daily. Ophthalmology was consulted and found no evidence of ocular pemphigus.

In October 2003, alendronate (Fosamax) 35 mg weekly and mycophenolate mofetil (CellCept) 1g twice daily were added. Prednisone was then decreased to 40 mg daily. The patient's blisters continued to resolve but she developed new-onset hypertension (currently managed by internal medicine) and thrombocytopenia to 101. CellCept was tapered to 1.5g daily for 2 weeks. Platelets were then re-checked, a normal value was obtained and CellCept was increased to 2 g daily while continuing with the prednisone taper.

In December 2003, the patient continued developing a few small blisters, consequently CellCept was increased to 3g daily, while the prednisone was tapered to 20 mg alternating with 10 mg every other day. Currently our patient continues to improve, having only a few erosions on the skin and in the mouth.

## DISCUSSION:

The term pemphigus encompasses a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell-cell adhesion of keratinocytes through a process called acantholysis. Pemphigus can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Each form of pemphigus has specific autoantibodies against normal epithelial structural proteins making unique disease states. The autoantibodies are pathogenic and capable of reproducing disease in vivo.

Pemphigus vulgaris is the most common form of pemphigus observed in North America and Europe. It is a chronic blistering disorder of skin and mucous membranes. The IgG autoantibodies in pemphigus recognize a 130-kd cell adhesion molecule of the epidermis, desmoglein 3, a member of the cadherin family of adhesion molecules. Some patients have additional IgG autoantibodies against desmoglein 1. Once bound to the desmogleins the autoantibodies interfere with desmosome assembly causing dissolution of cell-to-cell membrane contacts and blister formation. In pemphigus vulgaris the blister occurs deep, just above the basal layer.

All patients with pemphigus have antibodies directed at desmoglein 3 resulting in mucous membrane blistering. Patients with the additional anti-desmoglein 1 antibody will also have cutaneous involvement. The distribution of desmoglein 1 is superficial in both skin and mucous membranes, but it is more concentrated in the skin. Desmoglein 3 is situated in the deeper layers of the skin and is more prominent in the mucous membranes. This distribution, along with the compensation theory, explains the differential location of blisters depending on the autoantibody involved.

Painful mucous membrane erosions are the presenting sign of pemphigus vulgaris and may be the only sign for an average of 5 months before skin lesions develop. Often these erosions develop in the oral mucosa, but other mucous membranes may be involved including conjunctiva, anus, penis, vagina and labia. The skin of afflicted patients can show painful flaccid blisters anywhere,

although erosions are more common due to the fragile nature of these blisters. Rare associations with myasthenia gravis and/or thymoma have been reported.

Diagnosis is made by direct immunofluorescence of perilesional skin. A positive result will show IgG on the cell surface of keratinocytes. Indirect immunofluorescence may be used to detect circulating IgG and monkey esophagus is most sensitive for the pemphigus vulgaris antibodies. There is a positive but, imperfect correlation between the titer of anti-cell surface antibody and disease activity. Histopathology of lesional skin shows suprabasilar blister with acantholysis. The basal cells stay attached to the basement membrane and appear as a "row of tombstones".

The medical management of pemphigus vulgaris includes the use of systemic glucocorticoids and immunosuppressants such as mycophenolate mofetil, azathioprine and cyclophosphamide to reduce autoantibody synthesis. These medications have dramatically improved the prognosis of pemphigus but, the disease is still associated with a significant morbidity and a 5% mortality mostly due to the complications of immunosuppressive therapy. Mycophenolate mofetil (MMF, Cellcept) has been shown to have a rapid effect in lowering pemphigus antibody titers and to decrease disease activity. It also has fewer adverse reactions when compared to azathioprine. MMF reversibly inhibits inositol-monophosphate-dehydrogenase (IMPDH). Lymphocytes depend on this enzyme for de novo purine synthesis and proliferation. In this way, MMF selectively targets activated lymphocytes. Other potential therapies include plasmapheresis, intravenous methylprednisolone, rituximab, intravenous gamma globulin, cyclosporine, gold, dapsone, tetracycline and extracorporeal photochemotherapy.

**REFERENCES:**

Amagai M, Tsunoda K, Zillikens D et al. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol* 1999;40:167-170.

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## *Case #2*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Alyssa Nash, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 36-year-old woman presented to our clinic with a two-year history of an intermittent rash to her scalp and lesions in her oral mucosa, which were treated with antibiotics without significant improvement. Over the past month, she complained of numerous lesions on her scalp, axillae, trunk, buttocks, thighs, and oral mucosa. The patient denied fevers or chills.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

Penicillin

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

No history of smoking, alcohol or drug use.

### PHYSICAL EXAMINATION:

The patient had many superficial erosions and a few flaccid blisters involving the axillae, trunk, groin, buttocks, and thighs. The buccal mucosa demonstrated erythematous erosions. The patient was afebrile without evidence of secondary infection.

*Case #2 - Continued*

**LABORATORY EXAMINATION:**

The following were normal or negative:

General chemistry
Liver function tests
HIV antibody
PPD
RPR
DEXA bone densitometry study was consistent with normal bone and mineral content

The following were abnormal or positive:

Complete blood count
leukocytes 17,200
neutrophils 89.7%
Indirect immunofluorescence 1:160

**BIOPSY:**

CSP 04-740: There is an intradermal pustule with suprabasal separation and acantholysis. Neutrophils and eosinophils are present with in the pustule and upper dermis. Direct immunofluorescence shows intercellular staining for IgG.

**DIAGNOSIS:**

Pemphigus Vulgaris

**TREATMENT AND COURSE:**

The patient was started on 60 mg of prednisone per day (1mg/kg/day), as well triamcinolone acetonide in orabase. Alendronate (Fosamax) 35 mg each week, calcium 1000 mg and vitamin D 800 units daily were started for osteoporosis prophylaxis because of likely long-term prednisone therapy. The patient responded well to prednisone therapy and the dose was tapered to 40 mg per day over two weeks without evidence of new blisters. As a steroid sparing agent, mycophenolate mofetil (CellCept) was started at a dosage of 1 gram twice daily with plans for future escalation of the dosage if needed.

**DISCUSSION:**

The term pemphigus encompasses a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell-cell adhesion of keratinocytes through a process called acantholysis. Pemphigus can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus.

## *Case #2 - Continued*

Each form of pemphigus has specific autoantibodies against normal epithelial structural proteins making unique disease states. The autoantibodies are pathogenic and capable of reproducing disease in vivo.

Pemphigus vulgaris is the most common form of pemphigus observed in North America and Europe. It is a chronic blistering disorder of skin and mucous membranes. The IgG autoantibodies in pemphigus recognize a 130-kd cell adhesion molecule of the epidermis, desmoglein 3, a member of the cadherin family of adhesion molecules. Some patients have additional IgG autoantibodies against desmoglein 1. Once bound to the desmogleins the autoantibodies interfere with desmosome assembly causing dissolution of cell-to-cell membrane contacts and blister formation. In pemphigus vulgaris the blister occurs deep, just above the basal layer.

All patients with pemphigus have antibodies directed at desmoglein 3 resulting in mucous membrane blistering. Patients with the additional anti-desmoglein 1 antibody will also have cutaneous involvement. The distribution of desmoglein 1 is superficial in both skin and mucous membranes, but it is more concentrated in the skin. Desmoglein 3 is situated in the deeper layers of the skin and is more prominent in the mucous membranes. This distribution, along with the compensation theory, explains the differential location of blisters depending on the autoantibody involved.

Painful mucous membrane erosions are the presenting sign of pemphigus vulgaris and may be the only sign for an average of 5 months before skin lesions develop. Often these erosions develop in the oral mucosa, but other mucous membranes may be involved including conjunctiva, anus, penis, vagina and labia. The skin of afflicted patients can show painful flaccid blisters anywhere, although erosions are more common due to the fragile nature of these blisters. Rare associations with myasthenia gravis and/or thymoma have been reported.

Diagnosis is made by direct immunofluorescence of perilesional skin. A positive result will show IgG on the cell surface of keratinocytes. Indirect immunofluorescence may be used to detect circulating IgG and monkey esophagus is most sensitive for the pemphigus vulgaris antibodies. There is a positive but, imperfect correlation between the titer of anti-cell surface antibody and disease activity. Histopathology of lesional skin shows suprabasilar blister with acantholysis. The basal cells stay attached to the basement membrane and appear as a “row of tombstones”.

The medical management of pemphigus vulgaris includes the use of systemic glucocorticoids and immunosuppressants such as mycophenolate mofetil, azathioprine and cyclophosphamide to reduce autoantibody synthesis. These medications have dramatically improved the prognosis of pemphigus but, the disease is still associated with a significant morbidity and a 5% mortality mostly due to the complications of immunosuppressive therapy. Mycophenolate mofetil (MMF, Cellcept) has been shown to have a rapid effect in lowering pemphigus antibody titers and to decrease disease activity. It also has fewer adverse reactions when compared to azathioprine. MMF reversibly inhibits inositol-monophosphate-dehydrogenase (IMPDH). Lymphocytes depend on this enzyme for de novo purine synthesis and proliferation. In this way, MMF selectively targets activated lymphocytes. Other potential therapies include plasmapheresis, intravenous methylprednisolone, rituximab, intravenous gamma globulin, cyclosporine, gold, dapsone, tetracycline and extracorporeal photochemotherapy.

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## *Case #3*

***PRESENTED BY:*** *Harry Goldin, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 73-year-old woman presented 10 years ago with a three-week history of sores in her mouth and blisters on her trunk. After a diagnosis of pemphigus vulgaris was made, she was started on 80 mg/day of prednisone and 100 mg per day of azathioprine. Within 8 weeks, her lesions were controlled and the prednisone was tapered to 20 mg every other day with azathioprine 150 mg/day. Secondary to developing a cushinoid appearance, erratic emotions, and difficulty with sleep, prednisone was discontinued over the next year and she was maintained on 100 mg per day of azathioprine. Over the next several months, she stopped the azathioprine on her own. Lesions recurred on her scalp and failed to respond to numerous therapies including Diprolene gel topically, prednisone, azathioprine, and cyclophosphamide. The cyclophosphamide was started at 3 mg/kg per day (225mg) but was discontinued due to a drop in her white blood cell count to 2700. In April 1997, intralesional injections of triamcinolone were attempted and somewhat successful, however, she developed nausea and vomiting later the same day and refused further intralesional injections. In July 1997, she was restarted on azathioprine 100 mg per day with prednisone 20 mg every other day. The prednisone was tapered and discontinued by October 1998. In January 2003, the azathioprine was decreased to 50 mg per day. The patient continues to have lesions on her scalp despite these therapies.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

*Case #3 - Continued*

**SOCIAL HISTORY:**

Non-contributory

**PHYSICAL EXAMINATION:**

Initially, on her buccal mucosa, many erosions were seen. On her trunk, erosions with superficial vesicles were present. Currently, she is left with numerous crusts and erosions on her scalp.

**LABORATORY EXAMINATION:**

The following were abnormal or positive:

Over the course of therapies, the indirect immunofluorescence titer has varied between <1:20 to 1:80.

**BIOPSY:**

A biopsy revealed changes consistent with pemphigus vulgaris. Direct immunofluorescence examination showed intercellular IgG within the epidermis. There was no staining of the dermal-epidermal junction.

**DIAGNOSIS:**

Pemphigus Vulgaris

**DISCUSSION:**

The term pemphigus encompasses a group of chronic blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes, resulting in the loss of cell-cell adhesion of keratinocytes through a process called acantholysis. Pemphigus can be divided into three major forms: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Each form of pemphigus has specific autoantibodies against normal epithelial structural proteins making unique disease states. The autoantibodies are pathogenic and capable of reproducing disease in vivo.

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## *Case #3 - Continued*

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## *Case #4*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Lalitha Mamilla, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 47-year-old Pakistani man with a 5 year history of dermatitis herpetiformis diagnosed in Pakistan presented in 2002 with a pruritic rash on his face, arms, chest and back. He had discontinued his dapsone three weeks prior to the cutaneous eruption. In addition, he complained of a painful rash on his left side which had been present for one week. He denied fever, diarrhea, constipation, abdominal pain, weight loss, or any other systemic symptoms.

### PAST MEDICAL HISTORY:

Dermatitis herpetiformis

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

There were 2-3mm erythematous papules and vesicles distributed symmetrically on the face, elbows, extensor forearms, and lower back. Erythematous grouped vesicles were noted in the T4 dermatomal distribution.

*Case #4 - Continued*

**LABORATORY EXAMINATION:**

The following were negative or normal:
- Complete blood count
- General chemistry
- Liver function tests
- Thyroid function tests

**BIOPSY:**

CSP-03-7999: There was superficial perivascular and interstitial infiltrate of neutrophils, occasional eosinophils and nuclear dust. Several neutrophilic microabscesses were present within the dermal papillae. Direct immunofloresence of the perilesional skin showed foci of granular deposits of IgA along the subepidermal papillae.

