Table of Contents

Case # 1

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

History of Present Illness:
This 60-year-old African American male presented in December 2003 with a history of intermittently flaring discoid lupus erythematosus since age 27. Lesions involved the scalp, face, arms, chest, and back. On presentation, he complained of a severe exacerbation with the development of new painful deep lesions adjacent to the DLE lesions. He was using clobetasol ointment BID and SPF 35 sunblock. His history included intolerance to high dose prednisone secondary to severe mood changes, plaquenil-induced retinopathy, and treatment failure with doxycycline and nicotinamide.

Past Medical History:
Hemochromatosis (treated with phlebotomy in the past)
Coronary artery disease s/p stent placement
+PPD since 1970's (serial chest x-rays wnl)
Diverticulitis with fistula repair
Surgical repair of a ruptured Achilles tendon
Appendectomy

Medications:
Clobetasol ointment
Atenolol
Furosemide
Levothyroxine
Isosorbide
Felodipine
Ezetimibe
Atorvastatin

Allergies:
No known drug allergies

Family History:
Brother and aunt have discoid lupus erythematosus; mother died at age 54 from hepatic failure

Social History:
Retired police officer for the Illinois Department of Corrections; has 2 healthy daughters and 7 healthy grandchildren

Review of Systems:
Denies fever, chills, nausea, vomiting, diarrhea, constipation, muscle or joint aches; reported fatigue and transient muscle cramps with thalidomide, no paresthesias or other evidence of neuropathy

Physical Examination:
At presentation the scalp had large confluent hypopigmented atrophic plaques with peripheral hyperpigmentation and areas of erythema. There were violaceous atrophic plaques above the left

eyebrow, left cheek, and left temple with underlying and adjacent subcutaneous nodules and marked edema. There was scarring bilaterally on the cheeks and chin. He had atrophic hypopigmented plaques on the chest, central back, and upper arms. The left arm also had small, round, deep ulcerations with adjacent firm subcutaneous nodules. The legs were clear.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Aspartate aminotransferase	59 units/L	[nl: 14-50]
Alanine aminotransferase	88 units/L	[nl: 21-72]
Glucose	132 mg/dL	[nl: 70-110]

The following laboratory studies were normal or negative:

Antinuclear antibody	Complete blood count x 3
Liver function tests	Lipid profile x 2
Erythrocyte sedimentation rate	CH50
Protein C	Protein S
Anticardiolipin antibodies	
Basic metabolic panel (except glucose)	

Diagnostic Procedures and Tests:

8/03 Ophthalmologic exam: wnl

3/04 Neuropathy Symptom Score: normal study including right median, ulnar, peroneal and posterior tibial nerves, normal right brachial plexus latencies, normal femoral and sural nerve latencies, normal amplitudes.

3/04 Electromyelogram: normal study of right upper and lower limbs, motor unit potentials normal.

3/04 Clinical correlations: normal study of the right upper and lower limbs, no evidence found for a radiculopathy, myopathy, generalized polyneuropathy or entrapment neuropathy.

3/04 DEXA scan: wnl

6/04 Venous dopplers of lower extremities: wnl

6/04 Cardiac echocardiogram: wnl

6/04 Stress test: wnl

Histopathology:

12/03 Cheek: The epidermis shows thinning and flattening of the rete ridges. Follicular plugging is present. There is thickening of the epidermal and follicular basement membrane. There are pools of dermal mucin, confirmed by colloidal iron stain. A dense, diffuse infiltrate of lymphocytes is present in the dermis. Occasional plasma cells are also observed. There is a lobular panniculitis with hyalinized connective tissue and mucinous degeneration. Rare pseudomembranous changes are also seen.

Diagnosis:

Discoid lupus erythematosus with lupus panniculitis

Treatment and Course:

The patient had an incisional biopsy of an inflamed nodular lesion on the forehead, which was histologically suspicious for lupus profundus. There was marked improvement with low dose prednisone (10-20mg) and thalidomide 50 mg 5x/week. There has been no evidence of peripheral neuropathy. Clobetasol ointment was recently discontinued in favor of tacrolimus 0.1% ointment BID.

Discussion:

Lupus erythematosus panniculitis is characterized by deep dermal and subcutaneous nodules 1-4 cm in diameter; these are rubbery-firm, sharply defined and usually non-tender. The lesions occur most often on the head, face or upper arms. Many patients have DLE at other sites, or less often in the skin overlying the panniculitis. In these cases, the condition is sometimes referred to as lupus profundus. The panniculitis tends to follow a chronic course with recurrences and remissions. Resolution is often accompanied by large areas of depression and lipoatrophy. Histologically, there is a mostly lobular lymphocytic panniculitis, hyaline degeneration of the fat, hyaline papillary bodies, and dense, sharply circumscribed lymphocytic nodules in the lower dermis and fat; germinal centers are a sign of chronicity in long-standing lesions. Treatment with antimalarials is usually successful, but this was not an option for our patient given his history of retinopathy while on hydroxychloroquine. Due to his history of hemochromatosis and hepatic abnormalities, other immunosuppressive medications were also relatively contraindicated.

Thalidomide has been shown to be effective in various forms of cutaneous lupus that have been resistant to other therapies. It is an immunomodulatory drug that inhibits the production of tumor necrosis factor-alpha, a significant UVB susceptibility mediator, by enhancing TNF-α mRNA degradation. Evidence suggests thalidomide also selectively induces the activation of Th2 cells and/or inhibits Th1 cells, which are found in the cellular infiltrates of DLE. Thalidomide also has anti-inflammatory effects including decreased neutrophil chemotaxis and phagocytosis. Doses of 50-100 mg daily have shown similar efficacy to doses of 400 mg daily, with fewer adverse effects. Relapses following cessation of thalidomide are common, and may occur weeks to months after the drug is stopped. Common side effects include drowsiness, constipation and mood changes. Peripheral neuropathy may occur, and in this case the drug should be tapered or stopped. It usually presents as mild proximal muscle weakness with symmetric painful paresthesias of the hands and feet, often with lower limb sensory loss. Electrophysiologic studies may also detect asymptomatic disease. While motor weakness usually recovers after drug cessation, the sensory dysfunction may be permanent. The true incidence of peripheral neuropathy is unclear. Small studies of cutaneous lupus patients receiving thalidomide for their disease have shown rates ranging from 0-50%. The teratogenicity of thalidomide is well known and strict birth control regimens must be enforced for any woman of child-bearing age who is prescribed this medication. In addition, men receiving thalidomide must always wear condoms during intercourse, and their partners must take oral contraceptives, as the drug is detectable in semen.

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Case # 2

Case Presented by Michelle Bain, MD
and Marianne Schachter Rosen, MD

History of Present Illness:
This 3-year-old African American female presented at age 6 weeks for evaluation of a rash on the face, arms, and legs. According to her mother, the patient was born with red patches on her face. Subsequently, at age 5 weeks, new round targetoid lesions began to appear on the baby's frontal scalp, forehead, arms and legs.

Past Medical History:
The patient was born at 38 weeks gestation. Her mother had ruptured membranes four days prior to delivery and had Group B streptococcus colonization. Both mother and patient were treated with antibiotics.

Medications:
None

Allergies:
No known drug allergies

Family History:
No history of lupus or other autoimmune disorders

Social History:
Patient has achieved developmental milestones

Review of Systems:
No fevers or chills, no irritability, no vomiting, eating well, gaining weight appropriately, no mucosal involvement. Normal growth and development.

Physical Examination:
The patient had extensive erythematous coalescent plaques on the face, especially around the eyes, on the nose, lower forehead, and philtrum. The medial cheeks had focal areas of erosion and crusting. On the upper forehead, frontal scalp, left forearm, bilateral lower legs, left anterolateral thigh and bilateral soles were approximately 15 erythematous targetoid plaques with dusky to flaccid bullous centers. Cardiac exam was unremarkable. Upon re-examination one year later, there remained hypopigmented patches around her eyes, nose and cheeks with no atrophy, and her arms had faint hyperpigmented patches.

Laboratory Data:
The following laboratory studies were abnormal or positive:
10/25/02:

ANA	1:320	(nl: none detected)
RNP/Sm Ab	6 units	(nl: 0-19)
Smith Ab	5 units	(nl: 0-19)
Anti-SSA	429 units	(nl: 0-19)
Anti-SSB	7 units	(nl: 0-19)
Anti ds-DNA	none detected	(nl: none detected)

9/19/03:

ANA	none detected	(nl: none detected)
RNP/Sm Ab	0 units	(nl: 0-19)
Smith Ab	0 units	(nl: 0-19)
Anti-SSA	0 units	(nl: 0-19)
Anti-SSB	0 units	(nl: 0-19)

The following laboratory studies were normal or negative:
Complete blood cell count

Patient's mother: 11/15/02:

ANA	1:1280	(nl: none detected)
RNP/Sm Ab	4 units	(nl: 0-19)
Smith Ab	4 units	(nl: 0-19)
Anti-SSA	230 units	(nl: 0-19)
Anti-SSB	22 units	(nl: 0-19)
Anti ds-DNA	none detected	(nl: none detected)

Histopathology:
10/02 L thigh (S02-10257): The epidermis shows hyperkeratosis and parakeratosis with spongiosis and focal acanthosis. There is focal vacuolar degeneration of the basal cell layer, as well as basement membrane thickening. There are scattered dyskeratotic cells within the epidermis. In the dermis, there is a perivascular and interstitial mononuclear infiltrate with scattered nuclear dust. There are extravasated red blood cells and thickening of vessel walls.

Diagnosis:
Neonatal lupus erythematosus

Treatment and Course:
The patient was treated with cephalexin and topical mupirocin for secondary impetiginization of the lesions of the face. She was also treated with triamcinolone 0.1% ointment for the lesions on the body and hydrocortisone 2.5% ointment for affected areas on the face once the infection was treated. She also used tacrolimus ointment for the face. A pediatric cardiologist was consulted to rule out congenital heart block but the patient's mother did not take her to the appointment. Strict sunlight avoidance was stressed. It was recommended for the patient's mother to see her primary care doctor and have her labs checked for connective tissue disease, which were positive as above, although she was asymptomatic. The patient's lesions resolved leaving post-inflammatory hyper- and hypopigmentation.

Discussion:
Neonatal lupus erythematosus (NLE) is a disease of the developing fetus and neonate characterized by lupus skin lesions and/or isolated congenital heart block. These infants are generally female and born to mothers with anti-Ro (SSA) and/or anti-La (SSB) antibodies. Few mothers have U1RNP antibodies. Mothers may or may not show features of connective tissue disease at the time of birth of the affected infant. It has been estimated that an infant born to a mother with anti-Ro antibodies has a 1 in 20 chance of developing NLE syndrome. Isolated complete congenital heart block (CCHB) is rare, occurring in 1/15,000-20,000 live births and NLE accounts for 90% of those cases. In addition to the cutaneous lesions and congenital heart block, these patients can have thrombocytopenia, transient hepatic involvement, aplastic anemia, and neurologic symptoms secondary to nervous system vasculopathy.

Clinically, the cutaneous lesions present at birth or within the first 12 weeks of life. Lesions are often induced or exacerbated by sun exposure or may occur after phototherapy for neonatal jaundice. They are usually discrete annular inflammatory lesions resembling those seen in subacute cutaneous lupus erythematosus (SCLE) and are usually most prominent on the face, classically around the eyes, giving an "owl-like" appearance. New lesions may continue to develop for several months, but rarely arise beyond 6 months, consistent with the disappearance of maternal antibodies from the infant's circulation. The lesions tend to be transient and resolve without scarring. Some patients have persistent hyperpigmentation, hypopigmentation, epidermal atrophy, and telangiectasias. Biopsy of a lesion will show typical changes seen in SCLE, such as epidermal basal cell damage and a mild mononuclear cell dermal infiltrate. Particulate deposits of IgG are seen on direct immunofluorescence.

