Case Presented by Virginia C. Fiedler, MD, Michelle Bain, MD and Alexander L. Berlin, MD

History of Present Illness:
This 9-year-old African American girl presented with hair shedding and patchy hair loss since infancy. Additionally, her hair has been brittle. Her scalp is comfortable, without pruritus. The patient's mother has also noticed deviations of multiple finger joints since the age of 3 along with more recent similar changes in toe joints. These changes are not associated with pain or joint swelling. The patient denies decreased body sweating, but she does note increased sweating in the areas of scalp hair loss.

Past Medical History:
Febrile seizures as a child
Multiple finger and toe joint deviations starting at 3 years of age
History of ankle deformities treated with braces for 2 years

Medications:
None

Allergies:
No known drug allergies

Family History:
No history of autoimmune or other skin disorders; no joint abnormalities

Social History:
Patient is a 4th grade student and is doing well in school

Review of Systems:
Denies visual problems or arthralgias
Diet is adequate for protein

Physical Examination:
The patient had patchy alopecia that was most pronounced in the ophiasis distribution and also involved the vertex. The affected areas had miniaturized hair follicles. Hair pull test was positive for 5-6 hairs in catagen and telogen phases. Ears were not low-set. There was an increased distance between the nose and the upper lip, and the philtrum was difficult to appreciate. The patient had retained deciduous teeth, as well as hypodontia and partial anodontia. A 3-cm hyperpigmented patch was present on the upper chest. Hands and feet exhibited both varus and valgus deviations in multiple phalanges. Brachydactyly of the right 4th toe was also noted.

Diagnostic Procedures and Tests:
Hair mount: Normal.
Skull radiograph: Size of the cranial vault is borderline small. There is mild mid-face recession of facial bones. There is delayed eruption of some teeth.
Hand radiographs: There is delay in bone age of approximately 2 years; narrowing of the diploic space of the fourth and fifth metacarpals; cone-shaped epiphyseal development involving middle phalanges and, to a lesser degree, proximal phalanges.

Hip radiographs**:** Normal.

Diagnosis:
Tricho-rhino-phalangeal syndrome type 1

Treatment:
The patient was started on topical minoxidil 2% to the entire scalp daily. The patient was also referred to the genetics, rheumatology, and dental clinics.

Discussion:
Tricho-rhino-phalangeal syndrome (TRPS) belongs to a subset of ectodermal dysplasias that presents with multiple congenital anomalies and skeletal abnormalities. This subset includes the tricho-dento-osseous syndrome, Ellis-van Creveld syndrome, along with other syndromes.

TRPS is an uncommon disorder, although exact prevalence is unknown. Most commonly, it is transmitted in an autosomal dominant pattern with high penetrance; however, autosomal recessive inheritance and spontaneous mutations resulting in the TRPS phenotype have also been described.

TRPS is characterized by several distinct facial and skeletal abnormalities. Clinical findings of the head and neck may include the characteristic long flat philtrum, thin upper lip, bulbous tip of the nose ("pear-shaped nose"), and protruding ears. Hair is sparse, brittle, and slow-growing.

Hand radiographs typically reveal cone-shaped epiphyses. Clinically, hands and feet may also demonstrate brachydactyly and joint deviations due to premature closure of growth plates. These findings often may not be detectable before 2 years of age or older. Various hip malformations are common and include coxa plana, coxa magna, coxa vara, and slipped capital femoral epiphyses (Legg-Calve-Perthes disease) which may lead to osteoarthritis. Skeletal age lags behind the chronological age until puberty, and patients typically have mild to moderate growth retardation.

Three subtypes of this syndrome have been described to date. In addition to the above findings, which characterize TRPS type 1, type 2 patients typically exhibit multiple cartilaginous exostoses, loose redundant skin (sometimes misdiagnosed as Ehlers-Danlos syndrome), and mental retardation. Type 3 patients have more severe brachydactyly and growth retardation, but lack cartilaginous exostoses and demonstrate normal intelligence.

Mutations of chromosomal band 8q24.12 are responsible for all 3 subtypes of the disorder. Depending on its nature, deletion of the *TRPS1* gene, which encodes for a zinc-finger transcription factor, results in the clinical phenotype of either type 1 or type 3 TRPS. TRPS type 2 is a contiguous gene syndrome caused by a deletion in both the *TRPS1* gene and an adjacent *EXT1* gene. The *EXT1* gene encodes for exostosin-1, a protein that participates in polymerization of glucuronic acid and synthesis of heparan sulfate. Of interest, the *EXT1* gene product has been found to be highly expressed during brain development in mice, and this may explain mental retardation seen in patients with TRPS type 2.

Management of a patient with TRPS includes referrals for genetic counseling, dentistry, and rheumatology. As with most other ectodermal dysplasias, hair growth is only slightly improved with topical minoxidil, and topical steroids are of no value. Patients with more severe facial malformations should be referred to plastic surgery for surgical correction. While these patients may suffer from recurrent respiratory infections, their life expectancy appears to be normal.

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Case Presented by Lawrence Chan, MD, Iris Aronson, MD and Roopal Vashi Kundu, MD

History of Present Illness:
This is an 87-year-old Caucasian man with a 3-year history of ocular mucous membrane pemphigoid diagnosed by his ophthalmologist. The patient presented in October, 2001, with a 3-month history of tender blisters in his mouth, mostly involving his gingiva and palate. He had initially responded to therapy with dapsone 50 mg po bid.

Past Medical History:
No significant past medical history

Medications:
Dapsone 50 mg po bid
Multivitamin 1 tab po qd
Aspirin 81 mg po qd

Allergies:
No known drug allergies

Family History:
No history of autoimmune or other skin disorders

Review of Systems:
Occasional difficulty chewing food, ocular irritation, and photosensitivity.
Denies epistaxis, hoarseness, cough, dysphagia, weight loss, dysuria, or rectal bleeding.

Physical Examination:
The patient had conjunctival erythema with notable trichiasis and symblepharon formation in both eyes from the lower conjunctivae to the sclera. Erythema with shallow erosions and few intact blisters were noted on the attached gingivae and palate.

Laboratory Data:
The following laboratory studies were abnormal or positive:

Creatinine	2.4 mg/dl	[nl: 0.5-1.5]

The following laboratory studies were normal or negative:
- Complete blood count
- Serum electrolytes (except creatinine)
- Liver function tests

Histopathology:
01/00 Conjunctiva, Left eye (S00-736): There is a subepithelial blister with dermal infiltrate of lymphocytes, plasma cells, and histiocytes.

Immunopathology:
01/00 Conjunctiva, L eye (DIF): linear band of IgG, IgA, and C3 at the dermoepidermal junction
11/01 Gingiva, R mandible (DIF): focal IgA deposits at the attached dermoepidermal junction

Diagnosis:
Mucous membrane pemphigoid

Treatment and Course:
A biopsy of the oral mucosa in December, 2001, showed detached epithelium with focal IgA deposits at sites of focally attached epithelium, indicating extension of disease to the mouth. In January, 2002, doxycycline 100 mg po bid and niacinamide 500 mg po bid were added to the dapsone. Progression of his disease continued with the development of new ocular and oral lesions. In March of 2002, doxycycline and niacinamide were discontinued, dapsone was increased to a total of 125 mg po qd, and prednisone 40 mg po qd was added to his regimen. The patient noted some improvement in ocular disease.

In April, 2002, the patient was started on adjunctive immunosuppressive therapy with mycophenolate mofetil 500 mg po qd. This medication was gradually increased to a dose of 1500 mg po bid while dapsone and prednisone were slowly tapered. All oral symptoms resolved, but ocular inflammation persisted. The patient has required intermittent pulses of prednisone for flares. Supplementation with calcium and vitamin D was also initiated.

Treatment options including azathioprine, IVIG, and cyclophosphamide have been discussed extensively with the patient, but he has refused to initiate any of these therapies. The patient is currently maintained on mycophenolate mofetil 1000 mg po bid and prednisone 15 mg po qd. A recent indirect immunofluorescence was negative.

Discussion:
Mucous membrane pemphigoid (MMP) is a chronic autoimmune inflammatory subepidermal blistering disorder primarily affecting any or all mucous membranes, with or without clinically observable scarring. The diagnosis of MMP is based on erythematous patches, blisters, erosions, and/or ulcerations of one or more mucous membranes, and linear depositions of IgG, IgA, or C3 along the epithelial basement membrane zone detected by direct immunofluorescence.

Oral and ocular mucosae are most commonly involved, followed by nasal, nasopharyngeal, anogenital, laryngeal, and esophageal mucosae. Oral lesions, characterized by erythematous patches, blisters, erosions, and ulcerations, are located most commonly on the attached gingival and palatal mucosae. Ocular manifestations include conjunctival inflammation and erosions, shortening of fornices, ankyloblepharon, symblepharon, entropion, trichiasis, corneal neovascularization, and scarring. The skin is involved in up to 25% of patients with disease of the upper torso and head being most common.

There are multiple target antigens in MMP. Ten different epithelial basement membrane zone components have been identified and include bullous pemphigoid antigens 1 and 2 (BPAg1 and BPAg2), laminin-5, laminin-6, type VII collagen, beta-4 integrin subunit, and antigens with unknown identities: 45-kD protein, uncein, a 168-kDa epithelial protein, and a 120-kDa epithelial protein. An increased incidence of cancer has been identified in a subset of patients with autoantibodies targeting laminin-5 (epiligrin). Studies have also determined the association of HLA-DQB1*0301 allele with MMP. HLA-DQ molecules function immunologically by presenting antigen to T cells. The role of HLA-DQ molecules in the pathogenesis of MMP, however, is not yet known.

The medical management for MMP is divided into “high-risk” and “low-risk” patient strategies. High-risk patients include those with ocular, nasopharyngeal, laryngeal, and genital mucosae involvement. For high-risk patients, initial treatment for mild disease consists of dapsone (50-

200mg/day). If not tolerated or inadequate, prednisone (0.5-0.75mg/kg/day) and cyclophosphamide (0.5-1mg/kg/day) may be initiated. For severe or rapidly progressive disease, a combination of prednisone (1-1.5mg/kg/day) and cyclophosphamide (1-2mg/kg/day) is the preferred treatment. Alternatively, azathioprine (1-2mg/kg/day) can be substituted for cyclophosphamide.

Low-risk patients have oral mucosa or combined oral mucosa and skin involvement. Treatment options for these patients include the following: topical corticosteroids, tetracycline (1-2gram/day), and nicotinamide (2-3gram/day). For refractory disease, dapsone (50-200mg/day) or prednisone (20-40mg/day) with or without low-dose azathioprine (50mg/day) may be used. Case reports of other successful treatment options include topical mitomycin, IVIG, mycophenolate mofetil, sulfapyridine, and minocycline.

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Case #3

Case Presented by Iris K Aronson, MD
and Agnes Ju Chang, MD

History of Present Illness:
This 61-year-old Caucasian female was diagnosed with dermatomyositis by a muscle biopsy in July, 1998, after presenting to her primary care physician with erythema and scaling of the face, chest, and hands along with proximal muscle weakness and dysphagia. Her treatment consisted of prednisone and hydroxychloroquine, and later with calcium, vitamin D, and alendronate for steroid-related osteoporosis.

In 1999, she started to develop calcified nodules that extruded white milky material on the face, chest, shoulders, and back. She also noted progressive tightening of the face and neck which limited her range of motion. She continues to have persistent pruritic erythema and scaling and intermittent muscle weakness. The patient was referred to UIC in October of 2003, for treatment of the progressive cutaneous calcinosis.

Past Medical History:
Dermatomyositis
Hypertension
Hypothyroidism s/p thyroidectomy

Medications:
Levothyroxine 150 mcg qd
Prednisone 5 mg qd
Ezetimibe 10 mg qd
Lisinopril 10 mg qd
Alendronate 70 mg qweek
Sunblock SPF 30

Allergies:
Codeine

Family History:
Maternal aunt with rheumatoid arthritis

Social History:
Slow weight training program 3-4 times/week

Review of Systems:
Intermittent weakness of neck, shoulders, arms. Denies fever, chills, night sweats, weight loss, fatigue, vaginal bleeding, dysphagia, odynophagia, chest pain, shortness of breath, or cough.

Physical Examination:
The patient was cachectic in general appearance. She had a lipoatrophic appearance to both cheeks which also had multiple firm erythematous and violaceous plaques and nodules, some of which exuded white milky material. There were multiple firm, indurated red plaques along with diffuse groups of nodules on the neck, chest, upper back, shoulders, and arms. Erythema over

interphalangeal and metacarpal joints along with periungal telangiectasias were present. Both lower extremities had erythematous, scaly plaques.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Phosphorus	4.7 mg/dl	[nl: 2.4-4.5]
Triglycerides (8/03)	1210 mg/dl	[nl: <200]
Triglycerides (10/03)	363 mg/dl	[nl: <200]

The following laboratory studies were normal or negative:

Calcium	PTH
Calcitonin	Vitamin D, 1-25 dihydroxy
CA125	C3
Liver function tests	Alkaline phosphatase
Creatine kinase	Cholesterol
Erythrocyte sedimentation rate	LDL

Diagnostic Procedures and Tests:

'99 CXR showed scar tissue
'99 CT chest w/ contrast and biopsy of scar tissue was within normal limits
’99 Colonoscopy was within normal limits
’99 Bone density scan was consistent with osteoporosis
Pap smears are up to date and are within normal limits
Mammograms are up to date and are within normal limits

Histopathology:

7/98 Deltoid muscle biopsy: The histological picture of foci of regenerating “moth-eaten” myocytes along with the relative lack of necrosis and inflammation strongly suggests the diagnosis of dermatomyositis.

10/03 Right forearm (SD-03-0010099): The epidermis shows hyperkeratosis with focal scale crust and mild acanthosis. In the dermis, there are multiple foci of calcifications expanding into the lower reticular dermis, focally surrounded by a mixture of giant cells, lymphocytes, and neutrophils. Solar elastosis is severe. Calcium is also deposited within the elastotic collagen and perforated throughout the epidermis. There are no changes in the blood vessels.