**DIAGNOSIS:**

Dermatitis Herpetiformis with Herpes Zoster in T4 Distribution

**TREATMENT AND COURSE:**

The patient was started on dapsone 25 mg daily with gradual escalation to a dose of 100 mg daily with complete resolution of skin lesions. The patient was also started on gluten-free diet. With strict adherence to gluten-free diet, the patient is currently maintained on dapsone 25 mg daily. The patient was also treated with acyclovir 800 mg five times a day for 10 days with complete resolution of skin lesions on the chest within one week.

**DISCUSSION:**

Dermatitis herpetiformis (DH) is a cutaneous manifestation of celiac disease and is associated with gluten sensitivity in virtually all cases. DH is most common in Northern Europeans and rare in African-Americans and Asians. The mean age of onset is in the fourth decade but may range from age 2 to 90 years. Over 90% of patients have evidence of a gluten sensitive enteropathy that can range from intraepithelial lymphocytes in the jejunum to total villous atrophy of the small intestines. However, only 20% of DH patients have intestinal symptoms of celiac disease. Since both the skin and intestinal disease resolve with dietary gluten restriction and recur with return to a regular diet, it is clear that the dietary protein gluten is central to the pathogenesis of the cutaneous eruption. There is a strong genetic association with 90% of celiac disease and DH patients having the HLA Class 2 DQ2 genotype composed of the DQA1*0501 and DQBI*02 alleles, compared with only 20% of normal controls. Recently, it was proposed that the epidermal as opposed to tissue transglutaminase is the auto antigen in dermatitis herpetifomis. Epidermal transglutaminase was also found to co-localize with IgA in dermal papillae of DH

patients.

DH has symmetric distribution and favors the elbows, extensor forearms, back, buttocks and knees. The primary lesions are pleomorphic, with urticarial plaques, papules, and vesicles. On histopathology, if an intact vesicle is biopsied, a subepidermal blister containing predominantly neutrophils will be seen. On direct immunofluoresence, granular IgA deposits localized to the dermal papillae are found in 85% of cases, while continuous granular deposition of IgA along the basement membrane occurs in 5-10% of cases. Anti-endomysial antibodies are very specific for celiac disease and DH. In spite of this high specificity for gluten sensitivity, the preferred method for diagnosis is still direct immunofluoresence of the skin adjacent to a lesion.

DH is associated with increased frequency of malignancies, especially gastrointestinal lymphomas and a significant increase in non-Hodgkin's lymphomas. In addition, DH patients have a higher incidence of other autoimmune diseases such as thyroid disease, insulin dependent diabetes, lupus erythematosis, Sjörgen's Syndrome, and vitiligo.

The treatment of DH patients includes dapsone and a gluten-free diet. Symptoms may abate in as few as 3 hours or as long as 3 days after initiating dapsone therapy, and recur abruptly within 24 to 48 hours of discontinuation of therapy. Initial dosages of dapsone are 25-50 mg in adults with an average maintenance dose on a normal diet of 100 mg daily. If patients are intolerant to dapsone, therapy with sulfapyridine should be considered. H.M. Lewis *et al* have reported the advantages of a gluten-free diet in the management of patients with DH, including a reduction or complete elimination of medication requirements, resolution of the enteropathy, the feeling of well being, and a protective role against gastrointestinal lymphomas.

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## *Case #5*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Anne Snider, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 64-year-old Hispanic man presents with a one-month history of intensely pruritic, burning blisters which began on his hands and subsequently spread to his trunk. He denied having mouth lesions, dysuria, fever, or joint pain.

### PAST MEDICAL HISTORY:

Diabetes mellitus, type II
Hypertension
Coronary artery disease
Cataracts
Chronic renal disease

### MEDICATIONS:

Clonidine
Hydralazine

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Smoker

### PHYSICAL EXAMINATION:

There are tense bullae on his hands, extremities, groin, and axillae with superficial, erythematous erosions on his chest, hands, and legs. In addition, there are generalized urticarial papules and

plaques without mucosal or conjunctival involvement.

**LABORATORY EXAMINATION:**

The following were negative or normal:
- Complete blood count
- Comprehensive metabolic panel
- Liver function tests
- Lipid panel
- Anti-nuclear antibody

The following were positive or abnormal:
- Blood urea nitrogen 70 mg/dL (8.0-20.0 mg/dL)
- Creatinine 5.9 mg/dL (0.6-1.4 mg/dL)
- Glucose 215 mg/dL (65-110 mg/dL)
- Eosinophils 21.1% (0.0-5.0%)

**BIOPSY:**

CSP-03-12950: A 4 mm punch biopsy of a bulla from the left arm shows a subepidermal vesicle with dermal festooning. A dermal infiltrate contains numerous eosinophils.

Direct Immunofluorescence: A 4 mm punch biopsy of perilesional skin from the left arm shows linear deposits of IgG and C3 along the basement membrane supporting the diagnosis of bullous pemphigoid.

**DIAGNOSIS:**

Bullous Pemphigoid

**TREATMENT AND COURSE:**

The patient was placed on tetracycline 500 mg QID, niacinamide 500 mg TID, and clobetasol proprionate ointment 0.05% daily to the affected area. In addition, his symptoms were treated with hydroxyzine and aluminum subacetate soaks. Due to severe nausea and a decline in renal function, the tetracycline and niacinamide were discontinued. The patient is doing well using the soaks and topical steroids which have since been tapered to mid-potency. His pruritus has diminished and, due to the fact that he has not developed any new bullae, other systemic medications have not been initiated.

**DISCUSSION:**

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease. It is typically a disease of the elderly with an onset between 60 to 80 years of age. There may be a non-bullous, prodromal phase exhibited by mild to severe pruritus alone or in association with eczematous and/or urticarial lesions. The bullous stage is characterized by vesicles and tense bullae which develop on normal or erythematous skin often in association with annular, urticarial papules and plaques. The lesions predominate in the flexures and are frequently symmetric with infrequent scarring noted upon healing. Approximately 10-40% of BP patients develop oral cavity involvement, the lesions of which are transient and have few symptoms. Approximately half of BP patients develop peripheral blood eosinophilia, and 70% have elevated serum IgE levels. BP is a chronic disease characterized by exacerbations and remissions. BP patients carry a good prognosis as the majority will go into clinical remission within 10 years. Certain drugs can also induce BP such as diurectics (furosemide), neuroleptics, analgesics, D-penicillamine, gold and captopril.

BP is an immune-mediated disease with patients demonstrating autoantibodies directed against two components of the hemidesmosomes, which are adhesion complexes that anchor epidermal basal cells to the underlying basement membrane: the BP antigen 180 (BP 180, BPAG2, or type XVII collagen) and the BP antigen 230 (BP 230 or BPAG1). BP180 is a transmembrane protein with a large extracellular domain, specifically the NC16A domain. BP 230 is a cytoplasmic protein of the plakin family. Although these two antigens are recognized by autoantibodies, only antibodies to BP 180 have been proven to induce blistering. When autoantibodies bind to these target antigens within the dermo-epidermal junction there is complement activation and mast cell degranulation. Chemotactic factors are released resulting in neutrophil and eosinophil recruitment. The release of proteolytic enzymes by eosinophils and neutrophils results in tissue damage and bullae formation. The role that these inflammatory cells play in the pathogenesis of BP explains the better efficacy that anti-inflammatory agents such as niacinamide and tetracycline have in BP than in pemphigus.

The diagnosis of BP is made on the basis of clinical presentation, histological features and most importantly, a positive direct immunofluorescence (DIF) and indirect immunofluorescence (IIF). Histologically, BP will have subepidermal blister formation and an inflammatory infiltrate composed of neutrophils and eosinophils along the basement membrane zone and in the blister cavity, and the surrounding epidermis may show eosinophilic spongiosis. DIF of perilesional, uninvolved skin will characteristically demonstrate linear, continuous deposits of IgG and/or C3 along the basement membrane zone. $IgG_4$ and $IgG_1$ are the predominant IgG subclasses. IIF of serum shows circulating IgG autoantibodies to both BP 180 and BP 230 in the basement membrane of human skin or monkey esophagus. IIF studies using 1 mol/L sodium chloride (NaCl)-split skin which induces a split through the lamina lucida can be done to determine whether serum antibodies from patients with subepidermal autoimmune blistering disorders bind to the roof (epidermal), floor (dermal) or both of salt-split skin (SSS). Epidermal staining is highly specific for BP and most patients with pemphigoid will exhibit this pattern, however, IgG autoantibodies from BP patients have also been shown to bind both the epidermal and dermal sides as well as just the dermal side of SSS. IIF titers have not been shown to parallel disease activity as these titers mainly reflect reactivity to BP 230 (nonpathogenic) and, to a lesser extent, BP 180 (pathogenic). However, serum levels of autoantibodies to BP 180 detected by the BP 180 NC16A ELISA, correlate with disease activity in BP and may be helpful in guiding treatment

decisions in this disease.

Treatment of patients with BP is mainly based upon disease severity and the presence of concomitant diseases such as diabetes mellitus, hypertension and osteoporosis which are quite prevalent in the elderly population most afflicted with BP. However, systemic corticosteroids remain the mainstay of treatment in BP. For patients with generalized disease, oral prednisone at a dose of 0.5-1.0 mg/kg per day will usually control the disease within 1 to 2 weeks allowing the dose to be slowly tapered over about 6 to 9 months. Topical clobetasol proprionate ointment 40 g per day has been shown to control both localized and generalized BP with the same efficacy as oral steroids but with fewer systemic side effects. Other immunosuppressive drugs used to treat BP include azathioprine, chlorambucil, cyclophosphamide, methotrexate and mycophenalate mofetil. Dapsone 150-300 mg per day is another alternative treatment particularily useful if there is mucosal involvement. A therapeutic alternative to immunosuppressives is a combination of anti-inflammatory drugs such as niacinamide (500-2000 mg per day) and tetracycline or minocycline. Leflunomide, a novel immunomodulatory drug with a favorable safety profile, can be used as a single or combined therapy in the management of BP. More aggressive treatment with IVIg, plasmaphoresis, and extracorporal photophoresis is rarely needed, but when required is highly effective.

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## *Case #5 - Continued*

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***Case #6***

## UNKNOWN CASE

## *Case #7*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Jessie Cheung, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 39-year-old Hispanic woman was referred to our clinic status-post surgical release of bilateral ectropion with the incidental finding of squamous cell carcinoma and basal cell carcinoma in the scar tissue. She had a history of bilateral lower eyelid keratoses for 5 years treated with acid application in Mexico 4 years previously. She also notes asymptomatic lesions on her arms and knees since childhood.

### PAST MEDICAL HISTORY:

Hypertension

### MEDICATIONS:

Hydrochlorthiazide 25 mg qD

### ALLERGIES:

None

### FAMILY HISTORY:

Brother with similar lesions.

### SOCIAL HISTORY:

She denies the use of alcohol or tobacco products.

### PHYSICAL EXAMINATION:

The patient had bilateral infraorbital ill-defined ulcerated plaques. Her forehead and bilateral extremities had scattered, well-demarcated, ovoid pink plaques ranging from 0.5-1cm; some plaques on the hands had superficial erosions.

*Case #7 - Continued*

**LABORATORY EXAMINATION:**

None

**BIOPSY:**

Vista Health S03-1451 (Right cheek): There is ulceration, and and there are islands and cords of baseloid cells within the dermis. Some of the baseloid cells show keratinization.

CSP-03-9570 (Right arm): Within the upper half of the epidermis are numerous large keratinocytes with amphophilic cytoplasm and vesicular nuclei.

**DIAGNOSIS:**

Epidermodysplasia Verruciformis

**TREATMENT AND COURSE:**

The patient was started on imiquimod 5% cream (Aldara) at bedtime two times a week to the left infraorbital area. Follow-up 2 weeks later showed decrease in scaling and crust, and some erythema to the area of application. The frequency of application was gradually increased to every other night to the bilateral infraorbital areas and three times a week to the forehead. Scouting biopsies were performed with the finding of squamous cell carcinoma in-situ in the left lower eyelid. On follow-up, the patient was found to have a lesion on the medial right cornea; she underwent a lamellar keratectomy in October 2003. Pathology revealed squamous cell carcinoma in-situ of the bulbar conjunctiva. Plastic Surgery has performed a two-stage procedure to release the right ectropion. The patient is to start acetretin therapy.

**DISCUSSION:**

Epidermodysplasia verruciformis(EDV) is a rare genodermatosis characterized by generalized infection with a specific group of HPV types and the propensity for developing malignant skin tumors. About fifty percent of cases appear to be inherited in either an autosomal recessive, or X-linked fashion, and present with typical lesions in childhood. The other cases are sporadic and may present later in life.

The lesions associated with EDV are of 2 types; usually red to brown plaques that resemble pityriasis rosea or tinea versicolor, or flat wart-like lesions. The latter are usually caused by HPV types 3 and 10, and are considered benign. The PR-like lesions are usually caused by EV specific HPV types 5, 8, 9, 12, 14, 19, 20, 37, and 47, and are associated with an increased risk of malignant transformation, especially HPV types 5 and 8. Most of the tumors remain localized; however, metastases have been reported.