The characteristic cardiac lesion is isolated congenital cardiac heart block (CCHB). Most patients have third degree heart block at presentation, although progression from second to complete heart block has occurred. 40-67% of patients with heart block require pacemaker insertion, usually before their eighteenth birthday. Mortality from complete heart block is approximately 15% in the neonatal period, with another 10-20% mortality due to pacemaker complications. The histopathology of CCHB suggests an intrauterine inflammatory lesion, which results in subsequent scarring with fibrosis. Hepatic involvement occurs in 15% of patients with NLE. Patients may have hepatomegaly, with or without splenomegaly, with a cholestatic picture. Hepatic transaminases can be mildly to moderately elevated, but may be normal. There does not seem to be any long-term consequences from the neonatal liver disease. Hematologic abnormalities may be seen, including anemia, neutropenia, and thrombocytopenia.

Treatment of cutaneous lesions of NLE is usually with mild topical corticosteroid creams, topical tacrolimus, or topical pimecrolimus. Sunlight should be avoided. Aggressive treatment is not necessary as the lesions generally resolve without scarring. Pulsed dye laser has been reported to be effective for the treatment of telangiectasias. Pregnancies of women with known anti-Ro or anti-La antibodies should be monitored closely for CCHB with close fetal heart rate monitoring and fetal echocardiograms. If intrauterine bradycardia is noted, the mother should receive dexamethasone for 2-4 weeks. The fetal echo is to look for signs of cardiac failure, hydrops fetalis and development of oligohydramnios secondary to the corticosteroid therapy.
The later development of an autoimmune disease in a patient with a history of NLE likely reflects the genetic predisposition of a child to have a similar disease to their mother rather than being the result of having had NLE.

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Case # 3

Case Presented by David Eilers, MD
and Alexander Berlin, MD

History of Present Illness:
This 73-year-old Caucasian male has a long history of extensive pyoderma gangrenosum that originally started in September 2001, 4 months after brachytherapy for prostate cancer.

Throughout the years, the patient has had multiple treatment regimens. These included wound care with topical steroids, topical antibiotics, and calcium alginate dressings; oral and several courses of pulsed intravenous corticosteroids (3-5 g of intravenous solumedrol over 3-5 days), multiple oral antibiotics (including clindamycin, levofloxacin, doxycycline, and long-term bactrim for possible chronic prostatitis), dapsone 100 mg daily (no improvement), two trials of etanercept 25 mg SQ weekly (both times resulting in congestive heart failure), mycophenolate mofetil 1 g bid (still taking), cyclosporine up to 200 mg po bid (stopped due to elevated blood pressure), methotrexate (still taking), leflunomide (no improvement), IVIG (stopped before infliximab was started), and thalidomide 100 mg daily (stopped secondary to lower leg edema and abdominal bloating). The patient was unable to tolerate compression stockings.

In August 2004, the patient was started on infliximab protocol (5 mg/kg intravenous injections with induction at weeks 0, 2, and 6, followed by maintenance every 8 weeks) with methotrexate 7.5 mg po weekly to prevent the development of antibodies to infliximab.

Past Medical History:
Rheumatoid arthritis
Osteopenia with lumbar spine compression fractures
Chronic osteomyelitis
History of prostate adenocarcinoma s/p brachytherapy
Hypertension
Nonischemic cardiomyopathy with ejection fraction 40%
Paroxysmal atrial fibrillation

Medications:
Infliximab 5 mg/kg IV q 8 weeks (maintenance dose)
Methotrexate 7.5 mg po q week
Mycophenolate mofetil 1000 mg po bid
Metronidazole gel to ulcers bid
Calcium alginate dressings to ulcers bid
Betamethasone dipropionate around ulcers bid
Atenolol 12.5 mg po qhs
Furosemide 160 mg po bid
KCl 20 mEq po bid
Digoxin 0.125 mg po qd
Warfarin 5 mg po qd
Simvastatin 40 mg po qd
Tamsulosin 0.4 mg po qd
Docusate sodium 100 mg po bid
Fentanyl 100 mcg/hr patch q 3 days
Hydrocodone 5 mg/acetaminophen 500 mg 2 tabs po q 6 hours prn

Teriparatide 20 mcg sq qd
Ergocalciferol 50000 Unit po biw
Folic acid 400mg po qd
Loratadine 10 mg po qd

Allergies:
Penicillin – patient developed rash

Family History:
Grandmother with rheumatoid arthritis, sister with lupus

Social History:
Quit smoking 12 years ago, occasional alcohol

Review of Systems:
No fevers, no chills, no nausea, no shortness of breath, no chest pain

Physical Examination:
Prior to the initiation of the infliximab therapy, the patient had pink scarred plaques with erythema and superficial ulcerations with discharge on the right upper arm, left abdomen, right chest, and buttocks. Bilateral lower extremities showed edema, severe deformities of the ankle joints, and multiple sharply-demarcated irregular ulcers with undermined red to violaceous rolled borders and red bases.

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

Hemoglobin	9.7 g/dL	[nl: 12-16]
Erythrocyte sedimentation rate	80 mm/hr	[nl: 0-20]
TSH	1.49 uIU/mL	[nl: 0.7-1.5]
Serum protein electrophoresis		
Alpha-1	0.22 g/dL	[nl: 0.1-0.21]
Beta	1.24 g/dL	[nl: 0.58-1]
Otherwise normal, interpreted as consistent with acute inflammatory pattern		

The following laboratory studies were normal or negative:

Bacterial wound cultures	Blood cultures
Basic metabolic profile	Liver function tests
Creatinine	Lipid profile
White blood cell count	Urinalysis
Hepatitis B and C antibody screen	Urine protein electrophoresis
C3, C4	p-ANCA, c-ANCA

Diagnostic Procedures and Tests:
5/04 CT chest/abdomen/pelvis: no chest, abdominal, or pelvic adenopathy, numerous radioactive seeding present at prostate gland
6/04 L ankle 3 views: severe degenerative changes. Medial tibial cortex is thickened and mildly irregular. This is deep to apparent soft tissue defects

Histopathology:
06/03 L flank: Epidermis is unremarkable. Upper and mid dermis show perivascular and interstitial infiltrate, which consists of numerous neutrophils, few lymphocytes and

histiocytes, and occasional eosinophils. Lower dermis shows minimal scattered fibroblasts. Blood vessels show endothelial cell swelling with no fibrin deposits.

Diagnosis:
Recalcitrant pyoderma gangrenosum, ulcerative type

Treatment and Course:
Following clearance from cardiology (given the patient's history of congestive heart failure), the patient was treated with infliximab 5 mg/kg intravenously at weeks 0, 2, and 6, followed by injections every 8 weeks, together with methotrexate 7.5 mg po weekly. Following infliximab induction therapy, lesions on the upper body became scarred cribriform plaques with no active disease, while the lower extremity ulcers started to decrease in size and became less tender.

Discussion:
Pyoderma gangrenosum (PG) is an uncommon skin disorder with highest incidence between the ages of 25 and 55 years and with no clear gender preponderance. Based on clinical presentation, PG is frequently subdivided into ulcerative, pustular, bullous, or vegetative types. Fifty percent of patients with PG have an underlying systemic disorder. The most frequent systemic association of PG is inflammatory bowel disease. Up to 5% of those patients develop typical ulcerative or pustular lesions. Other associated conditions include rheumatoid arthritis and other rheumatic diseases, plasma cell dyscrasias, and other hematologic disorders.

The diagnosis of PG is typically based on clinical presentation. The histological findings are usually non-diagnostic. While it is frequently grouped with neutrophilic dermatoses, such as Sweet's syndrome, some authors believe that a lymphocytic infiltrate is the earliest finding in lesions of PG. Nonetheless, extensive dermal neutrophilic infiltrate, sometimes with abscess formation, is observed in PG. As well, a leukocytoclastic vasculitis with fibrinoid degeneration of blood vessels can be seen in up to 40% of patients.

The etiology of PG is unclear. Immunological factors have been implicated and such theories are supported by the response of the disease process to immunosuppressive medications. Since neutrophils are frequently thought to be involved in the pathogenesis of PG, agents that modify neutrophil migration or function, such as dapsone, colchicine, and clofazimine, have frequently been used for the treatment of PG. The role of T lymphocytes in the pathogenesis of PG is uncertain, but is likely important, if not central, since many of the available treatments decrease the number of circulating lymphocytes. Such treatment options include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. Alternatively, disease activity can be modified through alteration of lymphocyte function. This can be done either non-specifically, such as with the use of topical or oral corticosteroids, which inhibit multiple cytokine-mediated pathways, or through inhibition of specific cytokines. Thalidomide benefits patients with PG, suggesting a possible role for tumor necrosis factor-alpha (TNF-α) in the development of lesions. Indeed, higher levels of TNF-α have been observed in some patients with PG. Surprisingly, however, some investigators have found higher levels of TNF-α, as measured by ELISA following TNF inhibition. This was attributed to the rise in complexed or inactive TNF.

With the advent of biologic response modifiers, several newer treatments have been tried. Those therapies that are directed at TNF-α inhibition, such as etanercept and infliximab, have been found to be efficacious in the treatment of PG. Infliximab is a chimeric antibody consisting of a variable domain from a murine antibody and constant region from a human IgG1. Infliximab binds both free and membrane-bound TNF-α. While the majority of published case reports and

studies on the use of infliximab have involved patients with underlying inflammatory bowel disease, its efficacy in cases with other or no underlying conditions has been demonstrated as well.

The role of TNF-α in the pathogenesis of PG needs to be elucidated further and additional cytokines will likely be implicated in the future.

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Case # 4

Case Presented by Iris Aronson, MD
and Inderjit Gill, MD

History of Present Illness:
This 33-year-old Caucasian woman presented for evaluation of a rash on her lower legs present for approximately one year. The rash initially began during the third trimester of her second pregnancy with a single lesion on her left ankle. It worsened after delivery with lesions appearing on both lower extremities and extending proximally to the mid-calf region. She complained of severe pain, itching, and a burning sensation. Her primary care physician started her on gabapentin and oxycodone, with minimal improvement in symptoms. She had also tried topical hydrocortisone; however, this medication caused increased burning and was discontinued.

Past Medical History:
Psoriasis

Medications:
Pentoxifylline 400mg BID
Aspirin 81mg QD
Niacin 125mg QD

Allergies:
Penicillin
Seafood

Family History:
Father and paternal grandfather had a history of unknown skin cancer and died from myocardial infarction
No history of connective tissue diseases or autoimmune diseases

Social History:
Smokes ½ pack cigarettes/day, occasionally drinks alcohol, denies illicit drug use
Two healthy children; history of one miscarriage at 6 months due to preterm labor

Review of Systems:
Denies headache, fever, nausea, vomiting, respiratory complaints, chest pain, gross hematuria, weight changes, joint pain, muscle weakness, photosensitivity, or fatigue

Physical Examination:
The patient had purpura in a livedoid pattern with surrounding hyperpigmentation on bilateral ankles and dorsal feet. There were several superficial erosions with serous crusting. Her sensation to light touch was diminished at the distal toes.

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

Urinalysis(9/04)	Trace Protein	[nl: negative]
	Few Bacteria	[nl: none]

The following laboratory studies were normal or negative:

Comprehensive metabolic panel	Thyroid stimulating hormone

Liver function test	Complete blood count
Sedimentation rate	Serum protein electrophoresis
ANA	Anti-dsDNA
Rheumatoid factor	C-Reactive protein
Serum cryoglobulin	Rapid plasma reagin
Proteinase-3 antibody (P-ANCA)	Uric acid
Myeloperoxidase antibody (C-ANCA)	Urine Culture
Hepatitis C antibody	Hepatitis A IgM antibody
Hepatitis B surface antigen	Hepatitis B core IgM antibody

Diagnostic Procedures and Tests:

6/04 Venous duplex of bilateral lower extremities: no DVT; no venous reflux visualized; however plethysmography demonstrates evidence of reflux in the deep venous system on the right side

9/04 Arteriogram of abdomen and bilateral lower extremities: normal

9/04 EMG of lower extremity: bilateral peripheral neuropathy involving sensory nerves; no evidence of myopathy

Histopathology:

9/04 L Foot: The epidermis is acanthotic with focal scale crust, necrosis and festooning. The epidermis is separated from the dermis in some areas. There are an increased number of capillaries throughout the dermis showing wall thickening and fibrinoid degeneration with thrombotic occlusion of the lumina. Extravasated red blood cells are seen. The inflammatory cell infiltrate is sparse.