Diagnosis:

Dermatomyositis with calcinosis cutis

Treatment and Course:

In July, 1998, the patient was started on prednisone 60 mg po qd and was maintained on this dose for over a year. She has been tapered down to the current dose of 5 mg po qd since January, 2002. Hydroxycholoroquine was also started in July, 1998, but was discontinued in 1999 due to edema, mental dullness, and general malaise on high dose prednisone and hydroxychloroquine. Topically, she is using fluocinonide 0.05% cream bid with some improvement. She has tried tacrolimus 0.1% ointment which caused an increase in pruritus. The patient is also going to a wound clinic once a week for local wound care of the lesions on her cheeks. Pending labs and tests include an ANA, CH50, aldolase, and a pelvic ultrasound.

Discussion:

Dermatomyositis is an inflammatory myopathy with characteristic cutaneous findings including violaceous eyelid erythema (heliotrope rash), pink/violaceous papules over the knuckles (Gottron's papules), periungal telangiectasias, photoexacerbated eruption, and calcinosis. Calcinosis of the skin is reported to be more common in juvenile dermatomyositis (44-70%) and less so in the adult form (20%). Nodules and plaques of calcium deposits ranging in size from a few millimeters to few centimeters may occur in the skin, subcutaneous tissue, muscle, or tendons. Although onset of calcinosis is most often 1 – 3 years after illness onset, it has been reported to occur from the time of illness onset to as long as 20 years later. The calcinosis is thought to occur through a dystrophic mechanism by which calcium deposits in damaged or inflammed connective tissue, usually in the setting of normal serum calcium and phosphorus.

Four subtypes of dystrophic calcification have been recognized in the literature. According to one large series on juvenile dermatomyositis, 33% of patients developed superficial plaques and nodules in the skin or subcutaneous tissue; 20% developed larger nodular deposits called tumoral calcinosis; 16% of patients had calcinosis along fascial planes of muscles and tendons; 10% had extensive hard calcium deposition over all body surface areas (exoskeleton). A mixture of calcinosis subtypes was present in 22%.

The development of calcinosis has been associated with delay in diagnosis and initiation of appropriate and aggressive therapy for dermatomyositis in children. Patients with a chronic course, as well as those with a longer duration of active disease, may be more likely to develop calcinosis. The subtype of calcinosis may also be related to disease severity. The exoskeleton subtype is associated with chronicity of disease, and fascial plane deposition is associated with severity.

The natural history of calcinosis is variable, and spontaneous regression may occur by re-absorption or extrusion of the material. Improvement in calcinosis may be more likely in patients with inactive disease, increased physical activity, superficial plaques or nodules, and aggressive treatment. On the other hand, the progression of the calcinosis may be related to inadequately treated underlying myositis.

Current approaches to the treatment of calcinosis associated with dermatomyositis are based largely on anecdotal case reports. Recent reports suggest that early intensive anti-inflammatory therapy for dermatomyositis may be effective in preventing calcinosis. Regression of calcinosis, as well as slowing of progression, was observed in case reports following treatment with hydroxychloroquine, intravenous immunoglobulin, cyclosporine, and infliximab. Intralesional triamcinolone acetate and colchicine have been used with varying success.

Other treatments are targeted towards disrupting the calcium phosphate homeostasis. Diltiazem, a calcium channel-blocker, has been studied most extensively with positive results. In patients with juvenile dermatomyositis or systemic sclerosis treated with high doses, a reduction in lesion size as well as total resolution of calcinosis was observed. Aluminum hydroxide and probenecid, aimed to disrupt phosphate metabolism, have also shown variable success. Other potential therapies include bisphosphonates and warfarin. Surgical removal may offer symptomatic treatment, but recurrence of the lesions may occur.

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Case #4

Case Presented by Iris Aronson, MD
and Todd A. Johnson, MD

History of Present Illness:
This 55-year-old Polish female presented with morphea diagnosed by biopsy in March, 1994. She has used mid and high-potency topical steroids, hydroxychloroquine, and azulfadine with only mild symptomatic improvement in lesional skin. The patient was found to have a positive Lyme titer confirmed by Western blot in August, 1994, although she had no recollection of a prior tick bite. She has taken several anti-borrelial antibiotics, including a 3-week course of amoxicillin and an incomplete course of doxycyline. The patient was evaluated by infectious disease in June, 1995, and was determined to have no active Lyme disease. She has never received the Lymerix vaccine.

Past Medical History:
Carpal tunnel syndrome
Chronic sinusitis
Right shoulder tendonitis
Hypercholesterolemia
Uterine fibroids with episodes of bleeding

Medications:
Rofecoxib 12.5 mg po QD
Simvastatin 20 mg po QD
Cetirizine 10 mg po QD

Allergies/ Adverse Reactions:
Amoxicillin→ GI upset
Doxycycline→ anxiety, headaches, tinnitus

Family History:
No history of autoimmune or other skin disorders

Social History:
Moved from Poland to the United States in 1974 with two trips to Poland from 1974 to 1994
Vacationed in the Wisconsin Dells in the two summers prior to her positive Lyme titer

Review of Systems:
Occasional joint pains in the right shoulder and wrists
Denies fevers, skin "tightness," Raynaud's symptoms, dysphagia, or dyspnea

Physical Examination:
There is an indurated and atrophic plaque with mild hyperpigmentation at the periphery on the upper chest. There are three large, depressed, indurated, hyperpigmented plaques with hypopigmented centers on the back and one in the left axilla. The patient has no periungal telangiectasias, sclerodactyly, or mask-like facies.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Lyme enzyme immunoassay total antibody (08/94)	2.61	[nl: 0.00-1.00]
Lyme IgG Western blot (8/94)	Positive	[nl:negative]
Lyme enzyme immunoassay total antibody (8/03)	2.37	[nl:0.00-1.00]
Antinuclear antibody titer (11/97)	1:160	[nl:none detected]
Antinuclear antibody titer (8/03)	1:320	[nl:none detected]

The following laboratory studies were normal or negative:

White blood cell count	Erythrocyte sedimentation rate
Hemoglobin and hematocrit	Metabolic panel
Anti-Smith antibody	Liver function tests
Anti-centromere antibody	Rapid plasma reagin
Anti-RNP	Angiotensin converting enzyme

Diagnostic Procedures and Tests:

05/03 EKG: normal sinus rhythm, left atrial abnormality, left axis deviation

Histopathology:

03/94 Back (S94-12771): The epidermis is unremarkable. There is marked sclerosis and thickening of collagen bundles in the deep dermis expanding into the subcutaneous fat. A sparse lymphoplasmacytic infiltrate is seen at the periphery of the subcutaneous fat and in the deep dermis.

Diagnosis:

Morphea

Treatment and Course:

The patient has declined use of systemic agents at this time. She does not use her topical medications because she does not think that they help. Light therapy has been discussed.

Discussion

Lyme disease is the most common tick-borne disease in North America. It is a complex multisystem disease caused by the spirochete *Borrelia burgdorferi*(Bb). Molecular and serological studies have identified four genogroups within the species *Borrelia burgdorferi*: Bb sensu stricto found in North America and Europe, Bb garinii and Bb afzelii found in Europe and Asia, and Bb japonica recently isolated in Japan.

The etiology of morphea is still unkown. Since the first published observation by Miescher in 1949 that penicillin therapy can lead to stabilization and even complete remission of morphea, there has been a search for an infectious etiologic agent. Aberer's letter to *Nature* in 1985 delineated the clinical and histopathological similarities between morphea and acrodermatitis chronica atrophicans. His detection of antibodies to *B. burgdorferi* in 5 out of 10 patients with morphea suggested that this microbe may be the culprit.

Since Aberer's letter, there has been much investigation into *B. burgdorferi's* role in localized morphea with largely conflicting and inconclusive results. One trend evident in the literature is that if Borrelia does indeed play a role in the etiopathogenesis of morphea, there is a strong geographic relation between infection and the development of the disease. Most studies that have suggested a positive correlation between Borrelia and morphea have been conducted exclusively in Europe. More likely is that certain subspecies of *B. burgdorferii* may play a role in the

development of morphea. The causative agent of acrodermatitis chronica atrophicans, another cutaneous disease characterized by diffuse dermal fibrosis, is exclusively caused by *Borrelia burgdorferii* afzelii, which is common in Europe but rare in the United States.

Our patient moved to the United States in 1974 from Krakow, Poland. Between 1974 and her first positive Lyme titer in 1994, she has made two trips to Poland. She has no recollection of a tick bite in Poland, but she has frequently spent time outdoors picking blueberries. One possibility is that she became infected in Poland with Bb afzelii. However, for the two consecutive summers before her positive Lyme titer, she vacationed in the Wisconsin Dells. The Dells are located in a county designated as high risk for the transmission for Lyme disease by the Centers for Disease Control.

Our patient's IgG western blot banding pattern was p88+, p54/58+, p41+, p39+, p30/32+, p20/21+. According to the Dressler criteria used in the U.S. for the Western blot diagnosis of borreliosis, these results should be interpreted as positive. However, this Western blot pattern is also positive according to the Guiterrez European modified criteria for the diagnosis of borreliosis, which tests for Bb sensu stricto, Bb afzelii, and Bb garinii. Therefore, we cannot infer as to whether this patient's serology is more suggestive of Lyme disease acquired in the United States versus that acquired in Europe. Furthermore, reactivity to the subunits of the p17 antigen, which are subspecies specific, was not performed because subspecies other than Bb sensu stricto are rare in the United States.

Regarding treatment, this patient has had one incomplete course of doxycycline and two 3-week courses of amoxicillin. The Centers for Disease Control recommends a 3-4 week course of doxycycline or erythromycin for pen-allergic patients for early disease, and retreatment may be necessary. Late disease requires a 4-6 week course of IV penicillin or ceftriaxone. It is not clear whether or not this patient received a full dose of the amoxicillin. If one were to consider morphea a *Borrelia*-associated phenomenon, one possibility for this patient would be retreatment with a 4-6 week course of erythromycin.

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Case #5

Case Presented by Sophie Worobec, MD, Amy Paller, MD, and Amit Garg, MD

History of Present Illness:
This 24-year-old man was born with a colloidion membrane and subsequently developed large plate-like scales involving the trunk, arms, and legs. The scale was associated with intermittent mild pruritus. The patient also experienced decreased sweating over scaly skin surfaces and overheating with minimal physical activity. Over-the-counter moisturizers provided some relief from itching but had no effect on scaling. As a teenager, the patient was treated with isotretinoin 60 mg a day for almost one year; however, he did not note any significant improvement in scaling.

Past Medical History:
No significant past medical history

Medications:
Tazarotene gel 0.1% qd 1-2 times per week

Allergies:
No known drug allergies

Family History:
Noncontributory

Physical Examination:
The patient had patches of white scale over the forehead, nose, and cheeks. There were darker, plate-like sheets of scale that were adherent in the center and free at the edges involving most of the trunk, the arms including flexures, and the legs.

Diagnosis:
Lamellar ichthyosis

Treatment and Course:
The patient was started on urea cream 20% for the neck and 40% for the body to be used twice a day. With this regimen alone, the patient noted some improvement in scaling. Neither propylene glycol 50% solution applied to the legs nor a one month course of low-dose acitretin provided any further improvement in scaling.

The patient was then started on tazarotene gel 0.1% qd to the affected areas. Within 2 weeks, he noted the most significant improvement of all the previous treatments. Within one month, his scaling was minimal, and he no longer experienced decreased sweating and overheating with physical activity. Since then, he has been maintained on tazarotene gel 0.1% qd 1-2 times per week. The patient noted a return in the scaling of his skin after having run out of his medication for two weeks. After re-initiaing therapy with tazarotene gel, the patient again noted rapid clearing of the scale. Tazarotene gel 0.1% has been well tolerated by this patient.

Discussion:

Lamellar ichthyosis is apparent at birth when newborns usually present with a transparent covering that desquamates over 10-14 days. Over time, ichthyosis manifests as large plate-like scales that are attached centrally and have free edges. The scale is most prominent over the lower extremities. If present, erythroderma tends to be minimal. The palms and soles are variably involved and may range from hyperlinearity to severe keratoderma. Other associated problems may include scalp alopecia, decreased sweating with heat intolerance, and ectropion.

Lamellar ichthyosis is transmitted autosomal recessively. The mutation lies in the *tranglutaminase 1* gene locus on chromnosome 14. Transglutaminases catalyze calcium dependent cross linking of cellular proteins including involucrin and loricrin during the formation of the cornified envelope.

Tazarotene is an acetylenic retinoid with selective binding to RAR-gamma and RAR-beta receptors. Ninety percent of retinoid receptors located in the skin are of the gamma subtype. It is thought that tazarotene works through downregulating markers of differentiation including transglutaminase, involucrin, and keratins 6, 10, and 16. It is also thought that tazarotene may work through inhibiting keratinocyte proliferation by downregulating epidermal growth factor receptor and ornithine decarboxylase. Furthermore, tazarotene has been shown to induce novel genes, *tazarotene induced genes 1-3*, which are thought to account for its antiproliferative effect in psoriatic lesions. The expression of these genes has not been investigated in ichthyoses.

Tazarotene is non-mutagenic, non-teratogenic, and non-photosensitizing or phototoxic. It has low systemic absorption and is rapidly metabolized and eliminated. There does not appear to be any significant accumulation with long-term application. The main adverse effect is dose-related local irritation. As such, tazarotene may be a safe and effective therapeutic option in the treatment of congenital ichthyoses.

References:

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Case #6

Case Presented by Iris Aronson, MD
and Marianne Schachter Rosen, MD

History of Present Illness:
This 42-year-old Caucasian female presented in September, 2003, with a two-year history of intermittent red, tender nodules on her lower legs. Some of these nodules become abscesses that are incised and drained by her primary care physician. A biopsy performed at an outside hospital in December, 2002, was consistent with erythema nodosum, and the patient was started on naproxen without improvement. She has also been treated with intralesional triamcinolone and hydrocortisone 1% cream.