Defects in cellular immunity may contribute to the pathogenesis of EDV. The majority of patients have decreased numbers of T-helper cells with normal numbers of T-suppressor cells. Ultraviolet light appears to contribute to the cell-mediated immunodeficiency in these patients since most of the malignant tumors develop in sun-exposed areas and there is a lower incidence in darker pigmented individuals. Interestingly, these patients do not appear to have an increased risk for developing other viral or bacterial infections.

Preventing the progression of lesions from benign to malignant is the mainstay of management. Protection from UV light and radiation therapy should be started as soon as the disease is diagnosed. Aside from surgical invention for skin cancer, the treatment of EDV is difficult due to poor response and frequent relapse. Oral retinoids have been used but their effects are often reversible after discontinuation of treatment. The combination of retinoids and interferon alfa has been reported to successful in a patient with recalcitrant lesions. Intralesional interferon beta has been shown to be effective in benign lesions. There have been case reports of regression of disease from using tacalcitol ointment, cimetidine, and photodynamic therapy. A recent publication supports the use of acitretin to suppress squamous cell carcinoma, which could be applied to patients with EDV.

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## *Case #8*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Shirley Chi, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 42-year-old African-American woman presented with a three-month history of bilateral eyelid swelling which did not respond to oral antihistamine treatment. The patient has a history of juvenile dermatomyositis with an abnormal muscle biopsy which had been treated with oral corticosteroids and had resolved while in her early teens. She has no other skin lesions and does not report photosensitivity or muscle weakness.

### PAST MEDICAL HISTORY:

Juvenile dermatomyositis

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

There is no history of breast or ovarian carcinoma in other family members.

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

Bilateral periorbital edema is present, accompanied by erythema and decreased skin turgor of the periorbital area. Dilated capillary loops are subtle but present in the proximal nailfold of several fingers. There are no other skin lesions. Motor strength is 4/5 in both upper and lower extremities.

***Case #8 - Continued***

**LABORATORY EXAMINATION:**

The following are normal or negative:

Complete blood count
General chemistry panel
Thyroid functions tests
Aldolase
Rheumatoid factor
Complement levels
HIV antibody
RPR.

The following are abnormal or positive:

| | | |
|---|---|---|
| ANA: weakly positive, speckled | 1:160 | |
| LDH | 289 | (85-210) |
| Aspartate Aminotransferase | 51 | (0-40) |
| Alanine Aminotransferase | 67 | (0-35) |
| Creatine Kinase | 256 | (0-165) |
| Erythrocyte sedimentation rate | 42 | (0-35) |

**BIOPSY:**

CSP-03-6043: There is a subtle interface dermatitis, vacuolar type. The dermis shows abundant mucin and a perivascular lymphocytic infiltrate.

**DIAGNOSIS:**

Dermatomyositis with history of Juvenile Dermatomyositis

**TREATMENT AND COURSE:**

Oral prednisone was initiated at a dose of 60 mg daily. She also began using tacrolimus 0.1% cream twice a day to the periorbital region, and sunscreen was applied daily. She was referred to the division of Rheumatology for further follow-up and to Internal Medicine and Gynecology for appropriate cancer screening which were all normal. The patient responded well to the treatment with resolution of skin lesions, and has since been tapered off prednisone. She continues to use broad-spectrum sunblock daily.

**DISCUSSION:**

Dermatomyositis (DM) is an idiopathic inflammatory myositis characterized by vague prodromal symptoms, edema, muscle inflammation, and characteristic cutaneous manifestations including

the heliotrope rash, Gottron's papules, Gottron's sign, cuticular changes including periungual telangectasia, a photodistributed erythema or poikiloderma, and a scaly alopecia. In 1975, Bohan and Peter published a suggested set of criteria to aid in the diagnosis and classification of classic dermatomyositis and polymyositis. Four of the five criteria dealt with muscle disease-progressive, proximal symmetrical weakness, and increased concentration of muscle enzymes, an abnormal electromyogram, and an abnormal muscle biopsy sample. The fifth criteria described compatible cutaneous disease. A subset of DM patients characterized by biopsy-confirmed hallmark cutaneous manifestations of classic DM occurring for 6 months or longer with no clinical evidence of proximal muscle weakness and no serum muscle enzyme abnormalities has been termed amyopathic DM (formerly known as DM-sine myositis.) Dermatomyositis has been linked to cancer, and most large population-based cohort studies report a rate of 20-25%. Gynecologic malignant disease, in particular ovarian carcinoma, may be over-represented in patient with dermatomyositis.

Juvenile dermatomyositis is the most common inflammatory myopathy in children, affecting children 2 to 15 years of age with a mean age of onset of 6.9 years and an incidence of 3 cases per 1 million children per year. There is no increase in the incidence of malignancy in children with dermatomyositis over the normal population. It is commonly characterized as a vasculitis, but the major difference to adult disease is the greater potential for calcinosis. There is a high association between the presence of the TNF-alpha 308 allele and pathologic calcification, as well as longer disease duration.

Patients with juvenile DM have been described to follow 4 basic clinical courses: monocyclic course; polycyclic course; prolonger, chronic, continuous, non-ulcerative course; and ulcerative course. Approximately 40% of patients follow the benign monocyclic course, which is self-limited, responsive to steroids, and lasts 9 to 12 months with an excellent outcome. The long-term outcome of patients following a polycyclic course is also good to excellent, although they may experience 1 or more disease recurrences months to years after discontinuation of medication. Approximately 35-40% of patients experience chronic non-ulcerative disease that remains active for more than 2 years. Calcinosis is common in this group, as in the ulcerative group where patients have life-threatening ischemic ulceration of the gastrointestinal tract, skin, or both. There are no reports in the literature of dermatomyositis diagnosed in an adult with a history of juvenile dermatomyositis, as in this case in which the patient was originally treated with resolution over 25 years ago. This case is also unique in regards to the patient's initial presentation to our clinic with only bilateral eyelid edema. Differential diagnosis of edema of the eyelids would also include angioedema, contact dermatitis, trichinosis, erysipelas, hypoalbuminemia due to underlying renal or liver disease, thyroid disease, cardiac failure, superior vena cava syndrome, and cavernous sinus fistula.

The mainstay of treatment for DM is systemic corticosteroids, initially given at 0.5-1.0 mg/kg bodyweight. Early intervention with steroid-sparing agents, primarily immunosuppressive agents such as methotrexate, azathioprine, cyclophosphamide, mycophenolate mofitil, chlorambucil, or cyclosporine might be effective in inducing remission. Therapy for cutaneous disease in patients with DM is difficult, as skin manifestations are frequently persistent. As most patients with cutaneous lesions are photosensitive, daily use of a broad-spectrum sunscreen with a high sun protective factor is recommended. Hydroxychloroquine can also be given at a dose of 200-400 mg orally per day, and is effective in about 80% of patients when used as a steroid sparing agent. Jorizzo reports anecdotal success using topical 0.1% tacrolimus cream as an adjunctive treatment.

## *Case #8 - Continued*

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## *Case #9*

***PRESENTED BY:*** *Lissette Ortiz-Ferrer, M.D, Jerry Feldman, M.D. and Seth Wilentz, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 25-year-old Hispanic female presented to Cook County Hospital with a one-month history of facial erythema. She was given a two-week course of hydrocortisone 1% ointment, which afforded no relief. Upon returning to clinic, the patient complained that the rash began spreading to her arms and back. Furthermore, the patient complained of photosensitivity and that her "skin was beginning to burn." The patient denied any pain or weakness of her arms or legs.

### PAST MEDICAL HISTORY:

Non-contributory. No personal history of malignancy.

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory. No family history of autoimmune disease or malignancy.

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

Generalized, slightly violaceous erythema of the face is noted. There are large patches of erythema on the dorsal surfaces of the arms. Furthermore, there are erythematous patches and papules covering the metacarpal and proximal interphalangeal joints. On the back, a large plaque of erythematous, slightly atrophic skin with areas of both hyper- and hypopigmentation is noted

extending about the shoulders in a classic "shawl distribution." There are no capillary loops in the proximal nail folds. No muscle weakness is appreciated.

## LABORATORY EXAMINATION:

The following tests were negative or within normal limits:

Antinuclear antibodies, anticentromere, antisynthetase antibodies
Creatine phosphokinase (negative on multiple occasions)
Aldolase (negative on multiple occasions)
Myoglobin
Erythrocyte sedimentation rate
Muscle biopsy
Complete blood count
Basic metabolic panel
Liver enzymes
Urinalysis
MRI Pending

## BIOPSY:

CSP-03-14899 (back): There is interface dermatitis, vacuolar type with a few melanophages present in the upper dermis. A superficial lymphocytic infiltrate is present. Alcian blue stain shows a suggestion of increased mucin in the papillary dermis.

## DIAGNOSIS:

"Provisional" Amyopathic Dermatomyositis

## TREATMENT AND COURSE:

The patient is currently being treated with tacrolimus ointment 0.1% twice daily to the face and triamcinolone ointment 0.1% twice daily to the body, both with moderate results. She is being evaluated by gynecology and general medicine for a malignancy work-up.

## DISCUSSION:

Amyopathic dermatomyositis, as defined by Sontheimer, is a disease "characterized by biopsy-confirmed hallmark cutaneous manifestations of classic dermatomyositis (DM) occurring for 6 months or longer with no clinical evidence of proximal muscle weakness and no serum muscle abnormalities." Furthermore, he continues to report that if more extensive muscle testing

(pathological, electrophysiological, or radiological) is carried out, the results should be within normal limits. If the results of any "extensive" muscle tests are positive/abnormal, then the patient should be classified as having hypomyopathic DM (ie. positive classic DM skin changes, negative clinical exam, but positive muscle tests). Moreover, exclusionary criteria for the diagnosis of amyopathic dermatomyositis are as follows: (1) treatment with systemic immunosuppressives for two consecutive months or longer within the first 6 months of skin disease onset, as immunosuppressive therapy could mask onset of clinically relevant myositis and (2) use of drugs known to cause DM-like skin eruptions such as hydroxyurea, penicillamine or the lipid lowering agents known collectively as statins.

For the purpose of simplification and to emphasize these patients' most prominent clinical problem of skin disease, Sontheimer believes that both groups described above (amyopathic and hypomyopathic DM) should be grouped together under the functional designation of "clinically amyopathic DM" (C-ADM). In addition, for the purposes of clinical studies, a diagnosis of C-ADM should be considered "provisional" for disease duration between 6-23 months and "confirmed" for disease duration of 24 months or greater. These designations (provisional vs. confirmed) are used because it is not unusual for the classic skin manifestations of DM to present themselves prior to the classic muscle findings. Indeed, almost 100% of patients with clinically amyopathic DM who "progress" to myositis do so within 2 years of the onset of cutaneous manifestations (most who progress actually do so within 6 months).

In the United States the incidence of C-ADM is reported to be extremely low. Exact statistics are unknown, but the incidence is believed to be about 10% of the incidence of classic DM. One large, 20-year retrospective study of DM out of the Mayo clinic revealed that 32 (4%) of 746 patients with DM could today be classified under Sontheimer's definition of C-ADM (27 with amyopathic DM, 5 with hypomyopathic DM). Long term follow-up of 19 of these 32 patients reveled that 13 (68%) had no muscle disease after at least 2 years ("confirmed" C-ADM), 4 (21%) had no muscle disease after at least 1 year ("provisional" C-ADM), and only 2 (11%) developed weakness within 5 years of follow-up (Classic DM).

The cutaneous manifestations of C-ADM are indistinguishable from that of classic DM. These manifestations include (1) pathognomonic skin lesions, (2) characteristic skin lesions, and (3) compatible skin lesions. Pathognomonic skin lesions include: Gottron papules (violaceous papules overlying the dorsal DIP, PIP, or MCP joints) and Gottron's sign (symmetric violaceous erythema with or without edema overlying the dorsal hand joints, olecranon processes, patella, or medial malleoli.) Characteristic skin lesions include: periorbital violaceous "heliotrope" erythema with or without associated edema; periungual telangiectasia with or without dystrophic cuticles; and symmetric violaceous erythema overlying the hands, dorsal arms, deltoids, shoulders, neck, and V-area of anterior neck. Compatible skin lesions include: calcinosis cutis and poikiloderma.

The risk of interstitial lung disease (ILD) and malignancy in patients with C-ADM are 2 important points for discussion. The risk of ILD in patients with C-ADM seems to be inline with the risk of ILD in patients with classic DM, reported at 5-40%. According to the approximate 300 case reports of C-ADM about 10% report an associated, often fatal ILD. Furthermore, the risk of malignancy in patients with C-ADM is currently unknown, however according to the few case series investigating this topic, there seems to be an increased association. The cases series reporting on this topic place the associated risk of malignancy in C-ADM anywhere from 0-25%.

## *Case #9 - Continued*

Nevertheless, most authors do agree that patients with C-ADM, like those with classic DM, should be carefully evaluated for the possibility of developing occult malignancies.

Most patients with C-ADM are ANA positive. However, most of these patients do not produce myositis-specific autoantibodies or myositis-associated autoantibodies*.
Recent studies report the possibility of 2 new autoantibodies associated with C-ADM. Of 18 patients with C-ADM, 16 (89%) revealed autoantibodies to a 155-kDa autoantigen, the Se autoantigen, or both.