Diagnosis:

Livedoid vasculitis

Treatment and Course:

The patient was started on pentoxifylline 400mg QD (increased to 400mg BID), hydrocortisone 2.5% ointment bid, and daily compression stockings. She began complaining of worsening sharp pains in her legs. ASA 81mg QD and Niacin 125mg QD were added to her regimen, as her hypercoaguability workup was completed.

Discussion:

Livedoid vasculitis, also known as segmental hyalinizing vasculopathy, and atrophie blanche, is a thrombo-occlusive vasculopathy that was first described in 1967. It is a disease that predominantly affects the lower extremities of middle-aged women. Lesions are characterized by chronic, recurrent painful ulcers over the lower extremities that may begin as purpuric papules or plaques. These ulcers slowly heal leaving porcelain white scars (atrophie blanche) with surrounding hemosiderin-induced hyperpigmentation, telangectasia, and livedo racemosa. Histological findings include segmental hyalinization, endothelial proliferation, fibrin deposition, and thrombus formation in the vessels of the papillary and superficial reticular dermis. Fibrin, C3, and IgM can often be found in the vessel wall. There also may be perivascular extravasation of RBCs. There is little to no inflammation seen in dermis and vascular walls, which distinguishes this disease process from a true vasculitis.

Although the disease may be idiopathic, livedoid vasculitis has been described in combination with multiple systemic diseases (e.g. systemic lupus erythematosus) which may create an underlying hypercoaguable environment. The exact etiopathogenesis of livedoid vasculitis is unknown. However, the disease is believed to result from aberrations in the coagulation system.

This has been supported in the literature by the association of livedoid vasculitis with protein C deficiency, factor V Leiden mutation, prothrombin G20210A gene mutation, anti-phospholipid antibodies, elevated fibrinopeptide A levels, defective release of vascular plasminogen activator, anti-thrombin III deficiency, and decreased thrombomodulin expression.

Based on this probable mechanism, most of the treatment strategies target the coagulation system by increasing fibrinolytic activity, inhibiting thrombus formation, or inducing vasodilatation. Anticoagulants, either alone or in combination, have been widely used. Treatments include aspirin, dipyridamole, pentoxifylline, low-dose heparin, low molecular weight heparin, beraprost sodium, and tissue plasminogen activator (tPA). Vasodilators such as nicotinic acid, nifedipine, and sulfasalazine have been used to enhance oxygen delivery to the ischemic tissue. Fibrinolytic agents, phenformin, ethylestrenol, prostacyclin, and danazol have been used to target the thrombus formation in the papillary and reticular dermis. In small studies, PUVA therapy has been shown to be of benefit for patients that have failed alternative therapies. Hyperbaric oxygen therapy can be extremely helpful in reducing patient discomfort and healing the ulcerations of the livedoid vasculitis. Hyperbaric oxygen accelerates angiogenesis and fibrinolysis, inhibits collagen formation, and increases delivery of oxygen to tissue. Several recent studies have documented the dramatic response of recalcitrant ulcers to IVIg. Although the exact mechanism of IVIg's effect in livedoid vasculitis is not known, it is thought to involve regulation of cytokine production, inhibition of complement-mediated damage, and blockade of the Fas receptors by anti-Fas antibodies. Tissue plasminogen activator is also being studied as a therapeutic option, as it has been effective in treating other vascular occlusive disease processes.

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Case # 5

UNKNOWN CASE

Case Presented by Paul Storrs, MD
and Roopal Vashi Kundu, MD

Case # 6

Case Presented by Iris Aronson, MD
and Keith A. Lopatka, MD

History of Present Illness:
This 45-year-old woman presented with a six year history of a chronic rash of the trunk and extremities. The patient described the rash as hives and complained of an associated intense itching and burning. The patient stated the lesions can last up to four to five days and at times leave her with discoloration. She tried numerous topical corticosteroids and topical urea without improvement.

Past Medical History:
Irritable bowel syndrome
Raynaud's phenomenon
Proteinuria
Cataract, left eye
Osteoporosis
Pleurisy
Pneumonia
Lung calcification

Medications:
Ceftirizine 10 mg QD
Celecoxib 200 mg QD
Hydroxychloroquine 200 mg QD

Allergies:
Oral prednisone (CNS side effects)

Family History:
Father died of lung cancer at age 46, mother died of breast cancer at age 46
Two children with history of numerous infections

Social History:
Smokes 1 pack of cigarettes per day. Former professional ice skater.

Review of Systems:
Swelling of the feet, hands, knees. Intermittent numbness of the fingertips and feet.

Physical Examination:
The chest showed four well demarcated pink, erythematous blanchable plaques without scale. The arms and back had similar smaller plaques. The feet showed poorly demarcated erythematous scaly patches with areas of hemorrhagic crusting at the medial and lateral aspects.

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

Antinuclear antibody x2	1:320, 1:40	[nl: negative]
Complement		
C3 x3	61, 65, 79 mg/dL	[nl: 90-180]

Total (CH50) 10/04	43 mg/dL	[nl: 60-155]
Erythrocyte sedimentation rate	22 mm/h	[nl: 0-15]
Protein S	55 %	[nl: 60-140%]
24 hour total protein urine x2	260, 528 mg	[nl: <150 mg/24 hr]
Urinalysis		
Protein	3+	[nl: negative]

The following laboratory studies were normal or negative:

Alpha 1 antitrypsin
Antinuclear antibody
Antineutrophil cytoplasmic antibodies
Anticyoplasmic antibodies (SSA; SSB; Smith; RNP)
Basic metabolic panel
Cardiolipin antibodies IgG and IgM
C-reactive protein
Complement (C4)
Cryoglobulin screen
Glucose-6-phosphate dehydrogenase
Hemoglobin
Hepatitis B surface antigen
Hepatitis C antibody negative
Liver function tests
Lupus anticoagulant
Myeloperoxidase antibody
Partial thromboplastin time
Protein C
Proteinase 3 antibody
Rapid plasma reagin
Serum protein electrophoresis
Thyroid stimulating hormone
Twenty four hour urine creatinine

Histopathology:

9/03 Back: The epidermis shows diffuse vacuolar degeneration. There is thickening of the basement membrane. The capillaries in the papillary and reticular dermis show fibrinoid degeneration of the vessel walls with a perivascular infiltrate of lymphocytes, eosinophils, and neutrophils with nuclear dust. There is an extensive interstitial infiltrate of neutrophils. This neutrophilic infiltrate is also surrounding the sweat glands.

Immunopathology:

9/03 Back: faint granular deposition of C3, IgG, IgM along the basement membrane and papillary dermis.

Diagnosis:

Hypocomplementemic urticarial vasculitis

Treatment and Course:

This patient was recently started on ceftirizine and hydroxychloroquine daily. The patient has been seen by a pulmonary specialist who concluded that the patient has no pulmonary abnormalities associated with urticarial vasculitis. The patient is currently working toward a goal of smoking cessation.

Discussion:

Approximately 10% of patients with chronic urticarial lesions have urticarial vasculitis (UV), which can be a benign process unassociated with underlying disease or be a manifestation of serious illness and cause significant morbidity. In the majority of patients, UV is the presenting manifestation of a systemic disease, or it develops as a component of a chronic systemic illness. When associated with normal serum complement levels, urticarial vasculitis is typically benign and idiopathic. When it is associated with low serum complement levels, hypocomplementemic urticarial vasculitis (HUV) often indicates an underlying, potentially serious illness like systemic

lupus erythematosus, hypocomplementic urticarial vasculitis syndrome (HUVS), mixed cryoglobulenemia, or Sjogren's Syndrome.

Urticarial vasculitis is a manifestation of an inflammatory injury to capillaries and postcapillary venules of the skin. The skin lesions appear as erythematous, occasionally indurated, wheals that may contain foci of purpura. As compared to urticarial lesions, the lesions of urticarial vasculitis typically persist for greater than 24 hours and resolve with faint residual hyperpigmentation, indicating red blood cell extravasation. The lesions tend to be asymptomatic or painful, with a stinging or burning sensation. The lesions are typically smaller (0.5-5 cm in diameter) as compared to the larger 10 cm or greater lesions seen in urticaria. Other skin manifestations include angioedema, macular erythema, livedo reticularis, nodules, and bullae. The episodes of urticaria are chronic, range in duration from months to years, and vary in frequency. Approximately 70% of affected individuals are women. The prevalence of this disorder remains unknown.

Systemic manifestations include constitutional symptoms (fever, malaise, fatigue); arthralgia, occasionally arthritis, and very rarely Jaccoud's arthropathy; angioedema and dermal ulceration; iritis, uveitis, and episcleritis; pericarditis and cardiac valve disease; pseudotumor cerebri and peripheral neuropathy; pleuritis and obstructive lung disease; glomerulonephritis and interstitial nephritis; digital infarction and Raynaud's phenomenon. Not all of these organ systems are involved in an individual patient with HUV. Association with an underlying disease (secondary UV) or absence of such disease (primary, idiopathic UV) determines the presence and pattern of systemic involvement.

The most florid urticarial vasculitis lesions include most features of leukocytoclastic vasculitis: injury and swelling of endothelial cell nuclei with disruption of vessel wall, extravasation of red blood cells, perivascular nuclear dust, and fibrin deposition; and a neutrophilic or mixed infiltrate of neutrophils and lymphocytes with occasional eosinophils.

Most cases of normocomplementemic UV (NUV) are idiopathic. Secondary NUV has been described in a small number of patients with monoclonal gammopathy, neoplasia, serum sickness, viral infections (Hep B/C/EBV) and sensitivity to ultraviolet light or repeated cold exposure. Classification of idiopathic urticarial vasculitis based on serum complement levels is useful but arbitrary, because the relationship between idiopathic NUV, HUV, and HUVS has not been defined. Hypocomplementemic urticarial vasculitis syndrome (HUVS) is an uncommon disorder that resembles systemic lupus erythematosus. HUVS is a syndrome of urticarial vasculitis, arthritis or arthralgia, and serum complement activation with a marked decrease in C1q with autoantibody to C1q. It is possible that NUV may progress through HUV to HUVS. The category of HUVS would represent the sickest patients on the clinical and serologic continuum. A second possibility is that HUVS is distinct from NUV and idiopathic HUV. Under this assumption, there is no transition from NUV to HUV to HUVS. Recently, it has become clear that a small number of patients with idiopathic HUV have either an autoimmune disease that mimics SLE, namely HUVS, or a very rare disease defined by HUV, Jaccoud's arthropathy, and severe cardiac valvular incompetence.

Successful diagnosis and treatment depends on a careful initial evaluation followed by observation and repetition of appropriate diagnostic studies over time. The treatment of urticarial vasculitis begins with treatment of the underlying disease if one is identified. In both secondary and idiopathic urticarial vasculitis, the outcome of treatment with many drugs other than hydroxychloroquine, prednisone, dapsone, and immunosuppressive drugs has been variable. There are anecdotal or uncontrolled reports of successful treatment with H1, H2, and calcium

channel blockers, doxepin, indomethacin, methotrexate, colchicine, and pentoxyfilline alone or in combination. Such agents are not likely to control UV in HUVS, SLE, Sjogren's syndrome, or mixed cryoglobulinemia.

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Case # 7

Case Presented by Iris Aronson, MD
and Madhuri Ventrapragada, MD

History of Present Illness:
This 68-year-old Caucasian female with a history of pemphigus vulgaris and Guillain Barre syndrome presented with an 8 week history of erythematous edematous plaques. They appeared spontaneously and resolved within 1-2 days. The patient denied any pruritus but complained the lesions occasionally burned. Prior to presentation, she had two episodes of tongue swelling which resolved without treatment. She was diagnosed with urticaria and started on fexofenadine 180 mg qd, cetirizine 10 mg qd, and diphenhydramine 25 mg qd. Despite this regimen, new lesions continued to develop. The patient did not want to start oral prednisone for fear that it would worsen her baseline muscle weakness.

Of note, the patient developed pemphigus vulgaris in 1999 after starting accupril. She was successfully treated with prednisone, azathioprine, and 3 courses of IVIg. She has since been well controlled with azathioprine.