Past Medical History:
Seasonal respiratory allergies
Hypothyroidism
Urticaria

Medications:
Cetirizine 10mg po QD
Doxycycline 100 mg QD
Synthroid
Albuterol MDI 2 puffs prn

Allergies:
No known drug allergies

Family History:
Mother has a history of myasthenia gravis and protein S deficiency
Father has a history of hypothyroidism, hypertension, myocardial infarction at age 40, metastatic lung cancer, deceased at age 66
Paternal grandfather with a history of pulmonary tuberculosis 35 years ago and "black lung" from working in a coal mine
No history of liver disease

Social History:
No tobacco; rare alcohol use

Review of Systems:
Had low grade fever for one year when nodules first started, otherwise noncontributory

Physical Examination:
The patient had few erythematous, tender nodules on bilateral lower legs, one with scarring on the left posterior leg.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Alpha-1-antitrypsin	89mg/dl	[nl: 100-200]
Phenotype	M1S	[nl: MM]
Microsomal antibody	>70.0 IU/ml	[nl: 0-2.0]
Thyroglobulin antibody	>90 IU/ml	[nl: 0-2.0]
Protein C function	200%	[nl: 60-140]

The following laboratory studies were normal or negative:

White blood cell count	Histoplasma antibody
Liver function tests	Coccidiomycosis antibody
ANA	Protein S
Rheumatoid factor	G6PD
CH50	CMV RNA
Hepatitis B	Hepatitis C
Anticardiolipin antibodies	

EBV antibodies consistent with a convalescent or past infection

Diagnostic Procedures and Tests:

10/03 Chest X-ray: No abnormalities of the chest are seen.

Histopathology:

12/02 Left lower leg (S02-16981): The epidermis shows irregular acanthosis. In the mid-reticular dermis, there is ectopic fat with a mixed cell infiltrate consisting of lymphocytes, neutrophils and histiocytes. In the lower dermis, there is a focal collection of giant cells. The subcutaneous fat shows peripheral and focal panniculitis with thickening of the septae and a sparse infiltrate of lymphocytes and eosinophils.

Immunopathology:

12/02 Left lower leg (DIF): negative for antibodies against IgG, IgA, IgM, C3 and fibrinogen

Diagnosis:

Alpha-1-antitrypsin deficiency panniculitis

Treatment and Course:

The patient was recently started on doxycycline 100mg po bid.

Discussion:

Alpha 1-antitrypsin is a proteinase inhibitor that irreversibly inactivates neutrophil elastase. It also acts as an inhibitor of trypsin, chymotrypsin, plasmin, and thrombin. The release of elastase and collagenase from neutrophil granules is uninhibited with this deficiency, and the result is destruction of collagen and elastic fibers. Heterozygous deficiency occurs in 1 out of 50 people, while homozygous deficiency occurs in 1 out of 2500 people of European descent. The most common manifestations are emphysema and liver disease. A small percentage of patients will develop a panniculitis. Most patients that develop panniculitis have a homozygous deficiency (zz phenotype), but the heterozygous deficiency can produce a panniculitis as well.

The panniculitis resulting from alpha 1-antitrypsin deficiency affects males and females equally. Lesions are usually precipitated by minor trauma, and present as 1-5 cm painful, subcutaneous nodules on the extremities or trunk. Lesions may spontaneously drain, and multiple draining

sinus tracts can occur with coalescing of lesions into large plaques. This is a chronic and relapsing condition; new lesions appear as old ones resolve.

Histologically, early lesions show neutrophils in the reticular dermis and subcutaneous septae. There can be necrotic foci next to normal fat lobules. Later lesions show a mixed pattern of septal and lobular inflammation with many neutrophils and destruction of the fat and dissolution of the septae. Elastic tissue stains may show decreased elastic tissue in the affected areas. Late lesions have a macrophage and lymphocytic infiltrate with foam cells and fibrosis.

Diagnosis is established by decreased levels of serum alpha 1-antitrypsin. Relatives of affected patients should be screened. Patients should be instructed to avoid skin trauma, and they should eliminate smoking and alcohol as these can exacerbate pulmonary and hepatic disease. Dapsone and doxycycline have both been shown to be effective. Treatment with replacement of the deficient enzyme has also been successful in patients with severe homozygous deficiency. Systemic steroids may exacerbate the panniculitis. The panniculitis resolves with normalization of enzyme levels after liver transplantation.

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4. O'Riordan K et al. [alpha]1-antitrypsin deficiency-associated panniculitis: resolution with intravenous [alpha]1-antitrypsin administration and liver transplantation. *Transplantation*. 63(3): 480-482, 1997.
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Case Presented by Lawrence Chan, MD
and H. Tina Kim, MD

History of Present Illness:
This 83-year-old Hispanic male presented to his primary care physician with a violaceous, asymptomatic 'rash' on his face and tongue since April, 2003. He was on warfarin therapy for a deep venous thrombosis and pulmonary embolism and was found to have a high INR of 8. A head CT during initial work-up showed no acute findings. His warfarin was held one week prior to his presentation to dermatology. He denied any bleeding from the facial or oral lesions. He also denied any preceding trauma.

Past Medical History:
Coronary artery disease
Diabetes mellitus
Hypertension
Chronic obstructive pulmonary disease
Chronic renal insufficiency
Gout
Degenerative cervical disease and an old compression deformity at C6
History of deep venous thrombosis and pulmonary embolism 3/03

Medications:
Furosemide 40 mg QD
Enalapril 10 mg QD
Colchicine 0.6 mg QD
Atenolol 25 mg QD
Glyburide 2.5 mg QAM
Nitroglycerin patch 0.4 mg QD
Aspirin held
Warfarin held

Allergies:
Penicillin

Family History:
Noncontributory

Social History:
Denies alcohol or tobacco use

Review of Systems:
Hospital admission in 7/03 for chest pain during which he ruled out for a myocardial infarct. Denies any constitutional symptoms, headaches, dysuria, bone pain, paresthesias, dysphagia, gastrointestinal symptoms, or weight loss.

Physical Examination:
The patient had purpuric macules, patches, and thin plaques on the face, predominantly in a periorbital distribution, as well as on the cheeks, lips, chin, and forehead. His tongue showed

macroglossia with waxy purpuric papules and plaques especially on the dorsolateral aspect. He had no lesions on the trunk or extremities; he had no lymphadenopathy.

Laboratory Data:

The following laboratory studies were abnormal or positive:

SPEP: monoclonal peak in the beta region; hypoproteinemia, hypoalbuminemia, hypogammaglobulinemia.

UPEP: monoclonal peak in the beta region; beta monoclonal peak = 9 mg/dL; two monoclonal peaks in the gamma region.

Prothrombin time (7/03)	98 sec	[nl 9.8-12]
INR (7/03)	8	[therapeutic 2-3]
Creatinine	1.4 mg/dl	[nl: 0.8-1.3]
Albumin	3.3 g/dl	[nl: 3.4-5]
Urinalysis	+protein 100 mg/dl	[nl: negative]

The following laboratory studies were normal or negative:

Complete blood count	Calcium
Creatine kinase	Phosphorus
Troponin	Liver enzyme profile
Electrolytes (except creatinine)	PTT
Stool for occult blood	

Diagnostic Procedures and Tests:

4/03 Head CT: moderate atrophy; moderate old L parietal and small R lacunar cerebrovascular accidents, no acute findings

7/03 CXR: normal size and contour of heart; no hilar or mediastinal abnormalities

Histopathology:

8/03 R cheek (WS03-2215-1A): The epidermis is flattened with effaced rete ridges. There is eosinophilic globular material diffusely in the dermal stroma, including the papillary dermis as well as perivascular and periadnexal spaces. There are dilated capillaries with red blood cell extravasation. There is a perivascular infiltrate of lymphocytes, neutrophils, eosinophils and an increased number of stellate fibroblasts. The eosinophilic globular material stains with Congo red and polarizes with apple-green birefringence.

R abdomen (WS03-2215-2A): The epidermis is essentially normal. There is globular material focally deposited in the papillary dermis. There is a very sparse perivascular lymphocytic infiltrate in the dermis. The capillary walls are thickened, and extravasated red blood cells are seen in the reticular dermis. Congo red stain is positive focally in the papillary dermis and in certain collagen fibers throughout the dermis. Under polaroscopy, a diffuse apple-green birefringence, as well as birefringence around the adipocytes, is present.

Diagnosis:

Systemic amyloidosis

Treatment and Course:

The patient was restarted on warfarin by his primary care physician. Subsequently, he developed bright red blood per rectum and was admitted to the hospital for a lower gastrointestinal bleed with a high INR of 9.21. His hemoglobin remained within normal limits. His warfarin was

discontinued since he had completed 6 months of anticoagulation therapy following diagnosis of his deep venous thrombosis.

He has also seen hematology/oncology for the monoclonal gammopathy. Their plan is to perform a bone marrow biopsy and a full imaging work-up, including an echocardiogram, ultrasound of the liver, spleen, and kidneys, along with a bone survey for possible multiple myeloma.

Discussion:

Amyloidosis refers to the deposition of an eosinophilic, fibrillar, amorphous substance in extracellular tissue. Amyloid consists of a nonfibrillar protein called amyloid P and a beta-pleated sheet configuration of unrelated proteins that share the characteristic of apple-green birefringence of Congo-red stained preparations under polarized light. Both systemic and localized forms of amyloidosis may occur.

There are various types of systemic amyloidoses that are divided by etiology and associated fibril proteins. The amyloid that occurs in primary and myeloma-associated disease is composed of immunoglobulin light chain (protein AL). In secondary systemic amyloidosis and some heredofamilial forms, the fibrils are composed of protein AA, which is derived form serum amyloid A protein (SAA). SAA is an apolipoprotein that acts as an acute-phase reactant. In senile amyloidosis, the fibrils are composed of transthyretin (prealbumin).

The following lists the various types of systemic amyloidosis with the associated fibrils:
1) primary (AL), associated with an occult plasma cell dyscrasia,
2) myeloma-associated (AL),
3) secondary or reactive (AA), associated with chronic inflammatory systemic diseases,
4) heredofamilial, including
    a) familial amyloid polyneuropathy (transthyretin variant, apolipoprotein A1 or gelsolin),
    b) Ostertag (apolipoprotein A1 or lysozyme or fibrinogen alpha-chain)
    c) familial Mediterranean fever (AA)
    d) Muckle-Wells syndrome (AA)
    e) cardiomyopathic (transthyretin variant), and
5) senile systemic amyloidosis (transthyretin).

Our patient has a primary or myeloma-associated amyloidosis, both of which have AL fibrils from monoclonal immunoglobulin light chains. Light chains, usually of the lambda type, are found in the urine and serum of both groups of patients. These light chains are produced by a clonal plasma cell dyscrasia, that is either overt in the myeloma form or occult in the primary form. The differentiation between the two ends of the spectrum is not clear cut. Features that tend to favor myeloma include the following: a bone marrow biopsy with >15% plasma cells, large amount of monoclonal protein in the serum and urine, radiographic surveys with lytic bone lesions, hypercalcemia, and anemia.

Primary and myeloma-associated amyloidosis most commonly occur in elderly patients with a mean age of onset of 65 years and a male predominance. The classic presentation includes carpal tunnel syndrome (25%), macroglossia (10%), hepatomegaly (50%), edema (30%), and specific mucocutaneous lesions. Nonspecific constitutional symptoms include fatigue, weight loss, paresthesia, hoarseness, and dyspnea. Less common presentations include sicca syndrome, the "shoulder pad sign" (amyloid deposits in soft tissues of the shoulders), a rheumatoid-arthritis-like deposition in small joints, claudication in the legs or jaw, and lymphadenopathy (10%). AL amyloid deposition may occur in any organ other than the brain. Systemic manifestations also include autonomic neuropathy, hematologic complications, gastrointestinal bleeding, and cardiac

involvement. In fact, congestive heart failure and arrhythmias account for death in 40% of patients with AL systemic amyloidosis.

Cutaneous or mucous membrane lesions are seen in up to 40% of cases of systemic amyloid. The most common lesion is purpura (15-17%) due to amyloid infiltration in blood vessel walls. Petechial or ecchymotic lesions are usually after minor trauma (pinch purpura) in the flexural areas such as the eyelids, neck, axillae, umbilicus, and anogential regions. The most characteristic skin findings are waxy, smooth papules, nodules and plaques with a hemorrhagic appearance occurring in flexural areas, the central face, and oral cavity. Macroglossia occurs in 10% of cases and may result in dysphagia. Diffuse amyloid infiltration may produce a leonine facies and a sclerodermatous appearance. Less common cutaneous findings include bullae, dystrophic nails, alopecia, cordlike thickening of blood vessels, and acquired cutis laxa.

Serum protein electrophoresis shows a spike in less than 1/2 of primary and 2/3 of myeloma patients. Serum immunoelectrophoresis reveals a monoclonal protein in 2/3 of patients with AL amyloidosis (45% heavy chain; 20% light chains, or Bence Jones proteinemia). Total serum IgG is reduced in 1/2 of primary and 2/3 of myeloma-associated cases.

On histopathology, amyloid deposits appear as fissured amorphous material in the dermis, blood vessel walls, subcutaneous fat ("amyloid rings"), and surrounding adnexal structures. There is usually little to no associated inflammatory cell infiltrate. A fine-needle aspiration of the abdominal fat pad is up to 95% sensitive in detecting amyloid. A rectal biopsy has 75-80% sensitivity. A biopsy of lesional skin has up to 100% sensitivity, whereas biopsy of clinically normal skin has up to 55% sensitivity. Direct biopsies of the involved organ (tongue, heart, gastrointestinal tract, muscle, kidney nerves, ligaments) may be required to confirm the diagnosis.

The Congo red cotton dyes lead to apple-green birefringence under polaroscopy. Other special stains for amyloid include methyl and cresyl violet dyes, PAS, fluorescence with thiazole dyes. AL-type amyloid, in contrast to AA, retains polarization characteristics with Congo red after exposure to potassium permanganate. Immunohistochemical stains with anti-SAP or with antisera to the various types of fibril protein may be used.

The treatment of primary and myeloma-associated amyloidosis involves cytotoxic chemotherapy including melphalan, vincristine, cyclophosphamide, prednisone, colchicine, penicillamine, and azathioprine. The trial of chemotherapy may be given with or without autologous bone marrow transplantation. The prognosis of AL systemic amyloidosis is poor with median survival of 12-20 months for primary amyloidosis and 5 months for myeloma-associated amyloidosis.

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Case #8

Case Presented by Iris Aronson, MD, Shelley Halper, MD and Steven Mandrea, MD

History of Present Illness:
This 40-year-old Caucasian woman initially presented in September, 2002, with a 15-month history of painful papules on her hands and arms that crusted and remitted over one week. A biopsy in June, 2002, showed a neutrophilic dermatosis. Nasal cultures grew MRSA on two occasions. She was treated with trimethoprim/sulfamethoxazole, rifampin, and topical mupirocin to the nares with only partial improvement of arm and hand lesions.