Treatment for C-ADM can include various regimens/combinations of topical and local therapies including sun avoidance, sunscreens, topical corticosteroids, topical immunomodulators; and systemic therapies including antihisamines, steroids, antimalarials and various other immunosuppressive medication.

*Autoantibodies in patients with DM can be organized into 2 groups, namely myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA). MSAs include the antisynthetase autoantibodies (Jo-1, PL-7, OJ, EJ), Mi-2, and SRP. MAAs include PM-Scl, Ro, U1RNP.

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## *Case #10*

***PRESENTED BY:*** *Lissette Ortiz-Ferrer, M.D. and Melanie Zahner, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 43-year-old Hispanic woman presents with a one-year history of a slowly growing, asymptomatic lesion to her left cheek. A similar lesion began on her right cheek in the last 2 to 3 months.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

A 1.5 cm well-demarcated, purple to red plaque was present on the left cheek. On the right cheek, a 0.5 cm dull red plaque was also visible but less indurated. No lesions were seen elsewhere.

## *Case #10 - Continued*

### LABORATORY EXAMINATION:

The following were normal or negative:
Complete blood count

### BIOPSY:

CSP-03-13469: A biopsy of the lesion on the left cheek reveals a dense and diffuse infiltrate in the upper half of the dermis. The infiltrate is composed of neutrophils, eosinophils, and histiocytes. There is sparing of the papillary dermis, representing the so-called Grenz zone. No vasculitis is identified in these sections.

### DIAGNOSIS:

Granuloma Faciale

### TREATMENT AND COURSE:

Local injection of triamcinolone suspension in concentration of 2.5 mg/mL showed modest improvement of the lesion.

### DISCUSSION:

Granuloma faciale is a rare inflammatory condition of unknown etiology characterized by red to brown papules and plaques usually involving the face. Particularly, lesions may appear on light-exposed areas, and some lesions are photo exacerbated. Sites of predilection include the nose, cheeks, and ears. Cases of extra-facial involvement have been reported. It most commonly occurs in middle-aged Caucasian men, but has been reported in African-Americans and Japanese. Lesions usually have a smooth surface with follicular accentuation and may have telangiectasias. Ulceration and crusting is rare. Lesions develop slowly and rarely spontaneously involute. Tenderness, pruritus and burning have been described. Patients with granuloma faciale usually lack systemic symptoms though some may be associated with a rare peripheral eosinophilia.

There has been some confusion and evolution of the term granuloma faciale. In 1945, Wigley described a case of eosinophilic granuloma of the skin and this was probably the first case of what we now know as granuloma faciale. Later, Cobane et al used the term facial granuloma with eosinophilia to describe a similar entity. In 1952, Pinkus suggested the term granuloma faciale.

Some authors believe erythema elevatum diutinum (EED) and granuloma faciale represent different parts of the spectrum of the same disease. Both are rare chronic forms of cutaneous small vessel vasculitis and may share some pathogenic mechanisms. There are several

differences between the two. EED is characterized by multiple lesions on the extensor surfaces of extremities. The trunk is usually spared and facial lesions are rare. Histopathologic features of EED include a dense superficial and deep polymorphous dermal infiltrate where neutrophils are dominant and eosinophils are rare or absent. A Grenz zone is not present and the epidermis may be involved. EED may be associated with systemic disease, in particular, gammopathies.

Microscopically, granuloma faciale shows a normal epidermis with a dermal infiltrate. A Grenz zone, an area of unaffected tissue between the epidermis and dermal infiltrate, is present. The dermal infiltrate consists of lymphocytes, eosinophils, and neutrophils with leukocytoclasia. Fibrin deposition around blood vessels is evidence of vasculitis. In the later fibrotic stage, perivascular fibrin deposition predominates, and the number of inflammatory cells is greatly reduced. The exact pathogenesis is unclear, but some consider it a variant of leukocytoclastic vasculitis. Immunoglobulins, fibrin, and complement can be found at the dermal-epidermal junction and around blood vessels on direct immunofluorescence.

Granuloma faciale is known to be resistant to therapy. Numerous modalities have been tried with variable success. Laser therapy with the CO2, argon, pulsed dye, and long-pulsed tunable dye lasers have been tried with some success. Dermabrasion, cryotherapy, and intralesional steroids have been tried either alone or in combination with variable success. Multiple case reports exist of various medical treatments including dapsone, colchicine, isoniazid, clofazimine, gold, prednisone, and testosterone. Most patients are usually treated with intralesional or topical steroids with mild to moderate improvement.

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## *Case #11*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Seth Wilentz, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 41-year-old African-American male with a history of systemic stage IV sarcoidosis, presented to Cook County Dermatology in the spring of 2003 with a four-month history of evanescent urticarial plaques. A biopsy of his urticarial lesions revealed no evidence of vasculitis. His urticaria had been well controlled with 10 mg of cetirizine daily as needed. Six months later (November, 2003), this same patient returned with a one-month history of severe xerosis of his abdomen and bilateral upper and lower extremities.

### PAST MEDICAL HISTORY:

Systemic Sarcoidosis (Stage IV) with documented involvement of the lungs and lymph nodes. (There has been no evidence to date of eye, bone, or heart involvement)
Hypertension

### MEDICATIONS:

Prednisone 40 mg daily
Calcium carbonate 500 mg thrice daily
Ranitidine 150 mg twice daily
Cetirizine 10 mg as needed daily

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

## *Case #11 - Continued*

### PHYSICAL EXAMINATION:

Large, plate-like, brown, scaly plaques were noted on the bilateral arms, bilateral shins, and abdomen.

### LABORATORY EXAMINATION:

The following were negative or normal:

Complete blood count
General chemistry
Aspartate aminotransferase
LDH
ANA, anti-centromere
Rheumatoid factor
G-6-PD
DEXA scan: normal bone mineral content of all measured sites (lumbar, right and left femoral heads)

The following laboratory examinations were abnormal:

| | |
|---|---|
| ACE | 118 (8-52) |
| Alanine aminotransferase | 50 (0-40) |
| Alkaline phosphatase | 218 (50-120) |
| GGT | 426 (3-60) |
| Erythrocyte sedimentation rate | 38 (0-35) |

### BIOPSY:

CSP-03-15503 (right leg): There is hyperkeratosis and hypogranulosis. Several small epithelioid cell granulomas are present in the upper dermis. Special stains for organisms and polarization were negative.

CSP-03-4820 (right leg): Superficial perivascular dermatitis, mixed cell type with few eosinophils compatible with urticaria. No evidence of vasculitis or sarcoidosis seen.

### DIAGNOSIS:

Ichthyosiform Sarcoidosis

### TREATMENT AND COURSE:

Over the past 10 years, this patient's systemic sarcoidosis was well controlled on relatively low doses of daily prednisone (approximately 10 mg of prednisone per day with few disease

exacerbations requiring increased prednisone doses). Because of his long-term steroid therapy, his pulmonologist attempted to switch his immunosuppressive medication to methotrexate. Within months of switching to methotrexate, the patient began to experience increasing pulmonary (shortness of breath) and skin (ichthyosis) symptoms. Both his lung and skin findings rapidly abated with a course of prednisone 40 mg daily. Methotrexate was discontinued and currently the patient is being evaluated for treatment with etanercept.

**DISCUSSION:**

Sarcoidosis is a multi-system disorder of unknown etiology. It is classically characterized by the formation of noncaseating granulomas with secondary derangement of normal tissue anatomy or organ dysfunction. It affects all races, all ages, and both sexes with its highest incidence found in African-American women between the ages of 30-39 (approximately 100 to100,000). The most common organ systems involved are the lungs, lymph nodes, eyes, and skin. Sarcoidosis commonly affects multiple organ systems in an affected individual, however approximately 25% of patients have sarcoidosis limited to the skin. Sarcoidal skin disease manifests in a myriad of morphologies and presentations.

Sarcoidosis lesions are classified as specific or nonspecific; specific lesions contain granulomas, and nonspecific lesions are reactive processes. Common specific sarcoidosis skin lesions manifest as macules, papules, nodules, plaques, subcutaneous nodules, infiltrative scars, and lupus pernio. Uncommon sarcoid specific lesions include: eruptive, ulcerative, psoriasiform, morpheaform, erythrodermic, and ichthyosiform presentations. A common nonspecific lesion of sarcoidosis is erythema nodosum.

Ichthyosiform sarcoidosis is one of the most uncommon clinical presentations of sarcoid. Only 22 cases of ichthyosiform sarcoid have appeared in the literature. In the reports where race, sex, and age were documented the clinical characteristic of those with ichthyosiform sarcoid were as follows: (1) Race: 16 blacks, 1 West Indian, 5 unidentified. (2) Sex: 8 men, 9 women, 5 unidentified, (3) Age at presentation: men 48, women 32.

The skin lesions of ichthyosiform sarcoidosis characteristically involve the lower extremities, most notably the shins, but can be found elsewhere on the body. Typically, asymptomatic, large, plate-like, adherent, scaly lesions are noted. Histopathologic examination reveals granulomatous inflammation in the dermis with or without overlying epidermal changes consistent with ichthyosis vulgaris (compact orthokeratosis with diminished granular layer). Sarcoid is a histological diagnosis of exclusion and therefore special stains for fungal and mycobacterial organisms must be negative and polarization must not reveal foreign material.

In the 22 patients mentioned above, only 4 (18%) were already carrying the diagnosis of systemic sarcoidosis. Three (14%) patients had their systemic sarcoidosis diagnosed concomitantly with their ichthyosis and 10 (45%) received their diagnosis of systemic sarcoidosis 2 to 24 months after their presentation with ichthyosis (5/22 cases do not report the temporal association of ichthyosis and diagnosis of sarcoidosis). Indeed, of the 17 reported cases in which the temporal association between ichthyosis and systemic sarcoid is known, 10 (58%) presented to their physicians with only ichthyosis. Furthermore, it is important to note that systemic involvement of sarcoidosis was reported in 21/22 (95%) with ichthyosiform sarcoidal skin lesions. With the

statistics above in mind, ichthyosiform sarcoidosis should be regarded as an early cutaneous marker for systemic sarcoidal involvement and appropriate follow-up is warranted.

Treatment guidelines for ichthyosiform sarcoid are not specifically outlined, but in general, seem to improve dramatically with systemic immunosuppression. Of note, sarcoid is only one of the many etiologies of acquired ichthyosis. Other possible entities in the differential of acquired ichthyosis include hyper/hypothyroidism, lymphoma, malnutrition, medications, solid malignancies, mycobacterial infections, medication-induced connective tissue disease, and HIV infection.

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## *Case #12*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Seth Wilentz, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 75-year-old Hispanic male presented with a two-month history of hundreds of violaceous, contusiform nodules, some confluent to plaques, covering most of his entire skin surface. He stated that these nodules erupted individually and in crops. All lesions continued to enlarge and none spontaneously regressed. These nodules were firm and tender, but not ulcerated. Furthermore, the patient complained of muscle weakness and fatigue.

### PAST MEDICAL HISTORY:

Non-contributory. No personal history of malignancy.

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory. No family history of lymphoproliferative disease.

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

There were generalized violaceous contusiform nodules measuring 1 cm to 10 cm covering the entire skin surface. These nodules were firm and tender without ulceration. The areas of skin without obvious nodules were firm on palpation.

Neither lymphadenopathy nor hepatoslenomagaly was appreciated on clinical exam.

## *Case #12 - Continued*

### LABORATORY EXAMINATION:

The following were abnormal or positive:

| | | | |
|---|---|---|---|
| White Blood Cells: | 6.4 | Neutrophils %: | 12.7 (43.2-76.0) |
| Hemoglobin: | 10.8 (12.5-16.7) | Lymphocytes %: | 82.2 (15.0-45.8) |
| Hematocrit: | 31.9 (36.4-48.8) | Neutrophils #: | 0.8 (1.6-8.0) |
| Platelets: | 74 (142-408) | Lympocytes #: | 5.3 (0.6-4.8) |

Serum protein electrophoresis: 1. elevated Kappa/Lambda ratio @4.08 (1.41-2.83)
2. monoclonal peaks present in the gamma region

Immunofixation: reveals an IgG Kappa gammopathy

### BIOPSY:

CSP-03-3247 (chest): Hematopoietic neoplasm, favor lymphoma lymphoblastic type.
Note: There was a dense subepithelial infiltrate of leukocyte common antigen positive cells containing an inconspicuous nucleolus and a notched nucleus with dispersed, fine chromatin. The tumor cells were negative for CD20, CD30, CD3, CD5, CD68, UCHL-1, and S-100. Flow cytometry is recommended to further characterize this neoplasm.

CSP-03-4178 (back): Throughout the dermis, with the exception of the uppermost papillary dermis, is a diffuse infiltrate of large lymphocytes. Many lymphocytes have a notched nucleus with dispersed, fine chromatin. Numerous mitotic figures are present.
Comment: Flow cytometry surface markers studies show a dominant CD56, CD45, CD4, CD7, CD25, and CD38 population which is negative for CD2, CD3, CD5, CD8, CD16, and CD33. These features support the diagnosis of malignant lymphoma, blastic natural killer-cell type.