Past Medical History:
Pemphigus vulgaris
Guillain Barre syndrome
Hypertension
Deep vein thrombosis in the left leg
Herpes zoster

Medications:
Fexofenadine 180 mg QD
Diphenhydramine 25 mg QD
Cetirizine HCl 10 mg QD
Azathioprine 50 mg QD
Amlodipine 5mg QD
Metoprolol succinate 5 mg QD
Alprazolam .25 mg BID
Famotidine 40 mg QD
Calcium 1000 mg
Multivitamin

Allergies:
No known drug allergies

Family History:
Sister and patient's son have thyroid abnormalities
No history of other autoimmune diseases

Social History:
Denies smoking tobacco or drinking alcohol

Review of Systems:
Patient complains of frequent fatigue, and residual numbness of the fingers and toes. She denies any fevers, chills, nausea, vomiting, headache, shortness of breath or respiratory difficulties, gross hematuria, dysuria, diarrhea or constipation.

Physical Examination:
The patient has erythematous edematous wheals on her face, chest, back, arms and legs. Pt has no oral or ocular mucosal lesions.

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

CH50	<13	[nl: 31-66]
C3	54	[nl: 88-201]
C4	3	[nl: 10-40]
Pemphigus antibody	1:80	[nl: negative]

The following laboratory studies were normal or negative:

Complete blood count	Calcium
Liver function tests	Thyroid hormone
Electrolytes	Thyroglobulin antibody
ANA	Microsomal antibody
Hepatitis B	Cryoglobulins
Hepatitis C	

Histopathology:
10/04 L arm (S04-8326): The epidermis is essentially normal. The upper dermis shows diffuse edema and solar elastosis. There are infiltrates of lymphocytes, neutrophils, and eosinophils in the perivascular areas of the upper dermis. Minimal and focal fibrinoid degeneration of the capillaries are seen. Occasional leukocytoclasis is observed.

Immunopathology:
10/04 L arm (DIF): There is a broad band of IgG, IgA, and minimal C3 made up of fine speckles distributed along the upper dermis.

Diagnosis:
Hypocomplementemic urticarial vasculitis

Treatment and Course:
The patient is currently on fexofenadine 180 mg qd, cetirizine 10 mg qd, diphenhydramine 25 mg qd, and azathioprine 50 mg qd. She continues to develop new lesions.

Discussion:
Urticarial vasculitis (UV) is a disease in which patients develop urticarial lesions with histologic characteristics of leukocytoclastic vasculitis. Lesions often last more than 24 hours, may occur anywhere on the body, and leave hyperpigmentation. Patients more often complain of burning than pruritus. The histologic picture consists of blood vessel injury with infiltration by neutrophils, leukocytoclasis, and fibrinoid necrosis.

Urticarial vasculitis has been associated with connective tissue diseases such as systemic lupus erythematosus (SLE) and Sjogren's syndrome, and infections such as Hepatitis B and C, and lyme disease. It is also rarely associated with medications. UV is more common in women with a

peak incidence in the 4th decade of life. It can be either hypocomplementemic or normocomplementemic. One study showed patients with hypocomplementemic urticarial vasculitis (HUV) had a strong granular deposition along the basement membrane zone on DIF, much like what is seen in SLE. Given their clinical and histologic similarities it has been suggested that (HUV) be considered a subset of SLE.

Two major criteria for the diagnosis of hypocomplementemic urticarial vasculitis syndrome (HUVS) are urticaria and hypocomplementemia with low C1q levels and variable depression in C3 and C4 levels. Symptoms include angioedema, arthritis, glomerulonephritis, obstructive lung disease, ocular inflammation, and neurologic manifestations.

Treatment for cutaneous UV includes antihistamines and hydroxychloroquine. Systemic steroids are the main treatment modality for patients with internal involvement. Dapsone and mycophenolate mofetil are effective in treating HUV. While cyclosporine A or a combination of azathioprine and prednisone are used in treating those with HUVS. Interferon alpha may benefit patients with hepatitis C associated urticarial vasculitis.

The prognosis of urticarial vasculitis is variable. Normocomplementemic patients tend toward a benign course. Hypocomplementemic patients more commonly have systemic symptoms and progress to SLE.

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Case # 8

Case Presented by Lawrence Chan, MD, Iris Aronson, MD and Todd Johnson, MD

History of Present Illness:
This 65-year-old gentleman was diagnosed with mucous membrane pemphigoid in 1991 based on clinical and direct immunofluorescence findings. Throughout the patient's course his lesions have been limited to the ocular mucosa. He became blind due to his disease in 1993. In 1996 the patient had bilateral corneal transplants which subsequently perforated due to graft rejection. In 1996 and 1997 his vision was restored by bilateral vitrectomy and the implantation of Dohlman type keratoprostheses in each eye. Before implantation of the keratoprostheses the patient was completely blind.

Past Medical History:
Diabetes mellitus
Hypertension
Macrocytic anemia
Angina

Medications:
Dapsone 25mg BID
Metoprolol 50mg BID
Isosorbide 60mg QPM
Insulin NPH 22 units QPM
Metformin 500mg BID
Lisinopril 10mg qam, 5mg QPM
Patanol eye drop 5%
Timolol eye drop QD left eye
Latanoprost eye drop left eye QD
Polymyxin B/trimethoprim eye drop TID
Acetazolamide 500mg QD

Allergies:
Ampicillin has caused a rash, vancomycin caused red man syndrome, ciprofloxacin caused lip swelling

Family History:
Brother with diabetes mellitus type 2 and hypertension

Social History:
Internal medicine physician in India from 1961 to 1991, no alcohol, no tobacco

Review of Systems:
Consistently has blurry vision. Denies oral, nasal or genital lesions, epistaxis, hoarseness, cough, dysphagia, weight loss, dysuria, or rectal bleeding.

Physical Examination:
The patient has keratoprostheses in the right eye and left eye. The patient's visual acuity is 20/200 in the right eye and he is able to see fingers at a distance of four feet with his left eye. The skin, nasal, oral and genital mucosas are without lesions.

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

Hemoglobin	13.6	g/dl	[nl: 14-18]
Platelets	127	thous/ul	[nl: 150-400]
Prostate Specific Antigen	4.1	ng/ml	[nl: 0.0-3.4]

The following laboratory studies were normal or negative:
WBC
Electrolytes
Liver Function Tests

Diagnostic Procedures and Tests:
11/02 Liver ultrasound: normal

Immunopathology:
4/95 Conjunctiva (75-95): 2+ linear IgA at the basement membrane zone, also focal linear IgG, C3 and fibrin at basement membrane zone.

Diagnosis:
Mucous membrane pemphigoid with ocular involvement

Treatment and Course:
The patient required eight reparative surgeries to maintain his eyesight with the keratoprosetheses. Most recently the patient had a scleral patch graft placed in the right eye to prevent impending extrusion of the keratoprosthesis. The patient has been maintained on dapsone 25mg twice per day with stabilization of the disease. Higher doses of dapsone have induced leukopenia and thrombocytopenia. Although the patient's course has been complicated by several episodes of corneal melting and conjunctival infection, implantation of the keratoprostheses has afforded the patient sight for the past seven years.

Discussion:
Mucous membrane pemphigoid (MMP) is a chronic autoimmune inflammatory subepidermal blistering disorder primarily affecting any or all mucous membranes. The most commonly affected areas are the oral mucosa and conjunctiva. Scarring of the affected areas is typical but not universal. The course of the disease is usually chronic and progressive and may result in serious complications and death. Studies have shown that autoantibodies from patients with MMP may recognize a variety of different antigens present in epithelial membranes including BP 180, laminin-5, laminin-6, Beta 4 integrin and type VII collagen. According to an international consensus, detection of linear deposits of IgA, IgG or C3 at the epithelial basement membrane zone by direct immunofluorescence is one of the diagnostic criteria.

Ocular involvement in MMP is common and potentially sight threatening. Disease typically presents as unilateral or bilateral conjunctivitis that may progress insidiously to scarring. Chronic ocular involvement can result in shortened fornices, symblephara (i.e. fibrous tracts between the bulbar and palpebral conjunctival surfaces) and ankleblephara (i.e. fibrous tracts fusing the superior and inferior palpebral conjunctiva.) Scarring of the conjunctiva may additionally cause

entropion, trichiasis, superficial punctuate keratinopathy, corneal neovascularization, ulceration and ultimately blindness.

To address the issues of corneal transplant rejection and failure and shortage of donor corneas, investigators have developed artificial corneas or *keratoprostheses*. Dr. Claes H. Dohlman developed the Dohlman-Doane Boston keratoprosethesis (DDB) at the Massachusetts Eye and Ear Infirmary at Harvard Medical School. There are two types of DDB keratoprosethesis. Type 1 is for patients with intact lacrimal and blinking function whereas type II is for those with impaired lacrimal and/or blinking function. The Type I DDB keratoprosethesis sits directly on the cornea whereas the Type II DDB keratoprosethesis is implanted directly through the eyelid. Our patient has type I and type II implants in his left and right eyes, respectively.

Patients who have experienced repeated immunologic rejection of corneal grafts are potential candidates for keratoprostheses. Permanent severe ocular damage due to Stevens-Johnson syndrome and herpes simplex opthalmitis may also be indications for implantation of a keratoprosthesis. Keratoprosetheses are difficult to maintain, and usually require multiple post-implantation surgeries to continue functioning. Of greatest concern is "melting". Melting occurs when the corneal epithelium adjacent to the keratoprosthesis is denuded inducing dislodgement of the device. Melting predisposes not only to extrusion of the keratoprosethesis but also to potentially devastating infectious endopthalmitis. Our patient has suffered several episodes of melting, but restorative surgeries have allowed him to maintain his vision. Most recently a scleral patch graft was used to repair the damaged area of the cornea, thereby allowing continued functioning of the keratoprosthesis and preventing infection.

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Case # 9

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

History of Present Illness:
This 57-year-old Caucasian woman presented in August 2004 with a two-year history of an erythematous eruption on her arms, chest, upper back, hands, and face exacerbated by sunlight. She also reports muscle weakness, which developed around the same time as the onset of the rash. She has trouble climbing stairs, getting out of her car, and lifting plates out of the cupboard.

The patient has been evaluated by a number of outside physicians and has had 3 outside skin biopsies and a laboratory workup prior to presentation at UIC. She has been previously diagnosed with "lupus" and was to start azathioprine. Biopsies had been read as consistent with subacute cutaneous lupus erythematosus. At the time of presentation, she had been on hydroxychloroquine 200mg po bid for 3 months and reported mild improvement of her rash and muscle weakness.

Past Medical History:
History of lymphadenopathy of her neck (8/03) s/p lymph nodes biopsies.
Patient is followed closely by her hematologist who does not believe the patient has a lymphoproliferative disorder but that her lymphadenopathy is a reactive process
Hypertension
History of vertigo secondary to Meniere's disease

Medications:
Hydroxychloroquine 200mg po BID
Candesartan/Hydrochlorothiazide 32/12.5mg po QD
Amitriptyline 10mg po QHS

Allergies:
No known drug allergies

Family History:
Mother has a history of breast cancer
Father has a history of myelodysplastic syndrome
Sister has a history of melanoma

Social History:
Denies alcohol or tobacco; Retired schoolteacher

Review of Systems:
Reports muscle weakness; malaise; arthralgia of ankles, knees, and fingers; "burning" sensation of feet; weight loss, hairloss; "blue toes" unrelated to temperature, dry mouth, trouble chewing, and rectal incontinence. Denies fevers, chills, nausea, vomiting, dysphagia, or oral lesions.

Physical Examination:
The patient has diffuse erythema of the forehead, malar cheek, chin, ears, and posterior neck. There is no heliotrope eruption. Upper chest and upper back show erythema in a photodistributed pattern. Dorsal arms also show diffuse erythema extending to wrists and hands. The knuckles

are spared and there is no evidence of Gottron's papules. Few erythematous crusted papules are noted on the forearms and the back. Nails show mild periungual erythema. Musculoskeletal exam revealed lower extremity proximal muscle weakness; upper extremities were within normal limits.