Past Medical History:
Diabetes mellitus
Tension headaches
Venous insufficiency
Asthma
Allergic rhinitis

Medications:
Paroxetine
Furosemide
Potassium chloride
Loratadine/ pseudoephedrine
Naproxen
Metformin
Diazepam
Fluticasone/ salmeterol inhaled 1 dose inhaled prn

Allergies:
No known drug allergies

Family History:
Father has a history of actinic keratoses.
Maternal aunt has Hodgkin's disease.

Social History:
Smokes one pack of cigarettes a day; rare alcohol, denies illicit drugs

Review of Systems:
Chronic knee pain and occasional sores on tongue around her menstrual period
Denies fever, chills, nausea, vomiting, dysuria, chest pain, or shortness of breath.

Physical Examination:
The patient had numerous papules and pustules in varying stages of evolution on the dorsal hands and a few lesions on the palms. Some were firm and flesh-colored with a pseudovesicular appearance, while others were violaceous; some had dark crusts and others a surrounding ring of hypopigmentation. Her arms had few scattered erythematous crusted papules and healing erosions.

Laboratory Data:

The following laboratory studies were abnormal or positive:

White blood cell count	11.8 x 10^3/uL	[nl: 4.8-10.8]
Erythrocyte sedimentation rate x 2	30, 36 mm/h	[nl: 0-20]
Nasal culture (7/01)	MRSA	[nl: no growth]
Nasal and wound culture (9/02)	MSSA	[nl: no growth]
Glucose	132 mg/dL	[nl: 70-110]
Platelets	470 x 10^3/uL	[nl: 150-400]
Triglycerides	391 mg/dL	[nl: 45-170]

The following laboratory studies were normal or negative:

Hemoglobin	Platelets x 4
White blood cell count x 4	Liver function tests
Antinuclear antibody	Basic metabolic panel
Thyroid stimulating hormone	Rheumatoid factor
HIV screen	Erythrocyte sedimentation rate x 1
Hepatitis B surface antibody	Hepatitis C antibody
Glucose-6-phosphate-dehydrogenase	Hemoglobin A1C
Blood cultures (7/01; 9/02)	

Histopathology:

6/01 Surface ulceration; underlying epidermis shows a dense mixed cellular infiltrate with numerous neutrophils and nuclear dust. DDx: acute arthropod bite reaction; acute neutrophilic dermatosis; pyoderma is less likely.

8/01 Dense nodular neutrophilic inflammation and marked leukocytoclasia. There is papillary dermal edema with underlying dense nodular neutrophilic inflammation and marked leukocytoclasia extending throughout the dermis and into the subcutis. DDx: unusual acute neutrophilic dermatosis, superficial pyoderma gangrenosum and bowel bypass syndrome.

7/03 R elbow (S03-7549): neutrophilic dermatosis. The epidermis shows hyperorthokeratosis. There is also acanthosis with focal pallor. In the dermis, there is a diffuse dense infiltrate of polymorphonuclear cells and much nuclear dust. There are extravasated red blood cells. Capillaries are dilated and show no necrosis of their walls. The endothelial cells are prominent.

Immunopathology:

8/01 (DIF): some IgM granules at the basement membrane zone; one blood vessel with C3 deposition; fibrin deposition around one hair follicle.

Diagnosis:

Neutrophilic dermatosis

Treatment and Course:

Repeat nasal cultures grew methicillin-sensitive *Staphylococcus aureus*, and the patient was treated with cephalexin (to which the organism was sensitive) and topical nasal mupirocin. The patient continued to have intermittent flares while on antibiotics. Doxycycline 100 mg BID and niacinamide 500 mg BID were added with some improvement. Tacrolimus 0.1% ointment BID was also added. She continued to develop new lesions while on the above regimen. Doxycycline and niacinamide were discontinued and colchicine 0.6 mg po qd was started with no response. The colchicine was stopped, and she was started on dapsone 50 mg po qd with significant improvement.

Discussion:

In this case of neutrophilic dermatosis, Sweet's syndrome was initially considered. While lesions in this patient resembled those of Sweet's syndrome clinically, findings suggestive of leukocytoclastic vasculitis on histology made the diagnosis of Sweet's less likely. The clinical and histologic picture does support the consideration of pustular vasculitis of the hands which was first described by Strutton et al in 1995. The hands were the predominant site of involvement in these cases, whereas the additional and significant involvement of the arms is noted in this patient.

Galaria et al subsequently described a similar entity. In their three patients, histologic evaluation revealed neutrophilic infiltrates without features of vasculitis. They therefore proposed the term neutrophilic dermatosis of the dorsal hands (NDDH), and suggested that this was a subset of Sweet's syndrome. Several other patients with NDDH have subsequently been reported, with histologic findings ranging from a neutrophilic infiltrate without vasculitis to leukocytoclastic vasculitis of varying severity.

We propose that our patient represents another case of NDDH, with histologic findings of neutrophilic inflammation and leukocytoclasia. In addition, her significant response to dapsone is consistent with a neutrophilic dermatosis. We question whether the neutrophilic dermatosis in this patient has any relationship to the nasal *Staphalococcus aureus* carriage.

References:

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Case #9

Case Presented by Michelle Bain, MD
and Frank Tobin, MD

History of Present Illness:
This 13-year-old boy presented with a red, scaly rash on his forehead, nasolabial folds, neck, and ears along with tiny papules over the dorsal hands since the age of five. The eruptions worsen with heat and humidity and improve during the winter months, all the while being asymptomatic.

Based on clinical findings and histologic correlation, the boy was diagnosed with Darier's disease. Topical and oral antibiotics helped control the crusting associated with flares but were otherwise not helpful. Topical steroid preparations did not improve his rash. He was unable to tolerate topical retinoids secondary to skin irritation. He was also unable to tolerate a trial of isotretinoin 30 mg daily secondary to a significant increase in his triglyceride levels.

Past Medical History:
Attention deficit hyperactivity disorder

Medications:
Adderall

Allergies:
No known drug allergies

Family History:
Neither parent was found to carry the gene defect.

Social History:
The boy is an active, social eighth grader.

Physical Examination:
The patient had erythematous patches and follicular papules coalescing into plaques with thick, yellow greasy scale and crust on the scalp, frontal hair line, ears, posterior neck, and shoulders. There were tiny flesh colored and hyperpigmented scaly papules on the dorsal hands and feet. There were longitudinal red and white striations involving some of the fingernails and toenails with V-shaped nicking at the free edge of the nail plate.

Laboratory Data:
The following initial laboratory studies were abnormal or positive:

Total cholesterol	205mg/dL	[nl:<200]
Triglycerides	313mg/dL	[nl:40-160]

The following laboratory studies were normal or negative:
Thyroid panel
Liver function tests

Histopathology
6/00 Neck: The epidermis shows orthohyperkeratosis with mild acanthosis. Several areas show suprabasilar separation. Corp ronds and corp grains are seen in the granular and corneal layers, respectively

Diagnosis:
Darier-White disease

Treatment and Course:
A trial of calcipotriene cream to the affected area twice daily and doxycycline 100 mg twice daily was initiated. After several weeks of treatment, there was no significant change in the eruption. The patient was presented at the American Academy of Dermatology meeting in July, 2003. Intermittent low-dose isotretinoin in conjunction with a lipid lowering agent was recommended. Isotretinoin 10mg daily with gemfibrozil 600mg twice daily was started in September, 2003. The patient's skin improved markedly after one month of oral retinoid therapy. However, the patient's triglycerides increased (296-313 mg/dL), and the isotretinoin dosing schedule was changed to 10 mg five days a week. Following evaluation by a geneticist and a pediatric cardiologist, it was determined that the patient may have a fundamental hypertriglyceridemia, and weight loss and exercise were recommended.

Discussion:
Darier-White disease (keratosis follicularis) is a rare, dominantly inherited condition with altered keratinization of the epidermis, nails, and mucous membranes. It is characterized by the development of keratotic papules and plaques with greasy scale located in a primarily seborrheic distribution. Other findings may include longitudinal red and white striations of the nails with distal V shaped notches at the free edge of the nail plate. Clinical manifestations usually appear between the ages of 6 and 20, and patients often are misdiagnosed with seborrheic dermatitis for years. The disease results from a mutation mapped to chromosome 12 which encodes a sarco/endoplasmic reticulum calcium ATPase pump (SERCA2). The disrupted calcium signaling within keratinocytes is thought to interfere with desmosome assembly resulting in the characteristic acantholytic dyskeratosis.

The management of Darier-White disease is difficult. Patients frequently experience exacerbations during the summer months during which time cotton clothing and sunblock creams may be of benefit. Moisturizers containing lactic acid or urea frequently help reduce irritation and scale. Case reports and small studies have demonstrated the potential benefit of topical retinoid preparations. However, these treatments are frequently limited by skin irritation. Calcipotriol ointment has also been tried with limited efficacy. Essential fatty acid supplementation has been reported to improve symptoms. Systemic treatment with oral retinoids is effective in reducing hyperkeratosis and flattening papules. However, the disease is chronic and oral retinoids are difficult to tolerate for long periods of time.

References:

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Case #10

Case Presented by Lawrence Chan, MD
and Todd T. Davis, MD

History of Present Illness:
This 44-year-old man presented with asymptomatic papules on the dorsal hands since eight or nine years of age. He had previously been diagnosed with 'malignant warts'. No treatment had been attempted, nor biopsies performed. He denied having had rashes on the chest, scalp or face in the past, although he did complain of a rash on the back present for eight months.

Past Medical History:
Hyperthyroidism, status post partial thyroidectomy ~ 20 years ago.
Bipolar disorder with anxiety and depression

Medications:
Paroxetine
Valproic Acid
Risperidone
Levothyroxine

Allergies:
No known drug allergies

Family History:
Mother had similar lesions on hands and also had a chronic rash on back and chest.

Social History:
Smokes 1.5 packs of cigarettes a day
History of cocaine, alcohol and cannabis abuse – clean for over one year

Physical Examination:
The right upper back showed a 3x5cm area of superficially eroded papules coalescing into plaques with some hemorrhagic and serous crust. Seven months after the initial presentation, erythematous plaques with some crusting and scale were noted in the glabella and periorally. There were numerous discrete light brown verrucous 2-5mm papules with fine scale over both dorsal hands and extending onto the hypothenar palms. The fingernails showed red and white alternating longitudinal lines as well as distal V-shaped nicking.

Histopathology:
2/03 Dorsal hand: The epidermis shows marked orthohyperkeratosis and acanthosis. There are focal epidermolytic changes.

6/03 Dorsal hand: The epidermis shows marked orthohyperkeratosis and acanthosis with churchspiring. No parakeratosis, vacuolization or dermal infiltrate seen.

6/03 Right back: The epidermis shows marked hyperkeratosis with focal parakeratosis and hypergranulosis. Focally, there are dyskeratotic cells within the granular layer and lower stratum corneum. These changes resemble corp ronds and corp grains. The papillary dermis shows perivascular infiltration of lymphocytes and plasma cells. On one margin of the biopsy, villi formation with suprabasal separation is seen.

Diagnosis:
Acrokeratosis verruciformis of Hopf (AKVH) / Darier's disease

Treatment and Course:
At presentation, a biopsy of the dorsal hand was taken and a duoderm dressing was applied over the back lesion for two weeks with some improvement. He was then started on tretinoin 0.1% cream QHS to the dorsal hands and back. After three months with only partial improvement, two additional biopsies were taken from the dorsal hand and right upper back. Topical tretinoin has been continued on the back and face with slow improvement. Oral isotretinoin was considered, but due to the mild chronic nature of the process and the history of bipolar disorder, it has not been initiated.

Discussion:
First described by Hopf in 1931, acrokeratosis verruciformis is a localized disorder of keratinization. This rare genodermatosis is inherited as an autosomal dominant trait. Onset in infancy or early childhood is typical. Clinically, multiple, discrete, 2-5 mm, verrucous, convex to flat-topped, flesh to brown colored papules are typically seen on the dorsal aspects of the hands and feet, extensor forearms, and legs. The palms and soles may show punctate pits covered by pinhead-sized horny material. Nail involvement may be present and includes longitudinal red and white lines, fragility, and V-shaped notches at the free edge. Characteristically, lesions on the face, scalp, and sebaceous areas are absent.

Histologically, hyperkeratosis, acanthosis, and papillomatosis are seen. Although hypergranulosis is often present, dyskeratosis, parakeratosis and vacuolization are not seen. Church spires (localized elevations of the epidermis) commonly occur, but may be absent. There is no dermal inflammatory infiltrate.

The differential diagnosis includes flat warts, epidermodysplasia verruciformis, and Flegel's disease. The lack of parakeratosis and vacuolization rules out the former two and the lack of a dermal infiltrate rules out the latter.

Recently, the long suspected genetic link between AKVH and Darier's disease was confirmed in an English family. *ATP2A2*, the affected gene, codes for an endoplasmic reticulum calcium pump (SERCA2). A point mutation (C to T) results in leucine being substituted for proline. Since the affected amino acid is in the ATP binding domain of the molecule, the mutation renders it non-functional, i.e. unable to transport calcium. Although one might expect the mutation in AKVH to be in a region less important for function, this loss of function is similar to the phenotype of Darier's disease. The mechanism for the milder clinical phenotype remains unknown.

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Case #11

Case Presented by Claudia Hernandez, MD, Loyola University Medical Center and Keith A. Lopatka, MD

History of Present Illness:
This 34-year-old man with a history of kidney-pancreas transplant presented in July, 2003, with a nine-month history of a worsening pruritic eruption of the elbows and knees. He stated that the eruption began as small pruritic lesions concentrated mainly on the elbows and knees that have continued to increase in size and number and have begun to coalesce into large lesions. He has been treated with clotrimazole 1% + betamethasone 0.05% cream, terbinafine cream, mometasone furoate 0.1% cream, and triamcinolone 0.1% cream without improvement.