CMB: 03-89 (bone marrow aspirate): Bone Marrow showing extensive involvement by blastic natural killer lymphoma. Comment: The bone marrow is diffusely infiltrated by small to intermediate-sized, immature mononuclear cells. Flow cytometry surface marker studies demonstrate a dominant CD45 dim population which also shows expression of CD2, partial CD7, CD56, CD38, CD4, dim CD34 and dim TDT but is negative for myeloperoxidase, surface and cytoplasmic CD3, CD5, CD16, CD13, and CD33.

### DIAGNOSIS:

Blastic Natural Killer-Cell Lymphoma/Leukemia

### TREATMENT AND COURSE:

The patient was referred to Hematology/Oncology and was started on combination chemotherapy

with cyclophosphomide, doxorubicin, vincristine, and prednisilone. Unfortunately, the patient succumbed to his disease within 6 weeks of his presentation.

## DISCUSSION:

Natural Killer (NK) cells are specialized lymphocytes that are capable of nonspecific target cell destruction. They can mediate cytotoxicity without prior sensitization or specific antigen recognition reactions requiring major histocompatibilty complexes. NK cells are currently defined by their expression of a 220 kDa surface glycoprotein known as CD56, among other T-cell markers.

CD56 positive NK/T-cell lymphomas often affect the skin. Currently, cutaneous NK/T-cell lymphomas can be separated into the following groups: (1) blastic NK-cell lymphomas, (2) extranodal nasal NK/T-cell lymphomas, (3) extranodal nasal-type NK/T-cell lymphomas, and (4) CTCL with coexpression of CD56.

Blastic NK-cell lymphomas seem to be the least common of the cutaneous NK/T cell lymphomas. The clinical presentation of most patients mirrors that of the patient we present herein. Patients usually have widespread, rapidly growing, violaceous skin-infiltrating nodules and plaques. Constitutional symptoms are exceedingly common.

Similar to other acute leukemias/lymphomas, blastic natural killer-cell leukemia/lymphoma has a predilection for multi-organ involvement, lymphadenopathy, splenomegaly and rapid bone marrow involvement which often leads to the patient's demise within 1 year of presentation. Histologically, dermal aggregates of immature intermediate-sized lymphoblasts are seen. Mitotic activity is usually evident, as is extensive coagulation necrosis. On immunhistochemistry, most blastic NK-cell leukemias/lymphomas are CD56+, CD4+, CD45+, CD7+/-, CD2+/-, surface and cytoplasmic CD3-, CD5-, CD16-, and CD68-, as was the case in our patient's skin and bone marrow samples. Mismatched immunohistochemical findings between skin and bone marrow flow cytometry (as ours were regarding CD2) have been previously reported. EBV testing was not done in our patient, however unlike nasal and nasal-type extranodal NK/T-cell lymphomas, blastic NK cell lymphomas classically are not associated with EBV.

Over 70 patients with blastic NK-cell lymphoma have been described in the literature. The mean survival time of these patients is less than 1 year. The best chance for "long-term" survival seems to be allogenic bone marrow transplant, as one author reports survival for 2 patients at 76 and 98 months with this treatment. Otherwise, most authors treat blastic NK-cell lymphoma with combination chemotherapy. High complete responses are achieved, but relapse within months is almost universal.

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## *Case #13*

***PRESENTED BY:*** *Sidney Barsky, M.D. and Lalitha Mamilla, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 42-year-old African-American man was referred by the infectious disease clinic for evaluation of a slowly growing lesion of 6 months duration on his left thigh. He denied any trauma, fever, cough, shortness of breath, weight loss or other systemic symptoms.

### PAST MEDICAL HISTORY:

HIV infection
Hypertension
Asthma

### MEDICATIONS:

Zidovudine and lamivudine (Combivir)
Nelfinavir
Dapsone
Enalapril
Enteric coated aspirin
Albuterol

### ALLERGIES:

Sulfa drugs

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

There was a large erythematous to violaceous ulcerated crusted plaque on the lateral aspect of the left thigh. There were no palpable inguinal lymph nodes.

***Case #13 - Continued***

**LABORATORY EXAMINATION:**

Following tests were normal or negative:
- Complete blood count
- General chemistry
- Liver function tests
- Chest x-ray

The following tests were positive or abnormal:
- CD4: 125
- HIV viral load: >75,000

**BIOPSY:**

CSP-03-8544: A 4 mm punch biopsy showed pseudoepitheliomatus hyperplasia of the epidermis with microabscess formation. Within the dermis was an infiltrate of lymphocytes, neutrophils, histiocytes and occasional giant cells. Broad based budding yeasts were present.

**DIAGNOSIS:**

Cutaneous Blastomycosis

**TREATMENT AND COURSE:**

The patient was treated with itraconazole 200 mg twice daily with improvement of his lesion within 1 month and complete resolution by 4 months.

**DISCUSSION:**

Blastomycosis is caused by a dimorphic fungus, *Blastomyces dermatitidis*, that exists in nature in a mycelial phase and converts to a yeast phase at body temperature. The organism may produce epidemics of infection following a point source of infection or sporadic endemic infection. Endemic areas include the southeastern or south central states bordering the Mississippi or Ohio River basins, the Midwestern states and Canadian provinces bordering the great lakes, and a small area in New York and Canada along the St. Lawrence River. While all ages and genders can be affected, adult men are most likely to develop systemic infection, and children are more likely to develop acute pulmonary blastomycosis rather than chronic cutaneous disease. Immunosuppressed hosts are most susceptible to infection and dissemination. Interestingly, HIV is not commonly associated with blastomycosis.

The soil is the most important source of infection and the respiratory tract is typically the first site of infection. Blastomycosis can be a sub-clinical illness with subsequent protection against

progressive infection afforded by cellular immune mechanisms, but it may present with progressive disease with either pulmonary or extra-pulmonary disease or both. Skin disease is the most common extra-pulmonary site followed by bone, prostate and central nervous system. Secondary cutaneous dissemination is a common occurrence, and may even be the first sign of disease. Cutaneus manifestations may even be seen in the absence of overt pulmonary disease. Primary cutaneus blastomycosis is uncommon and results from direct inoculation of the skin from trauma, such as in the laboratory or from performing autopsies on infected persons.

Cutaneous blastomycosis can present with a variety of skin lesions. The most common cutaneus lesions are either ulcerative or verrucous plaques. The verrucous form has a raised, irregular border often with crusting. Borders of ulcers are usually sharp, heaped up, with the base commonly containing exudate. Histological examination of skin lesions demonstrates round, yeast forms with the characteristic broad-base budding and thick double contoured walls. Detection of fungus by cultures or histological exam confirms the diagnosis of infection.

Spontaneous resolution of chronic blastomycosis is very uncommon. Untreated blastomycosis can be associated with mortality rates approaching 60%. All patients with chronic pulmonary and extra-pulmonary blastomycosis should receive antifungal therapy. Current recommendations for patients with non-life threatening, non-CNS blastomycosis include treatment with itraconazole at an initial dose of 200 mg daily for at least 6 months. For patients not responding to therapy, the dose should be increased by 100 mg increments every 2 to 4 weeks to a maximum dose 200 mg twice daily. For patients with severe life threatening CNS disease, amphotericin B remains the drug of choice. AIDS patients with blastomycosis, transplant recipients, those receiving chronic glucocorticosteroids, and other significantly immunocompromised patients should also receive initial therapy with amphotericin B and subsequent therapy with an azole.

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Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with acquired immunodeficiency syndrome. *Ann Intern Med* 1992;116:847-853.

## *Case #14*

***PRESENTED BY:*** *Sidney Barsky, M.D. and Anne Snider, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 34-year-old African-American man presents with a two-month history of a lesion on his left cheek that he related to a "spider bite". This skin lesion was preceded by a two-month history of a "chest cold" with cough, fever and malaise.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Smoker. Occasional alcohol. No intravenous drugs. No recent travel or outdoor exposure.

### PHYSICAL EXAMINATION:

A 4 x 3 cm verrucous plaque with overlying black crust is seen on his left upper cheek. There is no palpable cervical lymphadenopathy.

## *Case #14 - Continued*

### LABORATORY EXAMINATION:

The following were negative or normal:

Chest X-ray
Mycobacterial culture

The following were positive or abnormal:

White blood count 11.7 k/μL (4.4-10.7 k/μL)
Fungal culture 2+ *Blastomyces dermatitides*
Tissue KOH yeast with broad-based budding
Bacterial culture 2+ *Streptococcus agalactiae*

### BIOPSY:

CSP-03-7067: A 4 mm punch biopsy shows pseudoepithelial hyperplasia. There is an infiltrate that contains lymphocytes, plasma cells, and giant cells. Occasional broad-based budding yeast are present.

### DIAGNOSIS:

Cutaneous Blastomycosis

### TREATMENT AND COURSE:

The patient was placed on itraconazole 200 mg daily. Two months into his treatment course his skin lesion resolved.

### DISCUSSION:

Blastomycosis is caused by a dimorphic fungus, *Blastomyces dermatitidis*, that exists in nature in a mycelial phase and converts to a yeast phase at body temperature. The organism may produce epidemics of infection following a point source of infection or sporadic endemic infection. Endemic areas include the southeastern or south central states bordering the Mississippi or Ohio River basins, the Midwestern states and Canadian provinces bordering the great lakes, and a small area in New York and Canada along the St. Lawrence River. While all ages and genders can be affected, adult men are most likely to develop systemic infection, and children are more likely to develop acute pulmonary blastomycosis rather than chronic cutaneous disease. Immunosuppressed hosts are most susceptible to infection and dissemination. Interestingly, HIV is not commonly associated with blastomycosis.

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progressive disease with either pulmonary or extra-pulmonary disease or both. Skin disease is the most common extra-pulmonary site followed by bone, prostate and central nervous system. Secondary cutaneous dissemination is a common occurrence, and may even be the first sign of disease. Cutaneus manifestations may even be seen in the absence of overt pulmonary disease. Primary cutaneus blastomycosis is uncommon and results from direct inoculation of the skin from trauma, such as in the laboratory or from performing autopsies on infected persons.

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**REFERENCES:**

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Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with acquired immunodeficiency syndrome. *Ann Intern Med* 1992;116:847-853.

## *Case #15*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Shirley Chi, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 32-year-old Indian man presented with a two-year history of the gradual appearance of facial swelling and redness, and generalized xerosis of the skin. Over the past several months, he had also noticed ulcerations on his fingertips and on the tips of his toes. The patient stated that he felt a constant tingling in his hands and feet that first began approximately 1 year prior.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

No reported exposure to Hansen's disease.

### SOCIAL HISTORY:

Born and raised in India; has lived in Chicago for the past 2 years.

### PHYSICAL EXAMINATION:

Facial edema and mild scaling is present, along with generalized xerosis of the skin. Several firm, erythematous 5-7 mm nodules are scattered along the trunk and extremities. Crusted ulcerations are present on the fingertips and distal digits of the feet. There are also large hyperpigmented patches on the chest, abdomen and back. Motor and sensory exams are normal, and the patient exhibits normal muscle strength. No nerve enlargement was appreciated.

## *Case #15 - Continued*

### LABORATORY EXAMINATION:

The following tests were normal or negative:

- Complete blood count
- Chemistry profile
- Liver functions tests
- G-6-PD enzyme level

### BIOPSY:

CSP-03-5437: Biopsy of a nodule taken from the right arm shows a diffuse granulomatous dermatitis. There is sparing of the immediate subepidermal zone. Numerous histiocytes are lipidized. Occasional Virchow/lepra cells are seen on the hematoxylin and eosin sections. Fite stain demonstrates numerous organisms within these cells (globi).

### DIAGNOSIS:

Hansen's Disease, Lepromatous Type

### TREATMENT AND COURSE:

The patient was started on the United States Treatment Regimen with dapsone 100 mg, rifampin 600 mg, and clofazimine 50 mg daily. The patient is responding well with resolution of digit ulceration and disappearance of cutaneous lesions since the initiation of treatment 6 months ago.

### DISCUSSION:

Leprosy is an ancient disease that is currently estimated to affect between 10 and 15 million people worldwide, mostly in the endemic regions of Asia (Indian subcontinent), in sub-Saharan Africa, South and Central America, the Pacific Islands, and the Phillipines. Although between 85-90% of American cases are in immigrants, Hansen's disease is endemic in the coastal southeastern United States and in Hawaii. In southern United States, cases may be related to armadillos, a natural host for the infectious agent, *Mycobacterium leprae*. *M. leprae* is an acid-fast bacillus which multiplies very slowly and is an obligate intracellular parasite. It grows best at 27-30 degrees C, hence its predilection for cooler areas of the human body. Mode of transmission is not proven, but intimate contact is needed. The majority of people are not susceptible to leprosy and after typical exposure will not develop the disease.