Laboratory Data:

The following laboratory studies were abnormal or positive:

ANA (8/04)	1:320	[nl: none detected]
Anti – SSa (8/04)	20	[0-19]
ANA (4/04)	1:320	[nl: none detected]
ANA (2/04)	1:1280	[nl: none detected]
Anti-dsDNA (2/04)	11	[0-10]
Creatine kinase (2/04)	144 U/L	[0-125U/L]
LDH (2/04)	218	[0-200]
ANA (5/03)	1:640	[nl: none detected]

The following laboratory studies were normal or negative:

Anti-dsDNA antibody (8/04, 4/04, 5/03)	Anti-Sm Antibody
Anti- SSb Antibody	Anti-U1 RNP Antibody
CH50	C3, C4
Creatine kinase (8/04)	Aldolase (2/04, 8/04)
CA-125	CBC
Urinalysis	ESR
Liver function tests	Basic metabolic panel
G6PD	Cryoglobulins
Cardiolipin IgG, IgM	Serum protein electrophoresis

Diagnostic Procedures and Tests:

6/04 Colonoscopy revealed a benign inflammatory polyp

9/04 Electromyography: Abnormal study. There is subtle electrophysiologic evidence of a myopathy. There is also electrophysiologic evidence of incidental bilateral median mononeuropathies at wrist.

9/04 MRI Lower extremities:

1. Mild inflammation in the gluteus medius muscles, particularly on the right, associated with perifascial edema. These findings are compatible with myositis and correspond to the recent EMG findings.
2. Mild inflammation at the gluteal muscle insertions on both greater trochanters.
3. Subtle perifascial edema about the quadriceps muscles of both thighs.
4. Bilateral hip and knee joint effusions.

9/04 Pelvic ultrasound was within normal limits

9/04 Mammogram was within normal limits

10/04 CXR showed no evidence of acute pathology in the chest.

Histopathology:

6/03 Mid back: The epidermis shows acanthosis as well as thinning. Vacuolar degeneration of basal cell layer is present with papillary dermal edema and thickened basement membrane. There is perivascular lymphocytic infiltrate in the papillary dermis.

12/03 Lymph nodes, neck: Moderate lymphoid hyperplasia with sinus histiocytosis. There is no evidence of malignant lymphoma in these biopsies. Immunophenotyping is confirmatory.

3/04 Mid chest: Epidermis is thin and shows flattening of the rete ridges and focal vacuolar degeneration of the basal cell layer. There is focal fibrinoid degeneration of the papillary dermis with thickening of the basement membrane. A lichenoid as well as perivascular lymphocytic infiltrate is present. Diffuse moderately severe solar elastosis is observed. The capillaries show fibrinoid thickening of their walls.

Immunopathology:

6/03 Right mid back (DIF): Compatible with dermatitis. There are rare IgM granules or a speckled dermis. The findings are minimal and nonspecific.

3/04 Left upper arm (DIF): Compatible with an unknown dermatitis. There is positive ANA with IgG seen in LE/MCTD but here the nuclei are stained with all the antibodies, including fibrin, so it may therefore be a nonspecific finding.

Diagnosis:

Dermatomyositis

Treatment and Course:

The patient is currently on hydroxychloroquine 200mg po bid (since 4/04) and betamethasone diproprionate ointment bid. Sun protection has also been strongly recommended. Patient reports improvement of her rash and muscle weakness. The patient was also evaluated by the rheumatology service who concurs with the diagnosis of dermatomyositis. The patient has residual muscle weakness. Other treatment options to consider include prednisone, methotrexate, and IVIG. She continues to be followed closely by her hematologist and internist.

Discussion:

Dermatomyositis is an inflammatory myopathy with proximal muscle weakness and characteristic skin findings including pink/violaceous papules over the knuckles (Gottron's papules), violaceous eyelid erythema (heliotrope rash), periungal telangiectasias, and a photoexacerbated eruption. The muscle weakness is seen symmetrically, most frequently involving the shoulder girdle and sometimes the pelvic region. Patients commonly notice difficulty climbing stairs and raising their arms above their heads.

Our patient presented with a pronounced photodistributed erythema and mild nailfold telangiectasias but lacked the other pathognomonic manifestations of dermatomyositis. Our main differential diagnosis in the patient was systemic lupus erythematosus. She had a high-titer ANA but lacked the anti-double stranded DNA, anti-Sm, and hypocomplementemia typically seen in SLE. She also complained of muscle weakness, and recent abnormal electromyography and MRI findings confirmed the diagnosis of myositis. Diagnostic criteria for dermatomyositis are as follows: 1) symmetric weakness of limb girdle muscles and anterior flexors of the neck 2) elevated muscle enzymes: creatine phosphokinase, transaminases, lactic dehydrogenase, and aldolase 3) abnormal EMG 4) characteristic myositis on muscle biopsy 5) the typical dermatologic features. Three criteria make the diagnosis probable, four confirm the diagnosis. Our patient met the criteria for the diagnosis of dermatomyositis.

In adult-onset dermatomyositis, there is a significant association with occult malignancy. A thorough search for malignancy directed by history and physical findings, laboratory workup and

imaging studies is warranted, especially in adults over age 40. In women, screening for ovarian cancer is also indicated. Lymphoproliferative malignancies such as non-Hodgkin's lymphoma have been reported in patients with dermatomyositis/polymyositis but are generally uncommon. Our patient has a history of lymphadenopathy and her lymph node biopsies were negative for a malignant transformation but showed lymphoid hyperplasia with sinus histiocytosis. A literature search has not revealed any reports of sinus histiocytosis being associated with dermatomyositis. She is being closely monitored by her hematologist.

Systemic corticosteroids are the mainstay of treatment at the first sign of muscle disease; and have been shown to lead to more rapid control of the muscle disease and a better clinical course for the patients. Prednisone is started at 1mg/kg and tapered 50% over 6 months and to zero over 2-3 years. Other systemic therapies include low-dose weekly methotrexate, azathioprine, cyclosporine, and high dose intravenous immunoglobulin. For cutaneous lesions, treatments include broad spectrum sunblocks, topical corticosteroids, antimalarials, methotrexate, and mycophenolate mofetil.

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Case # 10

Case presented by Sophie Worobec, MD
and Ashley Fowler, MD

History of Present Illness:
This 43-year-old African-American male with Noonan's syndrome, status post renal transplant in 2001, presented with a nine year history of an unknown dermatitis. He was initially seen in our clinic three years ago for facial hyperpigmentation, and poikilodermatous, non-pruritic, increasingly dry skin on his neck, chest, back, arms and legs. He had a single episode of a severe sunburn prior to his renal transplant and developed a worsening hyperpigmented, lichenoid eruption since the time of the transplant. His condition worsened with azelaic acid cream and NBUVB, and flared with the tapering of his immunosuppressive post-transplant medications. Prior biopsies have been non-specific. Most recently, a biopsy was performed for direct immunofluoresence to rule out disseminated discoid lupus erythematosus versus lichenoid drug eruption, and was compatible with lichen planus.

Past Medical History:
Noonan's syndrome
End stage renal disease secondary to focal sclerosing glomerulonephritis status post cadaveric renal transplant (2001)
Hypertension
Diabetes mellitus (newly diagnosed 8/04).

Medications:
Atenolol 100 mg po daily (since 2000)
Amlodipine 10 mg po daily (since 9/01)
Clonidine 0.1 mg po daily
Ranitidine 150 mg po daily
Prednisone 10 mg po daily
Cyclosporine (since 8/04)
Insulin (since 8/04)
Tacrolimus (oral) was discontinued 8/04.

Allergies:
No known drug allergies

Family History:
The patient states his maternal grandfather had a similar-looking rash, but much less severe. He has an identical twin with no skin problems. He has four healthy children.

Social History:
He denies tobacco or alcohol use. He works as a foreman at a construction company.

Review of Systems:
Non-contributory

Physical Examination:
The patient has a high anterior hairline, downward slanting palpebral fissures, prominent nasolabial folds, and a high arched palate. He has a webbed neck, mild pectus carinatum superiorly, mild pectus excavatum inferiorly, and widely set nipples. His skin is dry, thickened,

and poikilodermatous on his neck, chest, back, arms, legs and feet. The dorsal hands show thick lichenified plaques sparing the distal fingers. The palms, elbows, and knees are clear. His face is relatively spared with mild dyschromia on the scalp and forehead. Mucosal surfaces and nails are clear.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Creatinine	1.7	[nl: 0.5-1.5]

The following laboratory studies were normal or negative:

Complete blood count	Liver function tests
Basic Metabolic panel	Blood urea nitrogen
Hepatitis panel	Human immunodeficiency virus
ANA	KOH skin scraping
Cyclosporine level	DIF of skin, 9/03

Histopathology:

8/01 Right arm: There is epidermal thinning with flattening of the rete ridges. In the papillary dermis, there is an increase in the number of dilated blood vessels. In the upper dermis, there is a modest infiltrate of lymphoid cells as well as pigment incontinence.

6/03 Right thigh: The epidermis shows hyperkeratosis, focal parakeratosis, acanthosis, vacuolar degeneration of the basal cell layer and formation of numerous Civatte bodies. There is wedge-shaped hypergranulosis and saw-toothing. There is a lichenoid infiltrate consisting mainly of lymphocytes. Melanophages are observed in the papillary dermis, few extravasated red blood cells are seen.

Immunopathology:

9/04 Left hand (DIF): Anti- IgG, IgM, IgA and C3 staining shows large groupings of cytoid bodies.

Diagnosis:

Generalized lichen planus; Drug-induced lichen planus

Treatment & Course:

The patient has been applying triamcinolone 0.1% ointment and petrolatum daily with mild improvement. He has rare involvement on his face, and uses tacrolimus 0.1% ointment when needed, also with only with mild improvement.

Discussion:

A wide variety of drugs have been associated with drug-induced lichen planus. Also referred to as a lichenoid drug eruption (LDE), it can be clinically and histologically indistinguishable from idiopathic lichen planus (LP). The most commonly implicated medications include ACE inhibitors, thiazide diuretics, antimalarials, quinidine and gold. However, multiple drugs have been reported to induce lichenoid drug eruptions, including calcium channel blockers and beta blockers. There is usually a latent period of several months from drug introduction to the appearance of the cutaneous eruption, with a mean latent period of 12 months in one study. The mechanism of the drug-induced lichenoid reaction remains unclear. Interferon-γ and TNF producing CD4+ T cells, which are implicated in other lichenoid dermatoses are likely activated upon recognition of the drug antigen, thus causing epidermal injury.

Although there is significant overlap between idiopathic lichen planus and lichenoid drug eruptions, there are both clinical and histological features that can aid in differentiation. Lesions of LDE are more generalized and have symmetric involvement of the trunk and extremities. They often have an eczematous, psoriasiform appearance, and a predilection for sun-exposed areas. They rarely involve mucosal surfaces and have a greater tendency toward postinflammatory hyperpigmentation. Idiopathic LP often shows the classic flat-topped, polygonal, violaceous papules and plaques, with a predilection for the flexor aspects of the extremities. Mucosal involvement is more common in LP.

There are no pathognomonic histologic features for drug-induced lichen planus, but certain findings are more commonly observed when compared to idiopathic LP. Classically, the features more often associated with LDE include the presence of plasma cells, eosinophils, focal parakeratosis, and deep perivascular infiltrates. One group also found the presence of cytoid bodies in the cornified and granular layers to be part of their LDE-related criteria. These findings were not present in the reviewed cases of idiopathic LP. There is reportedly no significant difference in immunofluorescence findings between LDE and LP.

Our patient has both clinical and histological features suggestive of LDE. Beta blocker or calcium channel blocker therapy is the most probable cause of his eruption. The differential diagnosis includes idiopathic LP, as well as chronic GVHD. Although GVHD can resemble lichen planus both clinically and histologically, our patient initially developed skin changes prior to his transplant. Furthermore, chronic GVHD does not usually develop in renal transplant patients. We are currently working with the transplant team as well as the primary care physician to find alternative, but equally effective antihypertensive medications for this patient.

Curative treatment requires discontinuation of the offending drug. The time course between the cessation of the drug and resolution of lesions can take several weeks to months. Interestingly, the eruption may resolve and recur following withdrawal of the drug. This suggests that there may be additional factors other than the presence of the implicated drug that play a role in the pathogenesis.