Past Medical History:
Polycystic kidney disease
Diabetes mellitus
Kidney-pancreas transplant
Macular degeneration
Diabetic retinopathy
Cataracts
Bilateral lens implant

Medications:
Mycophenolate mofetil 750 mg BID
Tacrolimus 5 mg BID
Prednisone 5 mg QD
Lansoprazole 15 mg QD
Simvastatin 40 mg QD
Fexofenadine 180 mg QD
Aspirin 325 mg QD

Allergies:
Ciprofloxacin

Family History:
No history of psoriasis or other skin disorders

Physical Examination:
On initial presentation, the patient had twenty to thirty discrete 1 to 3 mm pink, red, fleshy papules concentrated on bilateral elbows, knees, and plantar surface of the feet.

Over the next two months, the lesions coalesced into ten to thirteen erythematous thick fleshy papules and nodules, several with hemorrhagic crusts, concentrated in the same distribution.

Histopathology:
11/03 Left elbow and left upper arm (S03-18588): The epidermis shows marked acanthosis with pseudoepitheliomatous hyperplasia, follicular plugs, and perforation. The upper dermis shows a dense mononuclear cell infiltrate consisting of foamy histiocytes, lymphocytes, and plasma cells. A deep dermal infiltrate with atypical cells and central

necrosis is present. The cells contain pleomorphic nuclei, abnormal chromatin pattern, and large or multiple nucleoli. Mitoses are frequently noted.
Stains for CD3, CD4, and CD8 show a predominance of T-cells. CD20 demonstrates the presence of scattered B-cells in the upper dermis. Stains for kappa and lambda light chains are positive. LCA (CD45) is diffusely positive. CD68 is densely positive. The following stains are negative: CD30, AFB, and PAS.

Diagnosis:
Post-transplant lymphoproliferative disorder

Treatment and Course:
At present, this patient is still in the initial stages of diagnosis and treatment. He is currently undergoing PCR for the detection of EBV, radiographic studies for lymph node abnormalities, and evaluation by hematology.

Discussion:
Post-transplant lymphoproliferative disorder (PTLD) was first described in the transplant population in 1968. Classification and treatment of the disorder remain unclear. Much of what is known regarding PTLD has been learned from single cases or small retrospective studies.

It has been established that Epstein Barr Virus infection plays a significant role in the pathogenesis of PTLD in the vast majority of cases. In the presence of the deliberate suppression of T-cell function to prevent graft rejection, it has been proposed that EBV infection leads to the uncontrolled proliferation of B-cells. This proliferation leads to the development of B-cell clones and thus the emergence of one or more clonal populations.

The incidence of PTLD varies according to the organ transplanted and the immunosuppressive regimen used. The incidence is highest in lung transplantation and lowest in kidney and bone marrow transplantation. Importantly, PTLD has been seen in all forms of antirejection therapy. A significant risk factor for the development of PTLD is primary EBV infection in the post-transplant period. EBV seronegative patients carry a much higher risk of developing PTLD than seropositive patients.

The histologic spectrum of PTLD varies from a reactive or hyperplastic morphology to prominent pleomorphic lymphoid cells resembling high-grade non-Hodgkin's lymphoma. Lesions may have one or more monoclonal subpopulations. Thus, more than one clone may coexist within the same lesion, or differing clones and differing histopathology may be seen at different sites in the same patient. The majority of studied PTLD's have been of B-cell origin, but several cases have shown a T-cell origin.

The clinical presentation of PTLD can be quite varied. Patients may present with systemic symptoms, localized involvement, or asymptomatic incidental findings. It appears that the onset of symptomatology affects the severity of presentation and clinical course. Widespread disease with multisystem involvement can be seen within weeks of transplantation. Between the first few months to less than 1 year post-transplantation, an infectious mononucleosis-like illness can be seen with constitutional symptoms and cervical lymphadenopathy. After one year of transplantation, PTLD tends to present locally, with fewer systemic symptoms, and runs a more gradual course.

Successful management involves early diagnosis and intervention. Histology is the most important criteria for diagnosis. Although no uniform approach for treatment exists, a general

treatment strategy has emerged. The first and initial strategy is simply the reduction of immunosuppression, as this can lead to permanent resolution. However, rejection of the transplanted organ is a concern, as there are no clear guidelines for the extent and duration of immunosuppression reduction. This reduction remains poorly defined and highly subjective. Antiviral therapy has not proven effective as prophylaxis and its value in treatment remains unclear. The second strategy is the response of localized areas to surgical excision or irradiation. The third strategy is chemotherapy, which is a treatment of last resort due to the associated high morbidity and mortality in this patient population. Different modalities have been tried with various degrees of success including interferon alpha 2b, anti-B cell monoclonal antibodies, CHOP, ProMACE-CytaBOM, and T-cell therapy.

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Case #12

Case Presented by Iris Aronson, MD
and Steven Mandrea, MD

History of Present Illness:
This 21-year-old man was diagnosed with systemic lupus erythematosus at the age of two. His lupus was systemic with involvement of the CNS, renal, musculoskeletal, hematologic, and cardiac systems. The patient presented to our clinic in December, 2002, with severe cutaneous disease with a photosensitive eruption over the face, chest, back, arms, and legs. The rash was associated with dryness and scaling, but no pruritus or burning. In the past, the patient had been treated with cyclophosphamide IV monthly for six months. More recently, the patient has been taking prednisone, azathioprine, mycophenolate mofetil, and tacrolimus ointment, as well as IVIG q4-8 weeks for about ten years.

Past Medical History:
Seizures
Mitral valve prolapse
Asthma
Bronchitis
Cataracts s/p surgery with implants
Hearing loss

Medications:
Intravenous immunoglobulin Q4WKs – premedicated with prednisone 120 mg in 3 divided doses
Prednisone 10 mg QD
Azathioprine 50 mg BID
Mycophenolate mofetil 500 mg QID
Tacrolimus 0.1% ointment to affected areas BID
Bullfrog sunscreen SPF 45 QD
Phenytoin sodium 200 mg QAM, 100 mg QD, 100 mg QHS
Amlodipine 2.5 mg QD
Metoprolol 25 mg QD
Hydroxyzine hydrochloride 25 mg QD
Clonazepam 0.5 mg PRN

Allergies:
Sulfa
Demerol
Codeine
Diphenhydramine
IVIG – hypersensitivity reaction requiring premedication with prednisone

Family History:
There are no known skin or autoimmune diseases in the family

Social History:
Significant school absence due to illness – recently graduated high school

Review of Systems:
Chronic fatigue, diffuse joint pains, photosensitivity, and symptoms of Raynaud's phenomenon

Physical Examination:
The patient had diffuse erythema and scaling on the scalp with multiple depressed scars. There were diffuse erythematous, scaly patches and plaques involving most of the face and neck, chest, back, and upper extremities. The fingernails were dystrophic with clubbing. The legs were less involved with a few erythematous scaly papules and macules. The palms and soles were clear. After more intensive treatment with IVIG (Q4WK from Q8WK), the erythematous eruption resolved with hypopigmentation and scarring.

Laboratory Data:
The following laboratory studies were abnormal or positive:

ANA	1:2560	[nl: negative]
Anti dsDNA	104 IU/mL	[nl: <30]
Complement		
C3	59 mg/dL	[nl: 88-201]
C4	2 mg/dL	[nl: 10-40]
C2	0.9 mg/dL	[nl: 1-4]
Total (CH50)	17 U/mL	[nl: 60-155]
White blood cell count	4.2 x 10^3/uL	[nl: 4.8-10.8]
Platelets	114 x 10^3/uL	[nl: 150-400]
Protein, total	5.6 g/dL	[nl: 6.0-8.5]
Albumin	3.2 g/dL	[nl: 3.5-5.0]
Urinalysis		
Occult blood	Moderate	[nl: negative]
Red blood cells	5-10/hpf	[nl: < 3]
Protein	100	[nl: negative]
Bacteria	Trace	[nl: negative]

The following laboratory studies were normal or negative:

Anticytoplasmic antibodies (SSA; SSB; Smith; RNP)	
Erythrocyte sedimentation rate	Hemoglobin
Basic metabolic panel	Liver function tests

Diagnosis:
Systemic lupus erythematosus and disseminated chronic cutaneous lupus erythematosus

Treatment and Course:
The patient continued to be treated by his rheumatologist with IVIG, prednisone, mycophenolate mofetil, and azathioprine. Thalidomide was suggested as a possible adjunctive agent for his severe cutaneous disease, and the potential risks and benefits of this medication were discussed with the patient. Given the significant potential side effect profile of thalidomide, especially the increased risk of thrombosis and peripheral neuropathy, this treatment was deferred. Over the past year, the patient has improved on the above treatment regimen. His cutaneous disease has improved greatly, leaving large patchy areas of hypopigmentation and scarring. The young man is now living on his own and is able to maintain a higher level of independence. Of note, during one of the patient's IVIG treatments 7 months ago, he experienced a hypersensitivity reaction with diaphoresis and shaking chills. This treatment was apparently with a different brand of IVIG than he had received previously. Since then, he has tolerated IVIG Q4WK, now with prednisone premedication. Attempts to taper the IVIG to Q8WKS have resulted in flares of his lupus.

Discussion:

This patient represents a case of severe childhood-onset systemic lupus erythematosus (SLE) that has responded well to intravenous immunoglobulin (IVIG). Although IVIG has traditionally been reserved for patients with idiopathic thrombocytopenic purpura and immunoglobulin deficiency disorders, it has proven effective in many cases of SLE that have been resistant or refractory to standard treatments. Francioni et al showed significant improvement in disease activity, erythrocyte sedimentation rate, and proteinuria in an open-label trial of 12 such patients. Adverse effects have been rare and have included nausea, flushing, musculoskeletal pain, and renal failure. Opportunistic infections have not been associated with treatment. The precise mechanism by which IVIG works in SLE is still unclear. Modulation of immune complex deposition or anti-idiotype interactions and depletion of anti-DNA antibodies are thought to play a role.

Mycophenolate mofetil is another nonstandard medication for SLE that has been helpful for our patient. The drug is hydrolyzed to mycophenolic acid, which inhibits purine synthesis, lymphocyte proliferation, and T cell dependent antibody response by selectively and reversibly blocking lymphocyte inosine monophosphate dehydrogenase. Very little toxicity has been noted with its extensive use in renal transplant patients to prevent rejection. Improvement in hypocomplementemia, anti-DNA levels, and overall disease activity have been reported with its use. Mycophenolate mofetil has also been shown to be quite efficacious in cyclophosphamide-resistant lupus, as with our patient, and especially in treating lupus nephritis. Large-scale studies in patients with SLE to prove the long-term benefit of mycophenolate mofetil still need to be performed.

References:

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Case #13

Case Presented by Iris Aronson, MD
and Frank Tobin, MD

History of Present Illness:
This 48-year-old Hispanic male presented with a slow growing lesion on fourth digit of his left hand. The lesion appeared approximately one year ago shortly after he sustained a penetrating injury to the finger with a metal wire. Three weeks after the injury, a retained piece of wire was removed from the wound. The wound never healed and evolved into a large, tender erosion. Prior treatment with unknown antibiotic pills and creams was unsuccessful. He received a biopsy at an outside institution which showed pseudocarcinomatous hyperplasia and a mixed cell infiltrate. Special stains were negative for organisms. Upon presentation in our clinic, a biopsy for tissue culture was negative. A repeat biopsy showed evidence of blastomycosis infection.

Past Medical History:
Asthma

Medications:
Albuterol MDI as needed

Allergies:
No known drug allergies

Family History:
Noncontributory

Review of Systems:
Denied any fevers, chills, nausea, vomiting, shortness of breath, muscle pain, or weakness.

Physical Exam:
The patient had a 7cm x 2.5cm friable eroded plaque with surrounding erythema and crust at the dorsal aspect of the fourth digit of his left hand.

Laboratory Data:
The following laboratory studies were abnormal or positive:

White blood cell	19.3/uL	[nl:4.5-10.5]

The following laboratory studies were normal or negative
Tissue culture was negative for bacteria, fungus, and acid fast bacilli.

Diagnostic Procedures and Tests:
7/03 Chest X-ray: an ill-defined round opacity in the right mid zone with a lucent area surrounding it, suspicious for an infectious or inflammatory process.
8/01 CT scan of the chest: focal chronic appearing lateral right middle lobe atelectasis. Appearance is nonspecific but consistent with treated blastomycosis. There are no visible cavitary lesions. No pulmonary nodules are present. There is subsegmental lingular atelectasis. There is no hilar, mediastinal lymphadenopathy or evidence of pleural disease.
7/03 MRI of left 4th finger: inflammation extending to the subcutis; no osseous involvement.

Histopathology:

7/03 Left fourth finger: there is marked pseudoepitheliomatous hyperplasia of the epidermis with intense neutrophilic infiltration in the dermis. GMS stain shows the presence of thick walled yeasts, with morphology consistent with *Blastomyces* species. AFB stain is negative.

Diagnosis:

Cutaneous blastomycosis

Treatment and course:

The patient was started on oral itraconazole 100 mg bid, then increased to 200 mg bid. The finger lesion rapidly improved within one month and nearly resolved after 3 months. The patient was evaluated by a hand surgeon who found no need for surgical intervention. He was also examined by an infectious disease physician who recommended continued treatment with oral itraconazole for a total of 6 months. Given the history of trauma at the site of infection, the patient may have had inoculation blastomycosis and a primary cutaneous infection. However, the nonspecific findings on the CT scan and chest x-ray prohibit definitive exclusion of previous pulmonary involvement. The patient is scheduled to have a follow up chest x-ray.

Discussion:

Blastomyces dermatitidis is a dimorphic fungus endemic to the Great Lakes region and the Mississippi and Ohio River valleys. The most common portal of entry is the respiratory tract. Pulmonary infections may spontaneously resolve or progress and occasionally disseminate to extrapulmonary sites, the most frequent being the skin. Lesions are typically described as violaceous verrucous papules, nodules, and plaques. Ulceration and pustules may occur. Involvement of subcutaneous tissue, bones, joints, the genitourinary tract, and the CNS have all been reported with systemic infections. Immunosuppressed hosts are most susceptible to infection and dissemination. Interestingly, HIV is not commonly associated with blastomycosis.

Approximately 10% of patients with blastomycosis have isolated cutaneous disease. However, it is suspected that many of these patients have asymptomatic pulmonary infections. Primary cutaneous blastomycosis frequently presents with regional lymphadenopathy. Cutaneous inoculation usually occurs in clinical settings during exposure to infected tissue, secondary to animal bites, and following nonspecific trauma. Inoculation blastomycosis is both clinically and histologically indistinguishable from disseminated skin lesions. The median incubation period for primary skin infections is typically 2 weeks, much shorter then the typical 45 day incubation period seen with pulmonary infections. IV amphotericin has been successful in the treatment of severe systemic infections. The current recommendation for treatment of non- life threatening blastomycosis is oral itraconazole at 200-400 mg daily for 6 months.