A diagnosis of leprosy must be considered in any patient with neurologic and cutaneous lesions. As with other infectious diseases, diagnosis is made by identifying the infectious organism in affected tissue, but this is difficult since the organism cannot be cultured. Skin biopsies from skin or nerve lesions, stained with Fite-Faraco stain, are usually done in the developed world, while in developing countries slit smears of the skin are performed to identify organisms. Classification

of the disease is based on clinical, histopathological and immunological parameters and divided into indeterminate (I) tuberculoid (TT), borderline tuberculoid (BT), mid-borderline (BB), borderline lepromatous (BL), and lepromatous (LL) disease. The World Health Organization (WHO) also introduced the classification of "paucibacillary" and multibacillary" disease. Paucibacillary disease includes indeterminate, tuberculoid and borderline tuberculoid leprosy whereas multibacillary disease includes borderline, borderline lepromatous and lepromatous leprosy.

Treatment regimens for Hansen's disease vary. The WHO recommendation for paucibacillary disease is 600 mg of rifampin under supervision once a month for 6 months and 100 mg of dapsone daily for 6 months. Multibacillary patients are treated with rifampin 600 mg and 300 mg clofazimine monthly, supervised, and 100 mg dapsone and 50 mg clofazimine daily, unsupervised, and until recently WHO recommended treatment for 24 months. The 7th Expert Committee noted that the recommendation for 24 months of therapy for multibacillary disease remains valid but indicated that 12 months might be sufficient without increasing risk of rifampin resistance, based on an ongoing trial and several follow-up reports of patients who had defaulted from therapy before completing 24 months of treatment. The WHO thus now recommends only 12 months of treatment for multibacillary disease. In the United States, one recommended treatment for persons with paucibacillary disease is 100 mg of dapsone plus 600 mg of rifampin daily for 12 months. For multibacillary disease, treatment consists of 100 mg of dapsone, 600 mg of rifampin, and 50 mg of clofazimine daily for 24 months.

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## *Case #16*

***PRESENTED BY:*** *Lissette Ortiz-Ferrer, M.D. and Melanie Zahner, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 18-year-old Caucasian man presents with a two-month history of pruritic plaques on his body. Treatment of the lesions with a topical steroid was unsuccessful.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

The patient is currently being detained in the Cook County Jail and has been there since the inception of the lesions.

### PHYSICAL EXAMINATION:

Involving the face, neck, trunk and upper extremities were erythematous, scaly, concentric and annular plaques.

## *Case #16 - Continued*

### LABORATORY EXAMINATION:

The following were abnormal or positive:
KOH exam with numerous hyphae
Fungal culture 2+ *Trichophyton mentagrophytes*

### BIOPSY:

No biopsy was performed.

### DIAGNOSIS:

"Tinea Pseudoimbricata"

### TREATMENT AND COURSE:

The patient was treated with Terbinafine 250 mg daily for 4 weeks. His lesions resolved completely and there has been no recurrence to date.

### DISCUSSION:

Tinea corporis includes all dermatophyte infections of glabrous skin with the exclusion of specific locations such as the palms, soles, and groin. The 3 most common causative organisms include *Trichophyton rubrum, Microsporum canis, and Trichophyton mentagrophytes.* Variations occur in specific geographic regions. The typical presentation is an annular lesion with an active, erythematous, and sometimes vesicular border. Commonly the center of the lesion exhibits clearing.

Tinea imbricata is a type of tinea corporis caused by the organism *T. concentricum* and is limited geographically to areas of the Far East, South Pacific, and South and Central America. Infection is usually acquired in early childhood and may persist for a lifetime. Some genetic susceptibility may predispose one to this persistent infection. The presentation is that of erythematous, scaly plaques with concentric and polycyclic rings in the center of the lesion.

This patient exhibits the clinical presentation that is usually seen with tinea imbricata. However, the organism cultured was *T. mentagrophytes*, one commonly seen in typical tinea corporis. This case represents an unusual presentation of tinea corporis infection with *T. mentagrophytes* masquerading as tinea imbricata.

## *Case #16 - Continued*

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## *Case #17*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Alyssa Nash, M.D.*

### HISTORY OF PRESENT ILLNESS:

A 60-year-old African-American female presented in July 2003 with a one-year history of a lesion on her right breast. The patient denied any burning, pruritus, or nipple discharge. The patient otherwise felt well, except for pain from recent dental surgery.

### PAST MEDICAL HISTORY:

Hypertension
Multiple odontogenic keratocysts

### MEDICATIONS:

Atenolol
Hydroclorothiazide
Potassium supplement

### ALLERGIES:

No known drug allergies

### FAMILY HISTORY:

No family history of skin cancer
No children

### SOCIAL HISTORY:

No history of smoking, alcohol or drug use.

### PHYSICAL EXAMINATION:

On the right areola, at approximately the 4 o'clock position, there was a 4 cm x 3 cm hyperpigmented plaque with a central area of erosion. The rest of the exam was negative for any breast masses, lymphadenopathy, or nipple discharge. There were scattered dark brown pits on her palms and soles. Also, the patient had a high arched palate as well as frontal bossing.

## *Case #17 - Continued*

### LABORATORY EXAMINATION:

A CT scan of the facial bones demonstrated three benign appearing cystic lesions involving the mandible and maxilla. Chest X-ray and pelvic ultrasound were unremarkable.

### BIOPSY:

CSP-03-9739: There are buds of basaloid cells arising from the underside of the epidermis. Several large islands of basaloid cells are also present.

### DIAGNOSIS:

Nevoid Basal Cell Carcinoma Syndrome

### TREATMENT AND COURSE:

The patient was treated with topical 5% imiquimod (Aldara) three times per week. The initial response was poor; therefore the application was increased to daily, and then twice daily as tolerated. The lesion has since responded nicely. The patient continues to follow with Oromaxillofacial surgery for her multiple mandibular cysts.

### DISCUSSION:

Nevoid basal cell carcinoma syndrome, also known as basal cell nevus syndrome and Gorlin-Goltz Syndrome, is an autosomal dominant inherited genodermatosis. However, fifty percent of cases represent new mutations. Also, this genodermatosis exhibits almost complete penetrance but variable expression.

The most frequently observed findings include basal cell carcinomas, odontogenic keratocysts, calcified falx cerebri, relative macrocephaly/frontal bossing, and palmar/plantar pits. These findings can be found in greater than 65% of patients with basal cell nevus syndrome. Basal cell carcinomas develop at an early age, usually beginning at puberty. Other findings in this syndrome include bifid ribs, medulloblastoma, milium, epidermoid cysts, and ovarian and cardiac fibromas. Eye findings include hypertelorism, congenital blindness, cataracts, and strabismus. Boys and girls are equally affected.

The cause of nevoid basal cell carcinoma syndrome has been linked to the Patched (PTCH) gene on chromosome 9q22-31. PTCH is a tumor suppressor gene whose product PTC binds to and inhibits the transmembrane protein smoothened. When activated, smoothened protein promotes cell growth in the hedgehog-signaling pathway. Therefore, PTCH inhibition of smoothened is critical to prevent tumorigenesis. Also, PTCH may participate in organogenesis as mice and insects with defects in PTCH exhibit developmental anomalies.

## *Case #17 - Continued*

Diagnosis of nevoid basal cell carcinoma syndrome is based on family history and or clinical findings. This may prove to be more difficult in African-American patients as they typically develop basal cell carcinomas later in life. It has been postulated that their increased pigment may be protective against the formation of basal cell carcinomas. The basal cell carcinomas may be treated with imiquimod cream, cryotherapy, electrodessication and curettage, simple excision, Moh's surgery, topical or oral retinoids, photodynamic therapy or topical 5-flourouracil. Genetic counseling should be offered to all patients as well as a referral to an ophthalmologist. Patients should also be followed closely by an oral surgeon with yearly panoramic radiographs as odontogenic keratocyts behave aggressively and can invade the jawbone if not removed completely. All patients should avoid sun exposure as well as exposure to x-rays and radiation. Use of broad-spectrum sunscreen and protective clothing is mandatory.

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## *Case #18*

***PRESENTED BY:*** *Sidney Barsky, M.D. and Shirley Chi, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 42-year-old Hispanic man was referred to our clinic from Cardiology for evaluation of multiple cutaneous and structural anomalies that had been present since birth to early childhood. The patient was accompanied by his sister who functions as his caretaker and states that he is mentally challenged.

### PAST MEDICAL HISTORY:

Congenital cardiomyopathy
Surgical correction of undescended testicle

### MEDICATIONS:

Verapamil
Furosemide
Potassium Chloride

### ALLERGIES:

None

### FAMILY HISTORY:

None

### SOCIAL HISTORY:

Mentally challenged, lives at home with sister/caretaker

### PHYSICAL EXAMINATION:

Short stature and abnormal facial appearance are noted, including ptosis of the eyelids, hypertelorism, thick lips, low-set ears and hairline, webbed neck, and the presence of thick curly scalp hair Valgus deformity of bilateral outstretched forearms is also present, as is mild pectus

excavatum. There are numerous lentigines on the torso and extremities. Severe edema is apparent on both legs and ankles, with hyperkeratotic, scaly skin.

### LABORATORY EXAMINATION:

The following were normal or negative:
Complete blood count
Chemistry panel

### BIOPSY:

No biopsy was performed.

### DIAGNOSIS:

Noonan Syndrome

### TREATMENT AND COURSE:

The patient was referred to the Cook County Hospital Division of Genetics for further counseling. He is being treated for his chronic lymphedema with compression stockings and emollients. He continues to be treated by Cardiology with verapamil and furosemide for his cardiac defect.

### DISCUSSION:

Noonan syndrome (MIM 163950) is an autosomal dominant disorder that is characterized by dysmorphic facial features, short stature, and cardiac defects. It was first completely described by Jacqueline Noonan in 1968, a pediatric cardiologist in Lexington, Kentucky, who reported 6 males and 3 female patients with pulmonary stenosis and a distinct clinical appearance. The phenotype also includes webbing of the neck, chest deformities giving a square appearance of the thorax, cryptorchidism, mild mental retardation, and a bleeding diathesis. Ptosis of the eyelids, down-slanting palpebral fissures, low-set posteriorly rotated ears, and skeletal malformations are noted in some cases. The characteristic cardiac anomalies are valvular pulmonic stenosis and left ventricular hypertrophy. Affected patients may also exhibit cutaneous signs including café-au-lait macules and xerosis. Lentigines, which are a cardinal feature of LEOPARD syndrome, are usually not seen in Noonan syndrome despite the recently discovered genetic association between the two syndromes.

Noonan syndrome is relatively common, with an estimated incidence of 1:1000-2500 live births, and an equal male to female ratio. Fifty percent of cases are sporadic, as seen in this patient. It is diagnosed clinically, but the genetic defect has been mapped to the long-arm of chromosome 12.

## *Case #18 - Continued*

More specifically, a study by a multinational group of investigators in 2001 identified missense mutations in protein-tyrosine-phosphatase, nonreceptor-type II (PTPN11) as a candidate gene for Noonan syndrome because it maps to the critical region on chromosome 12 and furthermore because its specific gene protein product, SHP-2, is essential in several intracellular signal transduction pathways that control diverse developmental processes.

As growth retardation is a consistent feature, studies have been done to attempt to increase the growth rate of these patients. Although children with Noonan syndrome are not usually growth hormone (GH) deficient, recombinant human GH has been shown to improve growth rate in affected patients in a similar fashion to that seen in patients with Turner's syndrome.

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## *Case #19*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Gina Dillig, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 3-year-old girl presented with disseminated papules for 18 months. She had been diagnosed with molluscum contagiosum and was using imiquimod 5% cream (Aldara) every evening with some improvement according to her parents. They deny redness or other signs of irritation. No fevers, irritability, eye redness, or photophobia were noted and development has been normal for her age.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

No known drug allergies

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

There are generalized 2-3mm yellow to brown dome shaped papules that are concentrated along the waist line, and bilaterally on the flanks and under the axillae. The lesions are non-tender and a few papules are atrophic and beginning to flatten. No café-au-lait macules were observed.

## *Case #19 - Continued*

### LABORATORY EXAMINATION:

The following laboratory studies were negative or normal
- Cholesterol
- HDL
- Triglycerides

The following laboratory studies were positive or abnormal
- LDL- 141 (0-130)

### BIOPSY:

CSP-04-2418 (Right thigh): The papillary dermis contains a cellular infiltrate consisting of histiocytes, lymphocytes and occasional touton giant cells.

### DIAGNOSIS:

Juvenile Xanthogranuloma (JXG)

### TREATMENT AND COURSE:

After a thorough workup, the child was found to have no visceral or ocular involvement and no signs of leukemia. The patient is doing well and we will continue to follow her closely.

### DISCUSSION:

Juvenile xanthogranuloma (JXG) is a benign, self-healing disorder characterized by solitary or multiple yellow to red to brown nodules on the skin and, occasionally, in other organs. It is essentially a disease of infancy or early childhood, although adults may also be affected. Histologically, JXG represents an accumulation of histiocytes lacking Birbeck granules (non-Langerhans cells), which can be differentiated from Langerhans cells by specific staining techniques. Affected persons have normal lipid metabolism. JXG is therefore classified as a normolipemic non-Langerhans cell histiocytosis. The patient's general health is not impaired and, in the absence of central nervous system and eye involvement, the prognosis is excellent.