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Case #11

Case Presented by Michelle Bain, MD
and Namrata Shah, MD

History of Present Illness:
This 11-year-old Hispanic male presented to the dermatology clinic with a diagnosis of X-linked hypohidrotic ectodermal dysplasia since the age of six months. This diagnosis was first considered when he presented with peg-shaped primary teeth to his dentist. After evaluation by pediatric genetics, the diagnosis of X-linked hypohidrotic ectodermal dysplasia was confirmed. The parents stated that the patient has had dry skin and decreased sweating since birth. The patient experienced a hyperthermic crisis with febrile seizures at age two months which resulted in neurologic damage and mental retardation.

Currently, the patient experiences overheating with minimal physical activity. The parents carefully control ambient temperatures to prevent hyperpyrexia. In addition to peg-shaped teeth, the parents reported the patient has had sparse, fine, slow-growing hair and periorbital wrinkling and hyperpigmentation.

Past Medical History:
Atopic dermatitis
Febrile seizures as an infant
Microcephaly
Mental retardation
Developmental delay
Failure to thrive
Allergic rhinitis

Medications:
Hydrocortisone 1% and 2.5% ointment QD prn to body
Artificial tears

Allergies:
No known drug allergies

Family History:
Maternal uncle with X-linked ectodermal dysplasia
Paternal aunt with microcephaly

Social History:
Enrolled in a special education program at school

Review of Systems:
Mild, diffuse pruritus
Occasional dry, irritated eyes
Denies fevers, difficulty chewing food, thick nasal secretions, recurrent respiratory infections

Physical Examination:
The patient had microcephaly and short stature. Skin was hyperpigmented and lichenified periocularly. Lips were thick, everted, and protruding. The cartilage of his left ear was noted to

be abnormally developed and both ears were large and low set. An accessory tragus was noted in the right preauricular region. The patient's nose was saddle-shaped with a wide nasal bridge and his face was slightly sunken centrally. Short and somewhat sparse hairs were seen on the scalp. Eyelashes, eyebrows, and body hair were likewise thin and sparse. The patient had five teeth, four of which were peg-shaped. The patient's right central incisor was originally peg-shaped but appeared normal due to reshaping by a dentist. There were lichenified, xerotic patches seen on the upper back. Follicular prominence was noted.

Diagnostic Procedures and Tests:
9/04 Starch iodine test: negative

Diagnosis:
X-linked hypohidrotic ectodermal dysplasia

Treatment and Course:
The patient was treated with hydrocortisone 1% ointment to be used daily as needed on mild/moderately xerotic and pruritic areas on the body. The importance of good skin care and moisturizing was discussed. He was given hydrocortisone 2.5% ointment to use daily as needed on more severely xerotic skin of the body. With this regimen alone the patient's skin remains well moisturized. The patient is being followed by pediatric genetics. He is also managed by dentistry for his teeth abnormalities.

Discussion:
Hypohidrotic ectodermal dysplasia (HED), also known as anhidrotic ectodermal dysplasia or Christ-Siemens-Touraine Syndrome, was first described by Thurman in 1848. HED is the most common ectodermal dysplasia. The syndrome is characterized by the triad of abnormal dentition, hypotrichosis, and partial or complete absence of sweat glands. Peg-shaped teeth, fine, sparse, slow-growing hair, and periorbital wrinkling and hyperpigmentation are common features. Furthermore, abnormalities such as a large lower lip, frontal bossing, saddle nose, and a central sunken face give these patients a characteristic facies.

Patients with HED typically possess normal intelligence but hypohidrosis can cause febrile convulsions and neurologic injury resulting in mental retardation. This patient's mental retardation has been attributed to a hyperthermic crisis as an infant and microcephaly. Of note, microcephaly is not a typical manifestation of ectodermal dysplasia and likely represents a separate inherited entity.

Increased atopic disease, feeding problems with failure to thrive, and recurrent respiratory infections (due to deficient mucus production by respiratory epithelia) are all well recognized in patients affected by HED.

In addition to the X-linked variant of HED, autosomal dominant and autosomal recessive forms have been described. Despite the different modes of inheritance, clinical features are similar. HED occurs in all racial groups. Autosomal dominant and recessive HED are much less common than the X-linked form.

Skin biopsy is not necessary for the diagnosis but when completed reveals a flattened thin epidermis with decreased sebaceous glands and hair follicles. Eccrine glands are absent or can be rudimentary.

Mutations in the gene ED1 (chromosomal locus Xq12-q13.1) are associated with X-linked hypohidrotic dysplasia. It has been determined that ED1 encodes the ligand ectodysplasin A, a membrane-associated protein produced in cells and tissues of ectodermal origin. Defects in the ectodysplasin signal transduction pathway are responsible for the hypohidrotic ectodermal dysplasias. The ectodysplasin signal transduction pathway is utilized by epithelial cells in developing eccrine sweat glands, teeth, and hair follicles and defects in the pathway result in abnormalities of these structures. When the pathway becomes activated, a transcription factor, NF-κB, alters gene expression affecting cellular proliferation and survival. Of interest, mutations in EDAR (ectodysplasin-A receptor) are responsible for the autosomal dominant and autosomal recessive variants of hypohidrotic ectodermal dysplasia. Clinical molecular genetic testing is available for ED1 and EDAR.

Although our patient has no features of immunodeficiency, a variant of hypohidrotic ectodermal dysplasia associated with immunodeficiency has recently been described in the literature. These patients have been shown to have a mutation in the gene *NEMO* which codes a signaling molecule gene in the ectodysplasin pathway. *NEMO* is essential for activation of the transcription factor NF- κB.

Management of HED entails avoiding heat and physical exertion, carefully controlling environmental temperatures, and cooling the body by external means. Early diagnosis is essential in these patients to prevent complications of hyperthermia. Dental intervention is typically necessary to facilitate mastication and for smooth language development. Moisturizers and artificial tears are also beneficial and add to patient comfort.

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Case # 12

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

History of Present Illness:
The patient is an 11-month-old boy that was originally seen in the dermatology clinic for evaluation of multiple café-au-lait macules. Given the size and number of the café-au-lait macules, the patient was instructed to follow up in neurofibromatosis clinic. The patient returned 5 months later for evaluation of multiple new asymptomatic lesions which developed over 1-2 months on the child's scalp. The child had remained healthy otherwise.

Past Medical History:
Café-au-lait macules

Medications:
None

Allergies:
No known drug allergies

Family History:
There is no family history of neurofibromatosis.

Social History:
The parents are the primary caregivers.

Review of Systems:
There are no apparent developmental delays.

Physical Examination:
The patient has scattered yellowish to orange papules and plaques on the scalp.
There are a total of nine light brown macules all greater than 0.5cm in size scattered on the trunk and extremities.

Histopathology:
3/04 Scalp: in the dermis there is a dense infiltrate composed predominantly of foamy histiocytes, occasional Touton giant cells, and numerous eosinophils.

Diagnosis:
Juvenile xanthogranulomas in association with multiple café-au-lait macules

Treatment and Course:
An ophthalmologic exam revealed no abnormalities. The child will have a repeat eye exam in 6 months. Given the patient's increased risk of juvenile myelomonocytic leukemia, it was recommended to the primary care doctor that the child's hematologic status be closely monitored.

Discussion:
Juvenile xanthogranuloma (JXG) is a benign, self-limiting, non-Langerhans cell histiocytosis frequently seen in young children. It is characterized by yellowish orange asymptomatic papules frequently occurring on the head, neck, and shoulders. Regression typically occurs within 3-6

years, sometimes leaving residual hyperpigmentation and atrophy. Ocular and visceral involvement has been rarely reported. The eye is the most common extracutaneous site affected with an incidence of 0.3-0.5%. Given that most patients with eye involvement have multiple cutaneous lesions and are under the age of 2, it is advised that this population be screened by an ophthalmologist every 6 months until they are 2 years of age.

JXG has a well known association with neurofibromatosis 1 (NF-1). Patients presenting with café-au-lait macules and JXG typically develop other findings that eventually lead to a definitive diagnosis of NF-1. Children with NF-1 have approximately a 200 to 500 fold increased risk of developing juvenile myelomonocytic leukemia (JMML). When NF-1 is found in association with JXG, this risk has been reported to increase by more than 20 fold. The prognostic significance of this triple association between NF-1, JXG, and JMML is still unclear. However, children with NF-1, with or without JXG, should be followed for presenting signs of developing hematologic malignancies.

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Case # 13

Case Presented by Claudia Hernandez, MD
and Agnes Ju Chang, MD

History of Present Illness:
This 80-year-old Caucasian woman with myelodysplastic syndrome presented with an asymptomatic eruption on the breasts for 9 months. An initial biopsy revealed a lichenoid dermatitis, and the patient was started on a regimen of triamcinolone 0.1% ointment and topical tacrolimus 0.1% ointment. The eruption persisted and continued to progress. A second biopsy was performed which was consistent with a low grade B-cell lymphoma. The patient has recently noticed new lesions on her abdominal scars.

Past Medical History:
Myelodysplastic syndrome 2/04
Patient has a two year history of pancytopenia, splenomegaly, and abdominal lymphadenopathy. First bone marrow biopsy (10/01) was inconclusive. Repeat bone marrow biopsy around the time of onset of rash was consistent with evolving myelodysplastic syndrome
Abdominal aortic aneurysm s/p repair 4/99
Lung adenocarcinoma s/p lobectomy 3/01
Aortic stenosis
Chronic sinusitis 3/03
Basal cell carcinoma 4/04
Hypertension
Hypothyroidism
Hypercholesterolemia

Medications:
Folic acid 1mg po qd
Aspirin 81mg po qd
Vitamin E 400units po qd
Levothyroxine 0.1mg po qd
Furosemide 20mg po qd
Atorvastatin 10mg po qd
Metoprolol 50mg po qd
Calcium + Vitamin D 1500mg po qd
Aldendronate 70mg po qweek

Allergies:
Ranitidine
Dipyridamole
Intravenous radiocontrast dye

Family History:
Mother has a history of breast cancer and myocardial infarction
Sister has a history of breast cancer

Social History:
Quit tobacco in 1985 – smoked 2 ppd for 40 years; Retired secretary. Widowed with 4 children.

Review of Systems:
Denies fevers, chills, night sweats, weight loss, anorexia, malaise. Otherwise feels well.

Physical Examination:
Physical exam revealed grouped erythematous purpuric papules ranging from 3-5mm clustered around bilateral areolas with surrounding few scattered papules on the breasts. Of note, a few of these papules are clustered on an adjacent small scar.

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

White blood cell count (9/04)	1.8 K/UL	[nl: 4.0-10.0]
Hemoglobin	11.6 gm/dl	[nl: 0-99]
Platelet count	79 K/UL	[nl: 150-400]
Absolute neutrophil count (9/04)	0.9 K/mm3	[nl: 2.0-7.0]

The following laboratory studies were normal or negative:

Lipid panel	Liver function tests
Metabolic panel	

Diagnostic Procedures and Tests:
6/04 CT scan of the chest, abdomen, and pelvis:

1. Enlargement of the mesenteric and retroperitoneal lymph nodes which is consistent with the recent diagnosis of lymphoma and has progressed in size and number from prior exam. There is marked splenomegaly, not significantly changed.
2. Lung nodule in the left lower lobe is slightly smaller. No new lung nodules or masses. No thoracic lymphadenopathy.

2/04 Bone marrow biopsy: Hypercellular bone marrow. Trilineage hematopoiesis due to relative erythroid hyperplasia. Peripheral blood smear with leukopenia, thrombocytopenia, microcytosis without anemia, mild anisopoikilocytosis and neutropenia. Dyserythropoiesis and dysgranulopoiesis. Myeloid cells show dysplastic granulation. The patient's neutropenia is most likely due to an evolving myelodysplastic syndrome.

Histopathology:
3/04 Right medial breast (S04-5267): Lichenoid dermatitis with superficial and deep perivascular chronic inflammatory infiltrate. No evidence of vasculitis.