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Case #14

Case Presented by Sophie Worobec, MD
and Todd T. Davis, MD

History of Present Illness:
This 16-year-old woman presented with a life-long history of lesions on the left cheek, back, left arm, left wrist, and left leg. The lesions have not enlarged in several years and appeared to 'grow with' the patient. The lower back lesions are occasionally tender to pressure, and the cheek lesion is occasionally painful with temperature change. The lesions are otherwise asymptomatic and do not change with menses.

Past Medical History:
Asthma

Medications:
Albuterol inhaler PRN
Reliv – multivitamin powder
Advil PRN

Allergies:
No known drug allergies

Family History:
Maternal grandmother had a similar lesion on her left wrist
No other known affected family members

Review of Systems:
Denies any history of melena or broken bones

Physical Examination:
On presentation, there were soft blue papules and nodules ranging from 3mm to 1cm on the left cheek, left upper arm, left wrist, and left posterior thigh. On the L upper back, there was a circular cluster of blue nodules each 3 to 6mm. There were two ~8cm linear arrays of blue nodules on both the left and right lower back.

Laboratory Data:
The following laboratory studies were normal or negative:
- Complete blood count
- Electrolytes
- Blood urea nitrogen and creatinine

Diagnostic Procedures and Tests:
4/03 CT head: Lobulated well-circumscribed 1.8x1.3 cm soft tissue density on the left lateral face, otherwise normal.
CT thorax: Nodular and plaque-like soft tissue thickening confined to the posterior subcutaneous fat at level of the scapula and T11-T12.

Histopathology:

3/03 Left thigh: The epidermis is essentially normal. Within the mid and lower dermis, there is a proliferation of dilated, anastamosing blood vessels lined by cuboidal cells. The cells are present in 2 layers predominantly. Hemosiderin pigment is noted.

Diagnosis:

Multiple congenital glomangiomata

Treatment and Course:

The patient was offered pulsed dye laser treatment. She has deferred treatment to date. She is being presented for clinical interest and therapeutic alternatives.

Discussion:

Glomus tumors are hamartomas derived from the glomus body, a neuromyoarterial body that acts as an arteriovenous temperature regulating shunt primarily on the palms and fingers. Glomus cells surround the Sucquet-Hoyer canal of the glomus body. Over 90% of glomus tumors are solitary. They are typically seen in adults in acral locations, frequently in the nail bed, and are painful. Less common multiple glomus tumors vary in lesion number from few to hundreds, have an earlier age of onset, are not frequently painful, and are histologically the same as solitary lesions. There are three variants of multiple glomus tumors: disseminated, regional, and congenital. Congenital multiple glomangiomas are rare, with fewer than 20 reported cases.

Histologically, glomus tumors are composed of sheets of darkly staining cuboidal cells in monotonous sheets containing small vessels. Solitary glomus tumors are usually encapsulated and are associated with ample nerve tissue. The glomangioma variant consists of dilated, convoluted abnormal venous channels lined by one to a few layers of cuboidal and oval epithelioid glomus cells. Few nerve fibers are seen. Glomangiomyoma, another variant, has many glomus cells in and around smooth muscle cells. Glomus cells stain with alpha-smooth muscle actin and vimentin; they are negative for cytokeratins and endothelial stains.

Congenital multiple glomangiomas present at birth and the lesions enlarge with the growth of the body. The lesions are frequently asymptomatic. Development of distant satellite lesions at puberty is often noted. Inheritance is autosomal dominant, however a positive family history is present in only 60% of cases. The gene, *glomulin*, has been identified on chromosome 1p21-22 and is believed to play a role in the differentiation of vascular smooth muscle cells. There are no reports of malignant transformation of these lesions. Treatment has included argon laser, carbon dioxide laser, surgical excision, and sclerotherapy. Laser treatment has improved pain and appearance, but only in superficial lesions. There are no reports of treatment with contemporary vascular lasers.

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Case #15

Case Presented by Michelle Bain, MD
and Alexander L. Berlin, MD

History of Present Illness:
This 4-month-old girl presented with a lesion on the posterior neck present since birth. The lesion started as a small red patch, but then gradually enlarged and became nodular. The lesion does not appear to cause any discomfort to the infant. Unspecified oral antibiotics have been tried by the primary care physician without improvement.

Past Medical History:
Pregnancy, labor, and delivery were uneventful

Medications:
None

Allergies:
No known drug allergies

Family History:
No history of neurofibromatosis

Review of Systems:
No fevers, irritability. No changes in eating, urination, or defecation patterns.

Physical Examination:
The patient had a 1.2 x 1.0 cm non-tender well-circumscribed indurated orange-pink nodule on the posterior neck.

Histopathology:
09/03 Posterior neck (SD-03-0008427): The epidermis shows parakeratosis with focal scale crust and acanthosis. There is a dense diffuse infiltrate involving the entire biopsy specimen. On higher power, the infiltrate consists mainly of foamy histiocytes with few lymphocytes. Several Touton giant cells are seen in the lower reticular dermis.

Diagnosis:
Juvenile xanthogranuloma

Treatment and Course:
After discussion of treatment options with parents, it has been decided that the lesion will be observed clinically over time for signs of spontaneous involution.

Discussion:
Originally called nevoxanthoendothelioma, juvenile xanthogranuloma (JXG) is the most common of the non-Langerhans cell histiocytoses. Five to 17% of patients may have clinical lesions at birth, with an additional 40-70% developing lesions within the first year of life. Adult-onset JXG has been described as well and typically occurs in the late twenty and early thirties. Whereas the latter does not show gender predilection, males predominate 1.5:1 in the childhood form. One

recent study by Dehner, however, found that male predominance may be as high as 12:1. The disease is also most common in Caucasians.

Clinically, JXG presents as an asymptomatic well-demarcated firm round or oval-shaped papule or nodule varying in size from 0.5 to 2 cm or larger. A predilection for the head and neck region has been noted, followed by the upper torso, upper extremities, and lower extremities. The color of the lesion may vary from flesh-colored to pink to yellowish to brownish. Patients may have small nodular (micronodular) or large nodular (macronodular) form, or a combination thereof. Approximately two-thirds of patients will have a solitary macronodular JXG lesion. In the small nodular form, multiple small dome-shaped papules 2-5mm in size can be appreciated.

JXG lesions may involve mucous membranes. Oral mucosal lesions, most often noted on tongue and hard palate, may ulcerate and bleed. Five percent of patients may have a soft tissue JXG, which typically presents as a mobile non-tender soft mass most commonly found on the head and neck. Extracutaneous JXG may involve the eyes (presenting as iris tumors, glaucoma, or hyphema), the orbit, lungs, liver, pericardium, myocardium, spleen, kidneys, central nervous system, and others. Most patients with visceral tumors have skin involvement with multiple lesions, but no ocular involvement. Visceral tumors may result in symptomatology secondary to mass effect and may also result in death as with cases of giant cell hepatitis.

The most commonly mentioned association of JXG is with café-au-lait spots and the risk of juvenile chronic myelogenous leukemia (JCML). Children with neurofibromatosis type 1 (NF1) and JXG have been found to have a 20- to 30-fold increased risk of JCML compared to NF1 patients without JXG. However, because of the early onset of JCML, children may not satisfy the diagnostic criteria for NF1. Therefore, café-au-lait spots, especially in the presence of family history of NF1, should arouse suspicion in a patient with JXG.

Histologically, JXG is characterized by a dense granulomatous infiltrate consisting of foam cells, foreign-body giant cells, and Touton giant cells, as well as histiocytes, lymphocytes, neutrophils, and eosinophils. The presence of Touton giant
cells, while not specific, is found in 85% of cases. The epidermis and adnexal structures are usually spared. In regressing lesions, fibroblasts and fibrosis gradually replace the infiltrate and may result in the clinical finding of anetoderma.

The etiology and pathophysiology of JXG is not clear, but a reactive histiocytic process to an unknown initial physical or infectious cause has been postulated. The natural history of the disease in most children is complete resolution of cutaneous and extracutaneous lesions within 3-6 years with the possible sequelae of hyperpigmentation or anetoderma. Spontaneous resolution in adults is not frequent. Conservative treatment is generally recommended, although patients or their parents may choose to have the lesions excised. Following excision, recurrences have been reported to occur. Ocular lesions have to be treated early to prevent complications.

When evaluating a patient with JXG, a complete review of systems and physical examination for café-au-lait spots and extracutaneous involvement are recommended, and a family history of neurofibromatosis should be sought. Screening for ocular JXG is generally reserved only for those patients with multiple cutaneous JXG’s appearing prior to 2 years of age.

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Case #16

Case Presented by David Eilers, MD
and Agnes Ju Chang, MD

History of Present Illness:
This 65-year-old Caucasian male underwent abdominal aortic aneurysm repair in June, 2003, which was complicated intraoperatively by bilateral lower extremity arterial thrombosis requiring extensive explorations, thrombectomies, and angiograms. He also received intraoperative thrombolytic tissue plasminogen activator infusion. Postoperative complications included acute renal failure, spinal cord infarction, and septic shock. On post op day #7, purpura and necrosis of skin on the abdomen, trunk, genitals, and legs were noted, and the dermatology service was consulted. Persistent "bluish toes" were also noted despite warmth and palpable pulses.

Past Medical History:
Abdominal aortic aneurysm s/p repair
Chronic obstructive pulmonary disease
Coronary artery disease
Peripheral vascular disease
Benign prostatic hypertrophy

Medications:

Terazosin	Albuterol/ipratropium inhalers
Enoxaparin	Fentanyl patch
Famotidine	Hydromorphone prn
Metoprolol	Prochlorperazine prn
Nicotine patch	Magnesium sulfate
Vancomycin	Piperacillin/tazobactam

Allergies:
No known drug allergies

Family History:
Noncontributory

Social History:
Tobacco 100 pack-years

Review of Systems:
Pre-operative: inability to void, erectile dysfunction, weight loss (negative malignancy work-up)
Post-operative: oliguria, mental status changes, fever, partial paralysis and sensory loss of lower extremities.

Physical Examination:
The patient had necrosis, purpura, and superficial erosions near the surgical wound sites on the trunk and abdomen. On the penile shaft and glans, there was dark purpura with scrotal edema. There was livedoid purpura on bilateral thighs. The feet showed dark purple toes with some necrotic crust and livedoid purpura on the plantar surface. His face, neck, and arms were clear. Oral and eye mucosae were clear.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Hemoglobin	9.2 g/dl	[nl: 13-17]
Creatinine	3.4 mg/dl	[nl: 0.5-1.3]
Blood urea nitrogen	39 mg/dl	[nl: 7-21]
Bicarbonate	18 mEq/L	[nl: 22-29]
Potassium	6.4 mEq/L	[nl: 3.5-5.1]
Chloride	113 mEq/L	[nl: 98-107]
White blood cell count	15.6 thous/mm	[nl: 33-10.5]
Neutrophils	80.4%	[nl: 50-65]
Bands	25%	[nl: 0-8]
Creatinine kinase	39,700 U/L	[nl: 35-232]
Partial thrombin time	37.1 sec	[nl: 22-34]

The following laboratory studies were normal or negative:

Sodium	Prothrombin time
Phosphorus	Liver function tests
Platelets	

Diagnostic Procedures and Tests:

3/03 CT scan of the chest/ abdomen/ pelvis: Diffuse bullous emphysema in upper lung zones. Intrarenal segment of abdominal aorta shows atherosclerotic aneurysm with a diameter of 6cm. Mural thrombus is noted at the periphery of aneurysm. A large aneurysm (4.5cm) of right common femoral artery is noted. Prostate is enlarged.

3/03 Ankle/Brachial Index (ABI): Right >1.0 Left >1.0

6/03 ABI Post Operative: Right 0.92 Left 0.65

Histopathology:

6/03 Peri-aortic lymph node (HS03-2372): Fibrosis with atheromatous matter and crystalline needles in the vessels. Cholesterol clefts are seen in the blood vessels that polarize. There is focal fat necrosis with numerous foamy histiocytes in the capsule. Blood vessels are engorged with red blood cells, and there are micro thrombi.

6/03 Superior and inferior R thigh (HS03-2588): The epidermis shows complete or partial necrosis. The rete ridges are flattened. The upper dermis shows extravasated red blood cells. There is necrosis of the hair follicular epithelium. The blood vessels show thrombosis. There is a sparse infiltrate with pyknotic nuclei.

Diagnosis:

Cholesterol emboli syndrome

Treatment and Course:

The patient was started on a lipid-lower agent and vancomycin and piperacillin/tazobactam for enterococcus and gram negative bacteremia. His condition continued to deteriorate with extensive skin necrosis of the rectum, perineum and buttocks. On postoperative day #10, he was transferred to the Loyola University Medical Center burn unit for further management. He had debridement of necrotic tissue on the perineum and buttock. He remained on pressors and on ventilatory support post-operatively until passing away five days later.

Discussion:

Cholesterol emboli syndrome is usually a disease of elderly, white men with atherosclerosis that carries a high mortality rate. Obstruction of small arteries can occur spontaneously, after

anticoagulation, or after invasive vascular procedures. Anticoagulants have been reported to contribute to cholesterol emboli by preventing adequate thrombosis over ulcerated atherosclerotic plaques. Reported medications include heparin, warfarin, streptokinase, and tissue plasminogen activator. Vascular procedures result in emboli through mechanical manipulation of the atherosclerotic plaques by wires, catheters, needles, and less often by injection of contrast media.

According to one study, the cutaneous findings of cholesterol emboli included livedo reticularis (49%), gangrene (35%), cyanosis (28%), ulceration (17%), purple toes (14%), nodules (10%), and purpura (9%). Several reports have also noted scrotal and penile necrosis and ischemia. Distal pulses are frequently normal. If there is multisystem involvement, the clinical syndrome may mimic a vasculitis, with the renal and gastrointestinal systems being the most common systems affected. Lab findings include elevated erythrocyte sedimentation rate, eosinophilia, and blood urea nitrogen/creatinine. Others include positive antinuclear antibodies, rheumatoid factor, P-ANCA with antimyeloperoxidase specificity, and hypocomplementemia.