Patients will present with the typical nodules on the skin in either a micronodular or macronodular appearance. Our patient has the micronodular variant characterized by numerous shiny, dome shaped 2-5mm discrete papules irregularly scattered on the upper body. Although the most common location for JXG is the head and neck, lesions can also been identified on the upper body, upper extremities, and the lower extremities. The lesions start out red to brown in appearance, however, they rapidly attain a yellowish hue. Both variants may have rare mucous membrane involvement.

## *Case #19 - Continued*

The micronodular cutaneous variant has important associations, including café-au-lait macules, neurofibromatosis type 1 (NF1), juvenile chronic myeloid leukemia (JCML), rare nervous system involvement, and eye involvement. A complete skin exam checking for café-au-lait macules is vital in establishing a diagnosis of NF1 as the coexistence of JXG and NF1 gives a 20 to 32 fold increased risk of developing JCML. A strong male predominance was found in patients with the triple association.

The eye is the most common site of extracutaneous involvement. Chang *et al* reported a survey of dermatologists and ophthalmologists who cited a 0.3% incidence of ocular complications in patients with JXG. A literature search in that same article showed a 0.4% incidence. Typical eye findings are vascular lesions involving the iris and ciliary body. These lesions can hemorrhage into the anterior chamber (hyphema) causing secondary glaucoma and blindness. Conjunctival or bulbar tumors may be present, however the posterior eye, uveal tract and retina are spared. Children at risk of ocular complications were 2 years and younger, had multiple skin lesions, and had newly diagnosed JXG. Most ophthalmologists recommended screening for all patients with cutaneous JXG although those diagnosed with ocular complications typically had an acute change in the eye, most commonly hyphema. Chang *et al* found no cases where asymptomatic screening resulted in a diagnosis of ocular JXG.

The macronodular variant is more commonly associated with visceral disease. Pulmonary lesions are most frequently reported followed by liver lesions causing hepatomegaly and lytic bone changes in the skull and long bones. JXG lesions have also been rarely reported in the pericardium, kidneys, spleen, ovaries and testes.

The pathogenesis is unknown however, it is often suggested that the histiocytes are producing a granulomatous reaction to a traumatic or infectious stimulus. On histopathology there is a nodular, poorly demarcated infiltrate of histiocytes involving the dermis and sometimes the subcutis. The cells are polygonal or spindle-shaped and plump with indistinct cytoplasmic borders. Mitoses are rare. Early lesions are fairly monomorphous, with inconspicuous foam cells, mature lesions contain foamy histiocytes and varying numbers of Touton giant cells. There are also scattered lymphocytes and neutrophils, rare plasma cells and sometimes eosinophils. Lesions of longer duration will show interstitial fibrosis and proliferating fibroblasts.

Immunohistochemistry is helpful to separate JXG from other Langerhans-cell and non-Langerhans-cell histiocytoses and fibrotic lesions. The histiocytes of JXG are negative for S-100 protein and CD1a, while positive for CD68, HAM 56, HHF35, vimentin and factor XIIIa. HAM 56 antibody appears to be the most reliable in identifying proliferating macrophages.

The nodular skin lesions of JXG tend to flatten with time. Within 3 to 6 years both the skin and visceral lesions usually regress spontaneously leaving hyperpigmentation, mild atrophy, or anetoderma. Treatment is only recommended for those rare cases when lesions impair organ function especially the eye. Topical steroids, radiotherapy and surgery are accepted treatment modalities however for the majority of cases no treatment is necessary.

## *Case #19 - Continued*

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## *Case #20*

***PRESENTED BY:*** *Sidney Barsky, M.D., Darryl M. Bronson and Alyssa Nash, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 27-year-old Hispanic man presented to our clinic for evaluation of a slowly growing lesion on his left leg. The lesion had been present since early infancy and had become warty in appearance. He reported several episodes of bleeding from this lesion following minor injury.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

A 6 cm x 5 cm brown, non-compressible, crusted and verrucous plaque is located on the left posterior lower calf. A 2 cm x 2 cm pink and brown verrucous plaque is located distal to the larger lesion. No mass or pulsation was detected by palpation. Both legs were of equal length and diameter.

***Case #20 - Continued***

**LABORATORY EXAMINATION:**

The following were negative or normal:
Complete blood count
Complete metabolic panel

**BIOPSY:**

CSP-03-4061: There is marked hyperkeratosis with papillomatosis. Dilated blood vessels are present within the papillomatous projections. Small well-formed vessels are present throughout the dermis and extend to the subcutaneous fat.

**DIAGNOSIS:**

Verrucous Hemangioma

**TREATMENT AND COURSE:**

An MRI of the left lower leg was scheduled, however the patient was lost to follow-up.

**DISCUSSION:**

Verrucous hemangioma is a rare, congenital, localized, vascular malformation that has been reported in the literature with a variety of names including hemangioma unilateralis neviforme, keratotic hemangioma, nevus angiokeratoticus, nevus keratoangiomatosus, and papulous angiokeratoma. In 1967, Imperial and Helwig introduced the term "verrucous hemangioma" and distinguished it from angiokeratoma and its variants. During a retrospective study, the authors examined 1175 individuals with clinical diagnosis of angiokeratoma and in 21 of these cases a diagnosis of verrucous hemangioma was made based on clinicopathological features.

Usually appearing at birth or in early childhood and involving the lower extremities, the lesions tend to be unilateral or grouped, discrete to confluent, bluish to red, well demarcated, soft and compressible. They range from 4 mm to as large as 5-7cm in diameter. The presence of small satellite lesions is typical. After a variable number of years, they become hyperkeratotic hemangiomatous papules, that may have a linear or serpiginous distribution, and their color varies from brown to characteristic bluish to black. Finally, probably as a result of trauma and secondary infection, the lesions become hyperkeratotic.

Histologically, verrucous hemangioma is a variant of capillary or cavernous hemangioma that is associated with secondary, reactive epidermal changes of hyperkeratosis, acanthosis, and papillomatosis. The superficial dermal component may resemble an angiokeratoma; however, a

deep angiomatous proliferation extends into the reticular dermis and subcutaneous tissue. Purulent and hemorrhagic crusts may be present.

Several authors believe that verrucous hemangioma is a clinical variant of angiokeratoma circumscriptum and both terms are used synonymously in the literature. However, the two differ both clinically and histologically. Verrucous hemangioma is usually present at birth while angiokeratoma circumscriptum appears in infancy and in preadolescence. Verrucous hemangioma generally shows itself as a single large lesion surrounded by smaller satellite lesions, while the angiokeratoma circumscriptum is usually composed of many small dotted lesions that may coalesce into a plaque. Finally, the histology of angiokeratoma circumscriptum resembles verrucous hemangioma, however the proliferation of blood vessels does not extend into the deep dermis.

It is important to distinguish between the two forms of angiomas as the prognosis and treatment differ. Verrucous hemangioma requires large, deep excision and is associated with a high frequency of local recurrence (33%). In contrast angiokeratoma circumscriptum responds to various treatment modalities (cryotherapy, electrocautery, and laser). Several authors have proposed early excision of verrucous hemangiomas while they are still small to minimize risk of scarring and reoccurrence. Finally, laser therapy as an adjunct to surgical excision may improve outcomes.

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## *Case #21*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Lalitha Mamilla, M.D.*

### HISTORY OF PRESENT ILLNESS:

A 45-year-old African-American woman presented with one-year history of a slowly enlarging asymptomatic mass on the right lateral lower abdomen. There was no history of preceding trauma.

### PAST MEDICAL HISTORY:

Insulin dependent diabetes mellitus
Depression

### MEDICATIONS:

Insulin
Glucophage
Venlafaxine
Trazadone

### ALLERGIES:

Penicillin

### FAMILY HISTORY:

Non-contributory

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

There was a 9 x 5 cm indurated subcutaneous mass with a hyperpigmented surface on the right lateral aspect of the lower abdomen. There were no palpable inguinal lymph nodes.

## *Case #21 - Continued*

### LABORATORY EXAMINATION:

The following were negative or normal:
Complete blood count
General chemistry

### BIOPSY:

CSP-03-13288: The dermis is filled with small aggregates of cells containing eosinophilic granular cytoplasm and small round nuclei. The epidermis is hyperplastic in the areas above the sheets of granular cells.

### DIAGNOSIS:

Granular Cell Tumor

### TREATMENT AND COURSE:

The patient underwent complete surgical excision of the tumor. Histopathology did not reveal any atypical mitoses, necrosis or pleomorphism. Further physical examination revealed two lesions on the right groin area which on biopsy were determined to be epidermal nevi. The patient has been doing well without any clinical recurrence.

### DISCUSSION:

Granular cell tumor was first described in the 1926 by Arbrikossoff and named granular cell myoblastoma. Granular cell tumor is a rare tumor that occurs mainly in adults (age 30 to 50 years) with a 1:3 male to female ratio. Every organ has been involved with skin and the mucous membranes being the most common sites. Tumors occur with equal frequency on the tongue and the skin, and together account for the approximately 80% of cases. The most common areas of the skin to be involved include the head and neck region, breast and proximal extremities. Common internal sites include the esophagus, larynx, tracheobronchial tree, entire gastrointestinal tract, skeletal muscle and bladder. Multiple lesions occur in 10-25% of cases, especially in African-American patients. Granular cell tumor usually presents as an asymptomatic or occasionally tender or pruritic, skin colored or brownish red, firm dermal or subcutaneous nodule, ranging in size from 0.5-3cm in diameter. Occasionally the surface can show ulceration or verrucous changes.

The histogenesis of granular cell tumor has been a source of controversy since its recognition. Early suggestions that granular cell tumor may have a myoblastic origin have been discounted and use of the term granular cell myoblastoma is discouraged. Most investigators currently favor a Schwann cell derivation based on immunohistochemical and electron microscopic findings.

Although granular cells express S100 protein and CD57 as many Schwann cell tumors, some differences exist between schwannomas and granular cell tumors. Recent immunohistochemical studies suggest a neural crest derived peripheral nerve related cell differentiation.

Histologically, broad fascicles of tumor cells infiltrate the dermis among the collagen bundles and are arranged in nests and sheets. Pseudeoepitheliomatous hyperplasia often overlies the tumor cells. The cells have abundant, granular faintly eosinophilic cytoplasm with round dark nuclei. Characteristic large cytoplasmic granules are called pustule-ovoid bodies. Rarely, a plexiform growth pattern has been described. A variety of epithelial and mesynchymal neoplasms can show granular cell changes including basal cell carcinoma, leiomyoma, angiosarcoma, schwannoma, leiomyosarcoma, and dermatofibroma.

The treatment is complete surgical excision with adequate margins. If incompletely excised, this tumor has a high local recurrence rate. In difficult cases, Moh's micrographic surgery with S-100 staining may be beneficial. Malignant granular cell tumors are extremely rare. The diagnosis of malignancy is established only when metastatic disease that has the same histological characteristics as the primary lesion is identified. Clues to possible malignant behavior are tumor size greater than 4 cm, and the presence of certain histological characteristics that include necrosis, vesicular nuclei with nucleoli, wide cellular sheets, any tendency to spindle cell structure, and any mitotic activity. Nevertheless, long term follow-up is advised, especially in patients with large granular cell tumor, since metastases from histologically benign lesions have been reported.

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## *Case #22*

***PRESENTED BY:*** *Lissette Ortiz-Ferrer, M.D. and Gina Dillig, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 5-year-old Middle Eastern girl presented in September 2003 with extremely dry and thick skin, which she has had since birth. Her mother remembers that she was "as white as a sheet and looked like a fish" when she was born. During the first few weeks of life her skin became red and very dry. She was diagnosed with eczema elsewhere, for which she has been on multiple therapies including tacrolimus (Protopic), triamcinolone ointment, and Lac-Hydrin. None of these have helped and cause pain and burning when applied. At the time of presentation she was using hydrophilic ointment, which provides mild relief. The patient's mother states that her skin tends to get a foul smell when infected but denies ever seeing blisters.

### PAST MEDICAL HISTORY:

Non-contributory

### MEDICATIONS:

Hydrophilic petrolatum

### ALLERGIES:

None

### FAMILY HISTORY:

The patient's parents are first cousins. She has 4 healthy brothers and sisters. No other family members have similar skin conditions.

### SOCIAL HISTORY:

Non-contributory

### PHYSICAL EXAMINATION:

Corrugated thickening of patient's skin over the joints, especially the wrists, elbows, and knees

was observed. Generalized xerosis with thick plates of scale were also seen. Her underlying skin was red. Hyperlinearity and waxy thickening were found on the palms and soles. Her face was spared but slight scaling was found in her scalp. A distinct odor to her skin was present. No blisters or erosions were observed.

## LABORATORY EXAMINATION:

The following laboratory studies were normal or negative:

Skeletal series
General chemistry
Aspartate aminotransferase
Alanine aminotransferase
Cholesterol
Trigylcerides
HDL
LDL
Complete blood count
Urinalysis

The following laboratory studies were abnormal or positive:

Albumin 5.4 (3.8-5.2)
Alkaline phosphatase 250 (50-120)

## BIOPSY:

CSP-03-12860 (Left thigh): There is marked hyperkeratosis on hair bearing skin. A stratum lucidum is present.