6/04 Left breast (S04-9525): Epidermis is unremarkable. In the dermis, dense collection of lymphocytes are seen which abuts the epidermis. They have hyperchromatic nuclei with moderate pleomorphism. There is an interstitial infiltrate between the collagen bundles forming "Indian files." Mitoses are not observed but there are scattered nuclear dusts. Immunostains: CD 20 is densely positive. CD79a is faintly positive. CD5 and CD3 shows scattered positive T cells. Immunglobulin kappa and lambda light chains are negative. Bcl-6 and CD 10 is negative. PCR analysis showed monoclonality of B-cell receptors. These findings are consistent with the diagnosis of a B-cell lymphoma.

Immunopathology:
3/04 R lateral breast (DIF): All stains are negative or show a nondiagnostic pattern

Diagnosis:
B-cell lymphoma

Treatment and Course:
The patient is being closely followed and monitored by her hematologist/oncologist. The patient had a long history of pancytopenia, splenomegaly, and abdominal lymphadenopathy. Although her bone marrow biopsy pointed to an evolving myelodysplastic syndrome, a definitive diagnosis was lacking. After the skin biopsy revealed a B-cell lymphoma, the patient was given the diagnosis of B-cell low grade non-Hodgkin's lymphoma with secondary skin involvement. The patient was treated with one course of anti-CD20 monoclonal antibody (Rituximab) but infusion had to be stopped secondary to a hypotensive episode. The patient is doing well otherwise and no other treatments are currently planned.

Discussion:
Cutaneous B-cell lymphomas are a group of malignant lymphomas derived from B lymphocytes at different stages of differentiation. Primary cutaneous B-cell lymphomas are defined as B-cell lymphomas originating in the skin, with no evidence of extracutaneous disease at presentation, as assessed by adequate staging procedures. In secondary cutaneous B cell lymphoma, the skin is the site of secondary involvement from a non-Hodgkin's B-cell lymphoma, as it is in our patient's case. Secondary cutaneous involvement has morphologic and phenotypic features similar or identical with those observed in primary cutaneous B-cell lymphoma. The classification of cutaneous B- cell lymphoma is confusing but according to the European Organization for Research and Treatment of Cancer (EORTC), three major types of cutaneous B-cell lymphomas and two provisional types are recognized. They include follicle center cell lymphoma, immunocytoma/marginal zone lymphoma, and large B-cell lymphoma of the leg, and provisional categories of plasmacytoma, and intravascular large B-cell lymphoma. We believe that our patient correlates best with the diagnosis of marginal zone lymphoma.

In cutaneous marginal zone lymphoma, patients usually present with asymptomatic, recurrent red infiltrated papules, plaques, and nodules localized preferentially to the upper extremities or the trunk. Systemic signs and symptoms are generally absent. Histology shows a patchy, nodular, or diffuse infiltrate involving the dermis and subcutaneous fat. Cells stain positively for CD20, CD79a, and Bcl-2, and they are usually negative for CD5, CD10, and Bcl-6. Usually monotypic expression of immunoglobulin light chains can be observed.

In the literature, patients with B-cell lymphoma in the breast or nipple area usually present with a mobile nodule or a mass. Our patient has a very unique clinical presentation with an unusual distribution as well as a distinctive morphology of the eruption. Moreover, it is also interesting that she continues to get new lesions on the scars from previous surgeries. There have been case reports of lymphomas arising in scars of herpes simplex, laparoscopic insertion sites, and pacemaker pockets.

Treatment of the lymphoma is selected after the classification of the lymphoma has been made through appropriate staging procedures. Secondary cutaneous lesions of extracutaneous B-cell lymphoma are treated with systemic therapy through the oncology service. Primary cutaneous lymphoma can be treated by local radiotherapy, surgical excision, or surgical excision followed by radiotherapy. Subcutaneous or intralesional interferon and anti-CD20 monoclonal antibody have also been reported as treatment options. There have been a few reports of resolution with systemic antibiotics in some patients with *Borrelia*-associated primary cutaneous B-cell lymphoma.

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Case #14

Case presented by Sophie Worobec, MD
and Keith A. Lopatka, MD

History of Present Illness:
This 64-year-old woman was admitted to the hospital for a gastrointestinal bleed. On push enteroscopy, the patient was found to have an angioectasia of the jejunum. This patient was subsequently noted to have telangiectasias of the forehead, cheeks, nose, lips, and floor of the mouth. On further questioning, the patient gave a history of frequent nosebleeds as a child and young adult. This patient also recalled that her father had frequent nosebleeds throughout his life.

Past Medical History:
Hypertension
Obstructive sleep apnea
Gastroesophageal reflux disease
Diverticulosis
Osteoarthritis
Coronary artery disease
Hyperlipidemia
Anxiety
Obesity
Fibromyalgia

Medications:
Meclizine
Gemfibrozil
Oxybutinin
Lansoprazole
Desloratidine
Acetaminophen
Fluoxetine
Estrogens conjugated and medroxyprogesterone
Salsalate
Zolpidem
Risedronate
Calcium

Allergies:
No known drug allergies

Family History:
Father with a history of nosebleeds throughout his life.

Social History:
Married with three children. Quit smoking 13 years ago. Denies alcohol use.

Physical Examination:
The patient had scattered matted red ectatic vessels of the forehead, cheeks, nose, lips near the vermillion border, and on the floor of the mouth.

Laboratory Data:
The following laboratory studies were normal or negative:
Complete blood count

Diagnostic Procedures and Tests:
04/04 CT of the abdomen, pelvis, and thorax with and without contrast: No arteriovenous malformations of the lungs or liver.
05/04 MRI of the brain with and without contrast: No evidence of arteriovenous malformations.

Diagnosis:
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Treatment and Course:
This patient was discharged from the hospital and has done well. She continues to be followed by gastroenterology, pulmonology, and neurology.

Discussion:
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease) is a group of autosomal dominant disorders that was first described over a century ago, characterized by epistaxis and telangiectasias. This condition occurs in a wide geographic distribution and affects many ethnic and racial groups. In Vermont, the prevalence was determined to be 1 in 16,500.

In the study of affected families, genetic linkages have been found on chromosome 9q33-q34 (HHT 1) and 12q (HHT 2). The HHT1 gene product on chromosome 9 produces endoglin and the HHT 2 gene product on chromosome 12 produces ALK-1. Both of these gene products are transforming growth factor β receptors, which play a role in vessel wall integrity. Transforming growth factor β has been found to modulate several processes of endothelial cells, including migration, proliferation, and adhesion and the composition and organization of the extracellular matrix. The restriction of vascular disease to discrete lesions suggests that an initiation event is required, which may include a mechanical, physiologic, or genetic event. HHT 1 has been correlated with higher prevalence of pulmonary arteriovenous malformations than HHT 2.

The clinical criteria for diagnosis of HHT are the presence of any two of the following: recurrent epistaxis, telangiectasias other than in the nasal mucosa, evidence of autosomal dominant inheritance, or visceral involvement. The clinical manifestations of this disorder are due to abnormalities of vascular structure. Telangiectasias and arteriovenous malformations are characterized by a lack of capillaries and consist of direct connections between arteries and veins.

The clinical manifestations involve vascular abnormalities of the nose, skin, lung, brain, and gastrointestinal tract. The most common manifestation is epistaxis caused by spontaneous bleeding from telangiectasias of the nasal mucosa. This may be so mild as to be undetected or so severe that it requires transfusions and iron supplementation. Epistaxis occurs in most patients by age 21 and it becomes severe in later decades in over half the patients. Telangiectasias of the skin present later in life. By age 40, most patients have multiple telangiectasias of the lips, tongue, palate, fingers, face, conjunctiva, trunk, arms, and nail beds. Most often these cutaneous telangiectasias are of little clinical importance, although they can be of cosmetic concern. Pulmonary arteriovenous malformations consist of the direct connections between a branch of the pulmonary artery and a pulmonary vein through a thin walled aneurysm. These malformations have a predilection for the lower lobes and are often multiple. Sixty percent of patients with these malformations have HHT and up to fifteen percent of patients with HHT will have these

malformations. These malformations create direct right-to-left shunts and can lead to profound dyspnea, fatigue, cyanosis, or polycythemia.

Neurologic symptoms include migraine headache, brain abscess, transient ischemic attack, stroke, seizure, and intracerebral and subarachnoid hemorrhage. Two thirds of neurologic symptoms result from pulmonary arteriovenous malformations. Brain abscess, transient ischemic attack, and ischemic stroke occur exclusively in patients with a right-to-left pulmonary shunt. Recurrent hemorrhage of the upper or lower gastrointestinal tract occurs in a minority of patients, but can be the most difficult to manage. Gastrointestinal bleeding does not usually occur until the fifth or sixth decade. Telangiectasias in the gastrointestinal tract may occur, approximating the size seen in the nasal mucosa, or larger arteriovenous malformations may occur. Liver involvement is rare, but important, as it can lead to high output cardiac failure.

In the follow up of affected persons, the lung and brain are of particular concern, because each may contain clinically silent lesions that can result in sudden morbidity and death. Presymptomatic intervention may substantially affect outcome. Family history is important for both pulmonary and neurological screening tests. Anyone with a history of a pulmonary arteriovenous malformation or with a family history of HHT should receive antibiotic prophylaxis before surgical procedures.

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Case #15

Case Presented by Claudia Hernandez, MD
and Inderjit Gill, MD

History of Present Illness:
This 66-year-old African American woman with end-stage renal disease on hemodialysis presented in July 2004 with a two year history of a right lateral thigh nodule. She developed a painful ulcer on her left lateral thigh approximately 2 months prior to presentation. She reported feeling "knots" in both legs at those sites where she later developed the painful ulcerations. Initial evaluation was performed by cardiology and she was placed on oral clindamycin for one week. The following week, she was hospitalized for the painful, non-healing ulcers. During her hospitalization, she was treated with intravenous clindamycin and ciprofloxacin. Dermatology was then consulted for evaluation.

Past Medical History:
Diabetes mellitus (insulin-dependent)
End-stage renal disease (on hemodialysis for one year)
Atrial fibrillation (treated with anticoagulation for greater than 5 years)
ICD placement for ventricular tachycardia
Osteoarthritis
Coronary artery disease with history of coronary artery bypass graft placement
Congestive heart failure/Cardiomyopathy
Glaucoma
Benign colon tumor with history of left hemicolectomy
History of cholecystectomy

Medications
Insulin Lispro/Insulin Glargine sq BID
Warfarin 2.5 mg 4 days per week, and 1.25mg 3 days per week.
Calcium Acetate 667mg QHS
Lisinopril 5 mg QHS
Atorvastatin 40mg QHS
Carvedilol 75mg QD
Isosorbide 30 mg BID
Rofecoxib 25 mg QD
Hydrocodone 7.5/500 mg prn pain

Allergies:
Penicillin

Family History:
Noncontributory

Social History:
Denies tobacco, alcohol, or illicit drug use

Review of Systems:
Severe pain and tenderness to touch at sites of both lower extremity ulcers

Physical Examination:
The patient had a large indurated plaque on the right lateral thigh with an underlying fibrotic nodule. On her left lateral thigh, she had a 2cm x 7 cm firm indurated plaque with a central necrotic eschar and ulceration. She had exquisite tenderness to light touch over both areas.

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

Blood Urea Nitrogen	30 ml/DL	[nl:7-22]
Creatinine	5.5 mg/dl	[nl: 0.7-1.5]
Hemoglobin	11.5 g/dl	[nl:12-15]
Glucose	273 mg/dl	[nl:70-100]
Calcium for PTH	11.0 mg/dl	[nl:8.9-10.3]
Iron	38 UG/dl	[nl: 42-135]
Vitamin D level	<5 ng/ml	[nl:20-57]

The following laboratory studies were normal or negative:

Calcium	Ionized Calcium
Phosphorus	Magnesium
Electrolytes	ALT
Parathyroid hormone (intact)	TSH
Ferritin	White blood cell count
Platelet Count	Hematocrit
Cryoglobulins	Hepatitis Panel

Diagnostic Procedures and Tests:
3/00 X-ray of L Hip: Calcific density in the soft tissue lateral to the acetabulum, probably represents calcified injection granuloma; extensive vascular calcification is noted
12/03 DEXA scan: Increased bone mineral density of lumbar spine and normal bone mineral density of femoral neck bilaterally

Histopathology:
7/04 L thigh (S04-12155): The epidermis shows mild acanthosis. There are an increased number of blood vessels with various size lumina throughout the dermis. The adipose tissue shows focal septal fibrosis with no significant inflammatory infiltrate.