The pathophysiology of cutaneous manifestation is thought to result from trapping of cholesterol crystals in vessels leading to tissue ischemia. In addition, cholesterol crystals may cause local inflammation by complement activation. Lower arterial pressure from atherosclerosis of large proximal vessels may also play a key role in development of necrosis. The source of thrombi is thought to be the abdominal aorta and its distal vessels.

Skin or muscle biopsy is the most effective way to diagnose cholesterol emboli. When examined histologically, crystals will polarize and appear as birefringent rhomboids. Characteristic clefts or spaces will also be evident within the lumen of thrombosed vessels.

Medical treatment is mostly based on anecdotal reports and has largely been unsuccessful. Medications that inhibit coagulation (i.e., heparin, warfarin), platelet aggregation (i.e., aspirin), or red blood cell viscosity (i.e., pentoxifylline) have been used with varying results. Others have used lipid-lowering agents, such as lovastatin, as well as hemostatic agents, such as vitamin K. Surgical treatments with removal of the primary source of emboli with thromboendarterectomy have resulted in resolution of cholesterol emboli; however, patients with extensive atherosclerotic disease may not be amenable to this treatment. Peripheral nerve blockade or lumbar sympathectomies have been used for persistent pain and gangrene. Extensive gangrene of the extremities may necessitate amputation.

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4. Fine MJ et al. Cholesterol crystal embolization: a review of 221 cases in the English literature. *Angiology* 1987; 38(10): 769-84
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6. Pennington M et al. Cholesterol embolization syndrome: cutaneous histopathological features and the variable onset of symptoms in patients with different risk factors. *Br J Derm* 2002; 146: 511-517

Case #17

Case Presented by Sophie Worobec, MD
and Amit Garg, MD

History of Present Illness:
This 17-year-old male of Scandinavian descent has a history of adrenal insufficiency and uncontrolled serum calcium regulation that was diagnosed at the age of seven. He has also had recurrent episodes of mucocutaneous candidiasis. Since the age of nine, the patient noted gradual lightening of skin surrounding several nevi and also in patches involving previously normally pigmented skin. At the age of 15, he began noticing patches of hair loss from the scalp. The hair loss was rapid and progressed to near total loss of scalp, facial, axillary, and pubic hair. The patient has noted abnormalities of his fingernails and toenails for as long as he can remember.

Past Medical History:
Bone fractures
Cataracts and legal blindness
Nephrocalcinosis
Retinitis pigmentosa
Seizures

Medications:
Hydrocortisone 20mg/m^2 QD
Florinef 0.1mg QD
Calcium carbonate 1500mg TID
Magnesium oxide 2gm TID
Dihydrotachysterol 2mg QD

Allergies:
No known drug allergies

Family History:
Noncontributory

Review of Systems:
Since initiating electrolyte and hormone supplementation, the patient has not experienced loss of consciousness or seizure. He has occasional weakness and muscle spasms of the extremities. He has occasional candidal eruptions in the mouth and groin area.

Physical Examination:
The patient has sparse depigmented hairs, mostly on the periphery of the scalp. Sparse pigmented hairs are present over the eyebrows, eyelashes, and upper lip. There are irregular patches of depigmented skin just outside of the vermilion borders of the lips. Erythema, scale, and pustules are present over the nasolabial folds and chin. There are numerous large irregularly pigmented papules and plaques, some surrounded by depigmented skin, over the scalp, face, chest, back, and abdomen. Many fingernails and toenails show tenting, scarring, and partial loss of nail plate.

Laboratory Data:
The patient has had multiple abnormalities in levels of parathyroid hormone, cortisol, and electrolytes.

Diagnosis:
Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome

Treatment and Course:
The patient is followed closely by his primary care physician and endocrinologist with routine physical examinations and determination of his circulating hormone and electrolyte levels. He has had multiple hospital admissions with symptoms related to electrolyte imbalance. The patient is treated with oral medication for mucocutaneous candidiasis as needed.

Discussion:
The autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome is characterized by mucocutaneous candidiasis, autoimmune hypoparathyroidism and Addison's disease. Since being recognized in 1929, APECED has been reported in over 140 patients in Finland and the United States.

Hypoparathyroidism affects 79% of patients and most frequently manifests as tetany between the ages of 2 and 11 years. The peak incidence of Addison's disease, which affects 72% of patients, is between the ages of 4-12 years. Both hypoparathyroidism and adrenal insufficiency appear to be due to circulating autoantibodies. Other glandular tissues commonly affected include the thyroid gland, the pancreas, and gonads.

Chronic or recurrent mucocutaneous candidiasis affects all patients and is often the first manifestation of the disease. The clinical severity of candidiasis ranges from mild angular cheilitis to thick, white, hyperplastic oral candidiasis that may progress to carcinoma. The anogenital surfaces and nails are also common sites of infection. Candida infection in these patients is often refractory to conventional topical therapy.

Specific immunodermatologic conditions associated with APECED include alopecia areata and vitiligo. Alopecia is present in 29% of patients and typically manifests between the ages of 5 and 9 years. It often begins as hair loss in patches and quickly becomes universal in most patients. Alopecia in these patients appears to be autoimmune mediated and independent of hypoparathyroidism. Vitiligo is present in approximately 13% of patients, and it has a variable extent and course. Some patients note return of normally pigmented skin without treatment, while others have depigmented patches that grow larger despite treatment.

APECED is also associated with ectodermal tissue dystrophies, the most common of which is enamel hypoplasia of permanent teeth. About 50% of patients also have pitted nail dystrophy not associated with ungual candidiasis. The mechanism of ectodermal tissue dystrophy is not known.

APECED is transmitted autosomal recessively, and the *AIRE* (autoimmune regulator) gene responsible for the disease is localized to the short arm of chromosome 21 (21q22.3). The gene encodes a DNA transcription factor that is expressed in lymphoid tissues, including the thymus. Mutations in *AIRE* result in a partial defect in cell-mediated immunity and in dysregulation of immune function with subsequent destruction of endocrine tissues.

References:

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Case #18

Case Presented by Iris Aronson, MD
and Todd A. Johnson, MD

History of Present Illness:
This 56-year-old female presented in December, 2002, with a generalized pruritic eruption which began 3 months prior to presentation. Her prior history included a 2-month course of oral terbinafine which was given to her for treatment of onychomycosis. The patient's generalized eruption appeared one month after discontinuation of the terbinafine for liver enzyme abnormalities. The patient further described photosensitivity to sunlight and she also developed arthralgias one month after presentation.

Past Medical History:
Sjogren's syndrome

Medications:
Diphenhydramine 25 mg QD prn pruritus

Allergies:
Amoxicillin
Bactrim
Sulfa

Family History:
No history of autoimmune or other skin disorders

Review of Systems:
Photosensitivity to sun, dry lips, xerostomia, xeropthalmia, and headaches, and arthralgias

Physical Examination:
The patient's scalp and helices were erythematous and scaly. Her face and oronasal mucosae were clear. Her chest, abdomen, back, arms, and legs had scaly erythematous annular and polycyclic plaques.

Laboratory Data:
The following laboratory studies were abnormal or positive:

AST	74 u/L	[nl:10-40]
ALT	66 u/L	[nl:10-50]
Antinuclear antibody titer	1:1280	[nl: none detected]
Anti-SSA	636 units	[nl: 0-14]
Anti-SSB	767 units	[nl: 0-14]

The following laboratory studies were normal or negative:

Anti-Smith antibody	Electrolytes
Anti-RNP/SM antibody	Total and direct bilirubin
Anti-histone antibody	C3, C4 complement levels
Anti-ds DNA	Hepatitis B and C panels
Anti-mitochondrial antibody	RPR

Diagnostic Procedures and Tests: 11/01 Ultrasound of the liver: normal

Histopathology:

11/02 Left arm (S02-07517): The epidermis shows hyperkeratosis and basal cell vacuolization. Occasional dyskeratotic cells are present in the epidermis. A perivascular lymphohistiocytic infiltrate is observed in the upper dermis. Colloid bodies are present in an edematous papillary dermis. No changes are seen in the blood vessel walls.

Immunopathology:

1/03 Right arm (S1-03): dusty speckles of IgM in focal areas of the upper dermis

Diagnosis:

Subacute cutaneous lupus erythematosus induced or exacerbated by terbinafine

Treatment and Course:

Taking into consideration the patient's already elevated liver function tests, we recommended she start prednisone rather than a potentially hepatotoxic immunosuppressants. After consulting with the gastroenterology and rheumatology services, the patient was started on prednisone 30 mg po qd and triamcinolone 0.1% ointment to lesions bid. After her liver enzymes normalized, she was switched to hydroxychloroquine 200mg po bid. since starting hydroxychloroquine, the patient has had significant improvement in cutaneous symptoms and arthralgias.

Discussion:

Cutaneous adverse reactions to terbinafine are usually mild with the most common being urticaria and erythema multilforme. Since the introduction of the anti-fungal terbinafine, there have been an increasing number of case reports describing the association of this medication with subacute cutaneous lupus erythematosus. These reactions usually occur in patients who have had a positive ANA titer in the past, a history of photosensitivity or a history of arthralgias. Our patient had all three of these findings at some point in her course.

Drug-induced lupus occurs in at least two forms. The first is characterized primarily by serositis, positive anti-histone antibody, and is linked to treatment with procainimide, minocycline, isoniazid and other agents. These patients tend to be slow acetylators. The second form manifests as SCLE with positive Anti-Ro antibody and is most often associated with administration of hydrochlorothiazide. Many of these patients have a prior history of lupus-like signs and symptoms.

Given the increasing number of reports of terbinafine associated SCLE , we recommend that an ANA screen be done prior to its use. The clinician should consider that terbinafine may induce or exacerbate a widespread eruption of SCLE in patients with abnormal ANA screens and/or a history of lupus-like complaints.

References:

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2. Callen J et al. Subacute cutaneous lupus erythematosus induced or exacerbated by terbinafine. *Archives of Dermatology*. 137; 1196-1198, 2001
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Case #19

Case Presented by Lawrence Chan, MD
and H. Tina Kim, MD

History of Present Illness:
This 50-year-old African American man initially presented to his primary care physician in March, 2002, with a 6-week history of shortness of breath, chills, anorexia, and weight loss. He worked as a truck driver and had driven through the southwestern U.S. a couple months prior to the onset of his symptoms. A chest CT at the time of initial work-up revealed a right upper lobe pulmonary nodule and lymphadenopathy. Culture of the nodule via bronchoscopy confirmed pulmonary coccidioidomycosis. He was treated with fluconazole 800 mg po qd for 5 months, which he stopped on his own secondary to dry mouth and dysgeusia. Within 3 months of stopping the fluconazole, he noticed several, mildly painful, draining lesions in both axillae, right shoulder, left inguinal area, and left thigh.

Past Medical History:
Asthma
Arthritis

Medications:
Multivitamin 1 tab QD
Ibuprofen 800 mg q8h PRN

Allergies:
No known drug allergies

Family History:
Noncontributory

Social History:
Works as a truck driver
Smokes 1 pack of cigarettes a day since age 17

Review of Systems:
Initial presentation of chills, shortness of breath, anorexia and weight loss
Occasional joint pains in the knees for several years

Physical Examination:
The patient had violaceous plaques with scale in both axillae, right shoulder, left inguinal area and left lateral thigh. He also had palpable lymph nodes in the right axilla and left groin.

Laboratory Data:
The following laboratory studies were abnormal or positive:

Pulmonary bronchoscopy culture +*Coccidioides immitis* (few colonies at 2 weeks)		
Right shoulder skin biopsy culture +*Coccidioides immitis* (many colonies at 4 days)		
Alkaline phosphatase	228 U/L	[nl: 50-136]
Rheumatoid factor	102 IU/mL	[nl: 0-15]
ESR	95 mm/hr	[nl: 0-15]

The following laboratory studies were normal or negative:

Complete blood count, including differential	TSH
Electrolytes, including chemistry 7 and calcium	ANA
Hepatic profile	RPR
Coagulation tests	HIV

Diagnostic Procedures and Tests:

3/02 PPD negative
3/02 CXR: right upper lobe infiltrate and right hilar densities
4/02 Chest CT: right pulmonary nodule, right paratracheal and hilar lymphadenopathy
6/02 Chest CT: R pulmonary nodule unchanged; R lymphadenopathy decreased
2/03 Xrays of femur, pelvis, and lumbosacral spine: all normal
2/03 Bone scan: no significant abnormalities in the long bones

Histopathology:

3/03 Right shoulder (W-SP 03-557): The epidermis shows hyperkeratosis with scale crust and acanthosis with pseudoepitheliomatous hyperplasia. Microabscesses are seen within the dermis. The dermis is heavily infiltrated with plasma cells, lymphocytes, eosinophils, and multinucleated giant cells. PAS stain shows several cocci organisms within the heavy inflammatory infiltrate.

Diagnosis:

Secondary cutaneous coccidioidomycosis

Treatment and Course:

The patient was restarted on fluconazole with improvement of his cutaneous lesions. A follow-up chest CT showed complete resolution of his pulmonary nodules and lymphadenopathy. A head CT for further evaluation of his headaches is pending.

Discussion:

Coccidioidomycosis, also referred to as coccidioidal granuloma, San Joaquin Valley fever, and desert rheumatism, is caused by the dimorphic fungus *Coccidioides immitis*. This soil-dwelling fungus is endemic in some areas of the southwestern United States, including Arizona, New Mexico, California, Nevada, Utah, and Texas, as well as in parts of Central and South America.

The most common route of infection is by inhalation, resulting in asymptomatic, acute and chronic pulmonary, and/or disseminated forms. Direct inoculation of the skin, causing primary cutaneous infection, may also occur. An indurated, generally painless nodule occurs at the site of trauma in 1 to 3 weeks, followed by regional lymphadenopathy.

Primary pulmonary infection typically presents with fever, cough, chest pain, and malaise, approximately 1 to 4 weeks after exposure. An early, generalized macular, erythematous rash occurs in some patients. In the 3rd to 7th week, a hypersensitivity reaction, such as erythema multiforme or erythema nodosum, may occur in approximately 10-15% of patients. These reactions may be associated arthralgias and/or anterior uveitis.