## DIAGNOSIS:

Congenital Ichthyosiform Erythroderma

## TREATMENT AND COURSE:

The patient was started on urea 10% in the morning and tazarotene 0.1% gel in the evening to the thick areas, hydrophilic petrolatum as needed and phisohex. Minimal improvement was seen after 1 month.

In October 2003, after parental consent and normal baseline tests, acitretin 10 mg daily was started. Sebulex shampoo was added while urea and tazarotene were discontinued. Within 2 weeks her skin desquamated to reveal diffuse erythema. After 2 months the patient started developing headaches. Although she denied nausea, vomiting or visual changes, the acitretin was discontinued.

The patient was then put back on the urea and tazarotene regimen. She has developed no skin infections to date and continues to do well. In late November 2003, the patient was enrolled in the National Registry for Ichthyosis and Related Disorders and awaits confirmatory genetic testing.

**DISCUSSION:**

Ichthyoses belong to a group of diseases characterized by abnormal cornification of the epidermis resulting in generalized scaling. Ichthyosis can present at birth or develop later in life. The disease can be limited to the skin or involve other organ systems. There is extreme heterogeneity in the presentation of individuals and a diagnosis can be challenging especially since the environment can alter the degree of dryness and scaling. Clinically differentiating ichthyoses forces the clinician to analyze the age of onset, quality of scale, presence or absence of erythroderma, ectropion, eclabium, other organ involvement and parental consanguinity. Classification may become easier as genetic testing becomes available to our patients.

Ichthyotic skin has abnormal quantity and quality of scale, compromised barrier function, and possible alterations in the rate of epidermal proliferation. Mutations in the genes that encode the epidermal differentiation keratins 1 and 10 cause the autosomal dominant condition, epidermolytic hyperkeratosis (EHK). Transglutaminase-1 catalyzes the cross-linking of proteins involucrin, loricrin and small proline rich proteins as well as the attachment of ceramides during the formation of corneocytes, participating in both the protein and lipid components of the stratum corneum. It is mutated in lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). Lipoxoygenases, which are crucial to the formation of the epidermal lipid barrier, have also been mutated in CIE.

CIE is an autosomal recessive ichthyosis presenting at birth with a collodion membrane, which evolves into generalized erythema and persistent fine, white scaling with little or no change in condition throughout life. Little or no ectropion, eclabium or alopecia is present and development is normal. The palm and soles are usually severely affected with fissuring keratoderma that contrasts to the fine white scale on the rest of the body. LI has large, platelike scale and erythema only in childhood. Ectropion and eclabium are more common in LI. Many patients do not fit into either of these categories and may have features of both CIE and LI, therefore a better term may be congenital autosomal recessive ichthyosis.

Diagnosis involves histopathology and genetics. Histopathology for CIE is nondiagnostic compared to EHK, which shows epidermolytic hyperkeratosis. Compared to LI there is focal or extensive parakeratosis, hypergranulosis and the epidermal acanthosis is more pronounced with a markedly increased cell turn over rate in CIE. Ultrastructurally findings of CIE overlap those of LI and other hyperproliferative disorders. Genetic testing should show mutations in transgultaminase-1 (TGM-1) or the lipoxengenases (ALOXE3 or ALOX12B).

Medical management begins at birth with proper care of the collodion, emollients and humidified air. Topical management should take into consideration the severely impaired desquamation and barrier function of the skin. Keratolytics are limited to urea, ∝-hydroxy acids (lactic and glycolic) and propylene glycol since salicylic acid has the potential for systemic absorption. Tacrolimus 0.1% should also be used with caution. Topical vitamin D and tazarotene have also

been effective, but emollients are the mainstay of symptomatic therapy.

Disease severity often necessitates systemic therapy with oral retinoids. Acitretin can be very effective in alleviating hyperkeratosis and scaling but, is less beneficial for the erythroderma.

Treatment with acitretin should be initiated and maintained at a low dose, 0.5 mg/kg per day where toxic irreversible side effects are rarely seen. Prior to initiation of therapy it is prudent to check the following laboratory values: complete blood count, liver function tests, fasting lipid panel, serum electrolytes, urinalysis and selective skeletal survey (all four limbs including hands and feet and lateral spine). During therapy check LFT's, lipid panel and urinalysis within the first month of treatment, then every 3 months for the first year and then every 6 months.

Erythrodermic patients have a special need for sufficient fluid, caloric, iron and protein intake to balance substantial loss through the skin. Some patients with ichthyosis are hypohidrotic and parents should be aware of the signs of heat intolerance, such as flushing and lethargy in hot weather and exercise. Ichthyotic patients are also more susceptible to fungal and bacterial infections, which should be treated promptly. Occasionally fungal infections may present with only increased pruritus and diagnosis requires a high index of suspicion. Treatment is lifelong and should involve a partnership with the patient and their parents.

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## *Case #23*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Jessie Cheung, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 50-year-old African-American male presented with a three-month history of a gradually worsening sore, red, peeling rash on his hands and feet. He denied any blistering or oral sores. Review of systems was negative. He denied any new sexual contacts. He was applying Vaseline to the rash with no noticable improvement.

He has a history of gastric cancer with metastasis to the liver and kidney, and he was started on capecitabine (Xeloda) in August 2002 with a good response. He is on a cycle of capecitabine daily for 14 days, and then 7 days off.

### PAST MEDICAL HISTORY:

Sarcoidosis, stage 4; stable, last steroid use was 7 years ago.

### MEDICATIONS:

Capecitabine 2 grams twice daily x 14 days, then 7 days off.
Fluticasone inhaler as needed
Salmeterol inhaler as needed
Albuterol inhaler as needed
Ranitidine as needed
Aluminum hydroxide/magnesium hydroxide/simethicone as needed

### ALLERGIES:

None

### FAMILY HISTORY:

None

### SOCIAL HISTORY:

He denies the current use of alcohol or tobacco products.

## *Case #23 - Continued*

### PHYSICAL EXAMINATION:

There was erythema and superficial desquamation over the bilateral palms and soles, especially over the fingertips. There was no appreciable anesthesia. The patient's range of motion of the distal extremities was limited by pain.

### LABORATORY EXAMINATION:

The following were negative or normal:
General chemistry
Complete blood count

### BIOPSY:

No biopsy was performed.

### DIAGNOSIS:

Chemotherapy-Induced Acral Erythema

### TREATMENT AND COURSE:

Capecitabine was discontinued after consulting with the patient's oncologist. The patient was started on triamcinolone 0.25% ointment twice daily and pyridoxine 200 mg daily with gradual resolution of the symptoms and re-epitheliazation of the skin at follow-up 2 weeks later. He was started back on a lower dose of capecitabine (1.5 gm) after a rest period of 2 weeks with no further complications reported.

### DISCUSSION:

Various synonyms may be found in the literature for the specific mucocutaneous reactions of chemotherapy-induced acral erythema (AE), including hand-foot syndrome, palmar-plantar erythrodysesthesia syndrome, palmar-plantar erythema, and Burgdorf's syndrome. AE occurs most commonly with cytarabine, doxorubicin, and fluorouracil, but has been reported in response to treatment with many other agents alone or in combination. The incidence ranges from 6-42%, and there appears to be no correlation between AE and the type of neoplastic disease, sex, or age of the patient. AE seems to be dose-dependent and both peak drug levels and total cumulative dose may determine its occurrence. The cause of AE is currently unknown. A hypothesis is that the chemotherapeutic agent inflicts a direct toxic effect on the skin by accumulating in the acral regions and extravasting into the tissue. Immunohistochemical studies suggest that cell-to-cell

interaction between NK cells and keratinocytes in the eccrine apparatus may induce AE. A retrospective study comparing the incidences of AE in patients with metastatic colorectal cancer who took capecitabine with or without celecoxib suggests that AE is an inflammatory phenomenon mediated by the overexpression of COX-2.

The severity and time of onset (usually 24 hours to 10 months) of the AE are variable. Clinically, AE first presents with a prodrome of dysesthesia of the palms or soles, which progresses within 2 to 4 days to burning pain, tenderness, and edema, associated with well-demarcated erythemsatous plaques. Rarely, a morbilliform eruption or faint erythema may also be noted on the scalp, neck, chest, and extremities. If chemotherapy is continued, the erythema and edema can spread to involve the entire surface of the palms and soles, and areas of central pallor may occur between the joints or on the fingertips and toes. Cessation, lengthening of drug administration interval, or dose reduction of chemotherapy usually allows for amelioration of the symptoms over a period of 2 to 4 weeks. Areas of pallor will blister and desquamate with extensive but superficial exfoliation. Re-epithelialization should occur within approximately 4 weeks of discontinuing therapy. A bullous variant of AE, specifically described in association with cytarabine and methotrexate, progresses to frank bullae formation with sloughing and full-thickness epidermal necrosis before re-epithelialization proceeds. There is one report of palmoplantar keratoderma occurring as a result of chronic AE, when the chemotherapy (Tegafur) was continued despite the onset of AE.

The histopathology of AE is nonspecific. Findings include mild spongiosis of the epidermis, vacuolar degeneration of the basal layer, scattered necrotic and dyskeratotic keratinocytes, and mild to moderate epidermal atypia with cellular enlargement, nuclear pleomorphism, and multinucleation. Dermal changes include dilated blood vessels, papillary edema, and a sparse superficial perivascular lymphohistiocytic infiltrate.

Supportive treatments such as topical wound care, elevation, and cold compresses may help to relieve the pain. Variable outcomes have been reported with the use of systemic corticosteroids, pyridoxine, blood flow reduction, and topical 99% dimethyl-sulfoxide (DMSO). Prevention of AE may be obtained with the application of ice water to the acral regions during chemotherapy infusion to decrease blood flow to the hands and feet, thereby preventing drug accumulation at these sites.

It is important to avoid the misdiagnosis of AE as a cutaneous sign of graft-versus-host disease. These two disease entities are not mutually exclusive but may occur simultaneously. Biopsy specimens from both conditions are initially quite similar; therefore, serial biopsies done at 3 to 5 day intervals may be necessary to distinguish between them if the diagnosis cannot be made on clinical grounds.

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## *Case #24*

***PRESENTED BY:*** *Jerry Feldman, M.D. and Anne Snider, M.D.*

### HISTORY OF PRESENT ILLNESS:

This 22-year-old African-American woman presents with asymptomatic, dark bumps along the edges of her hand and feet since childhood. She had no history of excessive sun exposure, hyperhidrosis, chronic trauma, or arsenic ingestion.

### PAST MEDICAL HISTORY:

None

### MEDICATIONS:

None

### ALLERGIES:

None

### FAMILY HISTORY:

No members with similar skin lesions.

### SOCIAL HISTORY:

Student

### PHYSICAL EXAMINATION:

There are hyperkeratotic, firm, hyperpigmented, dome-shaped, papules along the lines of transgredience of the palms and soles.

***Case #24 - Continued***

**LABORATORY EXAMINATION:**

Non-contributory

**BIOPSY:**

CSP-03-4686: A 3 mm punch biopsy of a papule from the instep of the left foot shows marked hyperkeratosis with a central dell. An elastic tissue stain shows normal elastic fibers.

**DIAGNOSIS:**

Focal Acral Hyperkeratosis

**TREATMENT AND COURSE:**

The patient tried fluocinonide ointment 0.05%, ammonium lactate 12% lotion, 10% urea cream, and tretinoin cream 0.01% all of which were unsuccessful in leading to any resolution of her skin lesions. Due to the fact that these skin lesions are asymptomatic, the patient did not want any systemic treatment.

**DISCUSSION:**

Focal acral hyperkeratosis (FAH), which was described by Dowd et al in 1983, is considered to be a variant of acrokeratoelastoidosis of Costa (AKE). Clinically, they are identical and differ only histologically as FAH lacks the elastorrhexis seen in AKE. Marginal papular acrokeratoderma (MPA) is a term recently proposed to encompass FAH, AKE, and other related disorders with keratotic papules along the borders of the hands and feet as many feel that these are probably genetic variants of one genodermatosis characterized by papules, with a variable genetic expression of dermal elastic fibers.

FAH is characterized by small, firm, waxy, papules which appear on the margins of the hands and feet during childhood. These lesions are usually asymptomatic but may be associated with hyperhidrosis. New lesions may slowly develop over the years.

Most patients with FAH have been females of African descent although the mode of inheritance is unknown. The differential diagnosis includes acrokeratoelastoidosis of Costa, degenerative collagenous plaques of the hands, keratoelastoidosis marginalis of the hands, verruca plana, acrokeratosis verruciformis of Hopf, colloid millium, xanthoma, and punctate palmoplantar keratoderma.

Multiple therapies have been unsuccessfully attemped for FAH including cyrotherapy, salicylic acid, topical retinoids, and prednisone. Good results have been seen with etretinate and acetretin

***Case #24 - Continued***

but recurrences are common upon discontinuation.

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