Secondary cutaneous coccidioidomycosis, as present in our patient, occurs from dissemination from pulmonary or cutaneous infection. Dissemination occurs in 0.5-7% of infected patients. Risk factors for dissemination include male gender, ethnicity (African American, Filipino, or Mexican), pregnancy, diabetes, immunosuppression including AIDS, and blood groups B and

AB. The skin is the most common site of extrapulmonary disease, but dissemination may also occur to subcutaneous tissues, bones, joints, and all organs, including CNS. Cutaneous manifestations include abscesses, granulomas, verrucous or atrophic plaques, pustules, ulcers, and sinuses; lesions resembling acne, rosacea, and warts have also been reported.

Diagnosis is made by either a positive culture of *C. immitis* or the presence of spherules on histopathology. Positive cultures usually occur within one week and may be confirmed with specific DNA probes. The saprophytic culture form is mycelial-arthroconidial and is highly infectious. The parasitic tissue form consists of spore-containing spherules up to 250 μm diameter, which may be seen in sputum, cerebrospinal fluid, pus, as well as tissue sections. Serologic tests, including precipitins and complement-fixing antibodies, may also aid with diagnosis. IgG complement fixation titers may be followed as a measure of disease activity. Skin testing is not reliable since a positive test indicates only previous exposure rather than actual infection; furthermore, a negative skin test may occur with dissemination or immunosuppression.

The histopathologic features of cutaneous infection include three primary patterns: 1) abscess formation with necrosis, 2) epithelial hyperplasia and granuloma formation with microabscesses, and 3) vascular and perivascular proliferative and inflammatory reactions. In addition, interstitial granulomatous dermatitis with neutrophils, eosinophils and leukocytoclasis may be a reactive manifestation of pulmonary infection.

The treatment of coccidioidomycosis is individualized, based on the extent of disease and the patient's immune status. Primary pulmonary infection is usually self-limited, and azoles (ketoconazole, fluconazole, and itraconazole) have not been shown to shorten the course of infection. For disseminated disease involving only the skin, an azole can be used. The length of treatment with azoles in clinical trials has ranged from 3-6 months; some recommend continuing the medication for an additional 6 months after clinical response. Response rates have been reported to be approximately 60% at doses of 400 mg po qd. However, relapse rates have ranged from 25-35% after treatment, possibly because the azoles are fungistatic and not fungicidal. Therefore, some patients, especially the immunocompromised, may require lifelong treatment. Amphotericin B is the agent of choice for aggressive pulmonary disease, meningitis, previous azole treatment failure, immunocompromised states, pregnancy, or in infants. If medical treatment fails, surgical excision may be an alternative.

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Case #20

Case Presented by Lawrence Chan, MD
and Marianne Schachter Rosen, MD

History of Present Illness:
This 21-month-old female with glutaric aciduria type 1 developed a rash around the mouth, groin, arms and legs. The child was being fed through a gastric tube. She had also been spitting up food for the past two weeks and was losing weight.

Past Medical History:
Glutaric aciduria type 1
Seizure disorder
Severe developmental delay
Cortical blindness
Severe dystonia

Medications:
LevoCarnitine 500mg GT q6 hours
Vi-Daylin drops 0.5cc qd
Ranitidine 15mg GT q8 hours
Phenobarbital 25mg GT q12 hours
Ibuprofen q6 hours as needed
Bacitracin ointment on G-tube and skin
Carbamazepine 60mg GT BID
Metoclopramide 2mg GT q6 hours

Allergies:
No known drug allergies

Family History:
Mother has a history of asthma
Maternal grandmother has a history of hypertension

Social History:
Vaccinations up to date

Physical Examination:
The patient had erythematous, scaly, partially eroded plaques behind the ears, on the lips, on the arms and hands, in the entire genital area, and on the legs.

Laboratory Data:
The following laboratory studies were abnormal or positive:

Zinc	40 ug/dl	[nl: 66-144]
Albumin	1.8 g/dl	[nl: 3.4-4.5]
Hemoglobin	9.7 g/dl	[nl: 11-14]
Platelets	702 thous/ul	[nl: 150-600]

Wound culture grew moderate *Pseudomonas aeruginosa*, few *Enterococcus*, rare *Escheria coli*, and few methicillin resistant *Staphylococcus aureus*.

The following laboratory studies were normal or negative:

White blood cell count
Blood urea nitrogen
Glucose

Diagnosis:

Acrodermatitis enteropathica

Treatment and Course:

The patient was treated with zinc supplementation and the rash improved. The patient passed away from complications of glutaric aciduria type 1 in August, 2003.

Discussion:

Acrodermatitis enteropathica (AE) is a rare condition caused by an inability to absorb sufficient zinc from the diet. Previously, the condition was often fatal in infancy or early childhood, but it is now rapidly cured by simple dietary supplementation with zinc salts. The term acrodermatitis enteropathica is now used to include all patients with acral dermatitis due to zinc deficiency of hereditary or nonhereditary etiology. Acrodermatitis enteropathica is transmitted autosomal recessively, and the implicated gene, *SL39A4*, has been localized to chromosomal region 8q24.3.

Clinically, patients with hereditary AE present days to weeks after birth if they are bottle-fed or soon after weaning if they are breast-fed. The acral dermatitis begins slowly with dry, scaly plaques on the face, scalp and anogenital areas. Perleche is a common early sign. Lesions are progressive with the development of vesicobullous, pustular and erosive lesions. The hands and feet then become involved with a brightly erythematous dermatitis of the palms and finger creases. Secondary infections are common. Within a few weeks, there is growth failure with intermittent diarrhea and anorexia. Associations with AE also include the following: alopecia, light and dark banding of hair, a seborrheic dermatitis-like eruption, delayed wound healing, photophobia, hypogeusia, hypogonadism with delayed puberty, low fertility is low in those who reach reproductive age, neural tube defects, emotional and mental disturbances.

Acquired AE presents with a similar eruption. Many infants previously thought to have hereditary disease have now been recognized as acquired AE due to low levels of zinc in their mother's milk. Unlike hereditary AE, once these infants with acquired AE are weaned, they no longer require supplemental zinc. No specific genetic factors have been found to cause low zinc in breast milk; rather, the mothers are likely zinc deficient due to demands during pregnancy and lactation. There are a number of other potential causes for acquired zinc deficiency including infection, gastrointestinal disturbances, dietary factors, trauma, malignancy, and renal disorders among others.

Diagnosis is confirmed with low plasma zinc levels; however, blood levels may fluctuate with stress, infection, or injury. A morning fasting specimen is recommended as there is a diurnal rhythm in plasma zinc concentration. Urinary zinc levels, which also fluctuate, may also be measured. Specimen collection and laboratory technique can contribute to false negatives as there may be contamination with environmental zinc. Hair zinc concentration reflects only long-term zinc status. Serum alkaline phosphatase will remain normal until profound and prolonged zinc deficiency occurs; it is considered a moderately sensitive indicator but not an early marker.

Treatment, regardless of etiology, is dietary or intravenous zinc salt supplementation. Zinc sulfate is recommended for oral supplementation, and zinc chloride for intravenous supplementation. Dramatic clinical response is noted within hours to days with improvement in rash and resolution

of diarrhea, mental disturbances, and alopecia. Supplementation is usually life-long for hereditary AE, and zinc levels should be monitored. High zinc levels may induce gastrointestinal disturbances such as nausea and vomiting. Associated elevated copper levels may alter immune function.

Glutaric aciduria type 1 is an autosomal recessive disorder characterized by progressive dystonia and dyskinesia. Following minor infections, patients may suddenly develop hypotonia, choreoathetosis, seizures, generalized rigidity, opisthotonos and dystonia. Other patients may develop these symptoms gradually during the first few years of life. Acute episodes of vomiting, ketosis, seizures, and coma may occur with intercurrent infection or stress. Death usually occurs in the first decade during one of the above episodes. Treatment is with a low protein diet and high doses of riboflavin and carnitine; however, clinical effect is variable.

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Case #21

Case Presented by Michelle Bain, MD
and Keith A. Lopatka, MD

History of Present Illness:
This 8-year-old boy presented with periods of pruritic, dry and scaly skin of the face, neck, and legs since age 2. The mother states that the boy was born with normal skin and did start having dry skin until the age of two. He has been treated with 12% ammonium lactate lotion and hydrocortisone 1% cream with only mild improvement.

Past Medical History:
Seizure disorder

Medications:
Phenytoin
20% urea lotion BID to areas of arms, legs, face, and trunk

Allergies:
No known drug allergies

Family History:
No history of skin disorders

Social History:
Doing well in school

Review of Systems:
No visual problems

Physical Examination:
The patient had hyperpigmented, adherent scale affecting the mid-forehead, nose, and nasolabial folds. Similar dark scale extensively involved the trunk and extremities with sparing of the axillary vaults, and antecubital and popliteal fossae. The scale over the shins was lamellar in configuration. The palms and soles were spared. The testes were descended bilaterally.

Laboratory Data:
04/03 Fluorescent *in situ* hybridization (FISH) analysis demonstrated deletion of the *steroid sulfatase* (STS) gene in band Xp22.3

Diagnostic Procedures and Tests:
06/03 Ophthalmologic examination revealed clear corneas bilaterally on slit lamp exam along with normal fundi, normal muscle balance, and normal vision.

Histopathology:
04/03 R trunk (S03-2963): The epidermis shows marked hyperkeratosis with focal parakeratosis, irregular acanthosis, and papillomatosis. The upper dermis shows a perivascular lymphocytic infiltrate.

Diagnosis:
X-linked ichthyosis

Treatment and Course:
The patient was treated with a trial of 12% ammonium lactate lotion with little improvement. Currently, the patient has been undergoing a trial of twenty percent urea lotion twice a day with good improvement. The patient and his family have been referred for genetic counseling.

Discussion:
X-linked ichthyosis is a relatively common genetic disorder of keratinization, affecting approximately 1 in 6000 males. It is inherited in an X-linked recessive pattern manifesting almost exclusively in males. The abnormal cutaneous scaling seen in this disorder is the result of a deficit in the steroid sulfatase enzyme (STS) caused by a deletion at Xp22.3 (distal part of the short arm of the X chromosome). Steroid sulfatase deficiency results in failure of removal of cholesterol sulfate in the stratum corneum, leading to persistent cell cohesion and interference with the normal process of desquamation.

X-linked ichthyosis is characterized clinically by generalized scaling of the skin with large, polygonal, dark brown scales more prominent on the extensor aspects of the limbs. Oxidation of keratin produces the dark appearance of the scales and gives patients a dirty appearance. The symmetrical distribution of scale is more evident on the extensor aspects of limbs, especially on the lower extremities. The scale may vary in size, but larger scale is generally present on the lower extremities versus the upper trunk. The palms and soles are nearly always spared, and the hair and nails are normal. Extracutaneous manifestations are frequent and include corneal opacities on the posterior capsule or Descemet's membrane in about 10-15% of affected males and female carriers. Cryptorchidism occurs in 12-15% of affected boys.

The diagnosis of this disorder depends on clinical appearance and confirmation with biochemical or genetic analysis. Histological examination of affected skin is nondiagnostic. The newer diagnostic techniques are reliable and involve analysis of genetic material with the use of Southern blot, *in situ* hybridization, and PCR. Biochemical analysis consists of demonstrating STS deficiency in tissue, either by demonstrating lack of enzymatic activity or by measuring an increase in one of its substrates.

Treatment of this disorder initially involves topical keratolytics, emollients, and hydrating agents including urea, propylene glycol, sodium chloride, and lactic acid. Warm weather may also help to reduce scale. Recent studies have suggested a potential role for topical tazarotene and calcipotriol in reducing scale. In severe forms of ichthyoses, systemic retinoids have been effective.

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Case #22

Case Presented by Sophie Worobec, MD
and Roopal Vashi Kundu, MD

History of Present Illness:
This 18-year-old Hispanic man presented with a scalp lesion since birth. The lesion was first noted as a dome-shaped nodule with a slightly irregular surface. It has gradually increased in size and developed alopecia over the growth. The lesion is nonpruritic and nontender.

Past Medical History:
No significant past medical history

Medications:
None

Allergies:
No known drug allergies

Family History:
Noncontributory

Physical Examination:
The patient has a 7 x 7 cm flesh-colored multinodular plaque on the right parietal scalp. Smaller adjacent plaques, including one on the right temple and right preauricular area, are also present.

Histopathology:
05/03 R scalp (S03-4049): The epidermis shows mild acanthosis, orthohyperkeratosis, and slight papillomatosis. In the dermis, multiple cystic structures containing keratin are seen lined by stratified squamous epithelium. Granular cells are seen in the innermost part of the lining. Hair shafts are seen within the cyst. The stroma shows fibrosis mainly around the cystic structures and adnexa.

Diagnosis:
Folliculosebaceous cystic hamartoma

Treatment and Course:
The patient is currently being evaluated for surgical treatment options.

Discussion:
Folliculosebaceous cystic hamartoma (FSCH) is a unique benign tumor formed from follicular, sebaceous, and mesenchymal elements. In 1991, Kimura et al. first described FSCH, appearing as flesh-colored exophytic papules or nodules, in 5 patients. Fewer than 25 cases are reported.

Folliculosebaceous cystic hamartoma is most commonly located on the head, especially the central part of the face and nose. A genital variant has also been reported. The age of onset is variable, but many FSCH lesions begin in childhood. The giant variant (several centimeters in size) appears to be congenital and enlarges during puberty. All reported cases of FSCH have been benign and no association with visceral neoplasms or Muir-Torre syndrome has been

identified. The etiology of FSCH is unknown; it has been proposed that folliculosebaceous cystic hamartoma may represent the final stage of trichofolliculoma.

The clinical presentation is not unique. However, the histopathologic features of FSCH are distinct and are comprised of prominent epithelial and mesenchymal components. Characteristic lesions show a central dilated follicular cystic structure with numerous sebaceous lobules arising from its wall. The cyst is lined by a stratified squamous epithelium. Rudimentary or mature hair structures may also be seen. Dense fibrous stroma, dermal collagen bundles, and adipose tissue are often found encompassing the cystic structures. Variable vascular and neural proliferation may occur. One report described perifollicular mucinosis. The main histologic differential diagnosis includes sebaceous trichofolliculoma, fibrofolliculoma, perifollicular fibroma, and dermoid cysts.

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