8/04 L thigh: Incisional biopsy (S04-13010): The epidermis shows hyperkeratosis with parakeratosis and mild acanthosis. There are an increased number of blood vessels with various size lumina and endothelial cell swelling throughout the dermis. Focal fat necrosis and many foamy histiocytes are seen in the subcutaneous fat. Extravasated red blood cells are observed within the adipose tissue with widening of the septae in the subcutaneous fat. Several globules of calcium are seen adjacent to the tissue.

Diagnosis:
Calciphylaxis

Treatment and Course:
The patient was first seen and evaluated as an in-patient consult. A punch biopsy of the left thigh lesion was performed. She then presented to clinic two weeks later with increasing pain and tenderness at the left hip. At this time a 1.5cm x 0.5cm incisional biopsy of the left hip ulcer was performed to aid in diagnosis. Throughout this time, the patient continued on hemodialysis three times a week with aggressive control of electrolytes, including calcium and phosphorus. She was

also continued on warfarin therapy for anticoagulation as indicated for atrial fibrillation. At subsequent clinic visits, it was noted that the left hip ulcer had developed a necrotic eschar, and surgical consultation was obtained for debridement. However, prior to surgical intervention, the patient developed fever, increased white blood cell count, and hypotension and was hospitalized for sepsis. Although she underwent extensive debridement during hospitalization, she unfortunately expired in October 2004, secondary to septic complications.

Discussion:

Calciphylaxis, also called calcific uremic arteriolopathy and uremic small-artery disease with medial calcification and intimal hyperplasia, is a syndrome of ischemic cutaneous lesions that result from vascular calcification and thrombosis of small and medium sized arteries in the dermis and subcutaneous tissue. Hans Selye first described the disease in 1962 using an experimental animal model and defined the disease process as due to a sensitizing agent that, under the influence of a challenging agent, would result in vascular calcifications. The disease is most commonly seen in hemodialysis patients, although rare cases without renal disease have been reported in the literature. It is now estimated that between 1 and 4% of hemodialysis patients will develop this life-threatening and painful disease. The mortality associated with the disease is reported to be as high as 50-60% and is usually secondary to infection or visceral organ involvement by the vasculopathy.

Lesions of calciphylaxis most commonly occur in areas of thick adipose tissue on the extremities, with the more proximal wounds having a worse prognosis. Wounds begin as either single or multiple, symmetrical, tender, erythematous or violaceous nodules. This progresses to pallor and a livedo reticularis pattern that then further evolves into a necrotic ulcer with eschar formation. Three main histopathological changes are seen: medial vessel calcification, vascular thrombosis, and extravascular calcification.

Several risk factors for the development of calciphylaxis have been identified. These include dialysis for greater than one year, younger age, female sex, Caucasian race, morbid obesity, recent weight loss, hypercoagulability from a deficiency of proteins C and S, low albumin level, diabetes mellitus, and concomitant warfarin therapy. Although the exact pathogenesis of calciphylaxis has not been elucidated, there has been significant research on the metabolic abnormalities that may play a role in the development of the disease. Chronic elevations in serum parathyroid hormone, calcium, phosphorus, and the calcium-phosphorus product have been linked to the development of calciphylaxis. Elevated phosphorus levels alone have also been associated with a phenotypic change in vascular smooth muscle that may promote vascular calcifications. It is believed that vascular calcifications occur due to an imbalance of calcification promoters, such as osteopontin and osteocalcin, and inhibitors of calcification, including osteoprotegerin and matrix GLA protein. A hypercoagulable state is also thought to be involved in the development of calciphylaxis lesions, due to the clinical lesions of cutaneous ischemia. Low levels of the anti-thrombotic proteins C and S and anti-thrombin III have also been reported in patients with calciphylaxis. As warfarin causes a functional decrease in proteins C and S, as well as matrix GLA protein, it has also been associated with an increase risk of developing this disease.

There are no treatment modalities that can reverse the changes of calciphylaxis. Most of the available treatments focus on early detection and prevention, as well as monitoring for signs of secondary infection. It is thought that normalization of the calcium-phosphate product and preventing both hyperphosphatemia and hypercalcemia through aggressive hemodialysis are of extreme importance. Vitamin D analogs can be used to suppress secondary hyperparathyroidism, however, there is some literature that supports a harmful effect on vascular smooth muscle cell

phenotype by high levels of calcitriol. Significant controversy has surrounded the benefit from parathyroidectomy. A study by Hafner et al, demonstrated a significant survival benefit, especially for patients with distal disease, from parathyroidectomy; however, prior studies had failed to come to a similar conclusion. Currently, parathyroidectomy should be performed in those patients with significant elevations in parathyroid hormone that cannot be medically controlled. Aggressive wound management and debridement, avoidance of trauma and local injections in areas of high adipose tissue, and systemic antibiotics should be used to care for skin lesions. In the literature some patients have benefited from hyperbaric oxygen and low molecular weight heparin therapy, as tissue ischemia secondary to vascular thrombosis is a major component of the disease process. More recently, one reported case of calciphylaxis was treated with low-dose tissue plasminogen activator, with significant healing of ulcerations. Due to the poor prognosis of calciphylaxis the most important step will be prevention of disease. Preventive measures include nutritional optimization, weight reduction, assessment of the dialysate prescription, and avoidance of concomitant warfarin therapy when feasible.

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Case #16

Case Presented by Michelle Bain, MD
and Namrata Shah, MD

History of Present Illness:
This 10-year-old male presented in March, 2004 with a linear depressed groove over the right forehead that was continuous with a progressively enlarging linear patch of hair loss on the right frontoparietal scalp of one year duration. The parents stated that five years prior to presentation the patient developed a linear violaceous patch on the right side of his forehead which gradually spread upward into the scalp. As the violaceous hue subsided, a depressed groove developed in the affected skin extending into the scalp creating the linear region of alopecia. The lesion was asymptomatic. The patient's general health was excellent. There was no history of antecedent trauma in the affected areas.

Past Medical History:
No significant past medical history

Medications:
None

Allergies:
No known drug allergies

Family History:
No history of a similar condition

Social History:
Patient is a 5th grade student and is doing well in school

Review of Systems:
Denies seizures, headaches, or visual changes

Physical Examination:
The patient had a 3 cm x 1 cm paramedian linear patch of alopecia with some outgrowing hairs at the right frontoparietal scalp that was continuous with a linear depressed groove (with no overlying epidermal changes) on the right forehead. Underlying cortical bones appeared to be normal. There was no facial hemiatrophy. No ocular lesions were noted. The patient's tongue was without atrophy. There were no other atrophic or sclerotic lesions on the body.

Diagnosis:
Linear morphea (*en coup de sabre)*

Treatment and Course:
Currently the patient is not treating the affected areas. He was using calcipotriene ointment BID for four months. The ointment was discontinued by the parents because no improvement was seen.

Discussion:
Linear morphea of the frontal or frontoparietal region of the scalp is termed *en coup de sabre* because the lesion is similar to the scar which results from the stroke of a saber. *En coup de*

sabre was first described by Addison in 1854. The condition is typically unilateral, paramedian, and extends from the forehead into the frontal scalp. It has a slow but progressive course. Morphea *en coup de sabre* can initially present as an inflammatory violaceous band which leaves a hairless sclerotic or atrophic linear area as the inflammation subsides. The lesion can extend to the nose or upper lip and can present with or without facial hemiatrophy. Several cases of bilateral *en coup de sabre* have been reported.

En coup de sabre can be associated with CNS signs and symptoms such as headaches, visual changes, and seizures. Ipsilateral tongue atrophy has also been reported. EEG has been shown to reveal maximal dysrhythmia over the affected areas. Serologic abnormalities such as elevations in serum antinuclear antibodies (ANA) and rheumatoid factor have been reported in patients with *en coup de sabre.*

The etiology of *en coup de sabre* remains unknown. It has been suggested that linear morphea follows Blaschko's lines and that the propensity for development of linear morphea is determined during embryogenesis. Modalities utilized in the treatment of localized scleroderma include methotrexate, calcipotriene, topical steroids, PUVA, and antimalarials. A recent small study showed that the trend in antihistone autoantibody (AHA) titers seemed to mirror disease activity in linear scleroderma and may serve to monitor response to therapy.

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Case #17

Case presented by Iris Aronson, MD, Suzanne Westphal, MD, Marianne O'Donoghue, MD and Ashley Fowler, MD

History of Present Illness:
This 55-year-old woman presented to our clinic in September 2004 for evaluation of a rash, which developed after taking terbinafine for treatment of onychomycosis. She began a course of terbinafine, 250mg po daily, in May 2004 and completed a 5-week course. She briefly discontinued the course because she ran out of medication. One week later, she developed an erythematous eruption on her shoulders. She continued terbinafine for 5 more days, but then sought medical attention because the rash continued to progress, involving her back, abdomen, thighs and ears. She was initially treated with triamcinolone cream for presumed pityriasis rosea without improvement. At that time a skin biopsy was performed and was read as suggestive of drug-induced subacute cutaneous lupus erythematosus versus discoid lupus versus pityriasis rosea. She was then referred to the University of Illinois.

Past Medical History:
Hashimoto's thyroiditis
Hypertension

Medications:
Levothyroxine 150mcg po daily
Losartan 50mg po daily

Allergies:
Enalapril → dizziness

Family History:
No known history of autoimmune or other skin disorders

Social History:
Denies tobacco or alcohol use

Review of Systems:
Reports recent photosensitivity and history of photosensitivity while taking hydrochlorothiazide many years ago; occasional headaches, and left hip pain.

Physical Examination:
The patient had scattered erythematous slightly scaly papules and annular patches and plaques with raised borders over the arms and back. There was mild erythema of the chest in a V-distribution and resolving erythematous and hyperpigmented papules on the abdomen. Legs showed multiple scattered telangiectatic macules.

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

ANA	positive	[no titer given]
Anti-Ro (SS-A) Ab	5.78	[nl: <1.00]

The following laboratory studies were normal or negative:

Anti-dsDNA Ab	Complete blood count
Anti-La (SS-B) Ab	Creatinine

Anti-SM Ab	ESR
Urinalysis	Liver function tests

Histopathology:

08/04 Right back: The epidermis shows vacuolar changes with colloid bodies in the basal cell layer. There is focal thickening of the basement membrane. There is an interface dermatitis with a perivascular and periadnexal infiltrate. The papillary dermis is edematous with areas of fibrin degeneration. Apoptotic cells and exocytosis of lymphocytes are seen within the mid-epidermis.

Diagnosis:

Terbinafine-induced subacute cutaneous lupus erythematosus

Treatment & Course:

Initially, the patient was treated with triamcinolone cream and clobetasol 0.05% lotion without any improvement. She stopped these medications. At the time she presented to our clinic, the lesions had begun to improve on their own, and continued to resolve without any medication. She is now completely clear.

Discussion:

Drug-induced subacute cutaneous lupus erythematosus (SCLE) is a distinct subtype of cutaneous lupus erythematosus with unique clinical, serologic, and immunologic features. Drug-induced SCLE is clinically indistinguishable from idiopathic SCLE and presents with photosensitive symmetric superficial non-scarring annular polycyclic and/or papulosquamous lesions. It is associated with anti-Ro antibodies, less commonly with anti-La antibodies, and shows a correlation with HLA-DR3 and/or -DR2. Drug-induced SCLE differs from drug-induced lupus erythematosus (LE), the latter of which resembles systemic LE, but generally presents with the absence of skin manifestations, and the presence of antihistone antibody, which is fairly specific for drug-induced LE. Classically, drug-induced LE has been linked to treatment with procainamide, hydralazine, minocycline, and isoniazid.

Drug-induced SCLE was first recognized in 1985 in association with hydrochlorothiazide therapy. Since that time, it has been linked to a variety of other drugs, most commonly, calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors. Recently, several reports of the induction of subacute cutaneous lupus erythematosus by terbinafine have been reported, and suggest a link between terbinafine therapy and the onset or exacerbation of SCLE. Most patients developed their skin disease within 4-8 weeks of beginning terbinafine therapy. In the reported cases, some patients appeared to have an underlying predisposition for collagen vascular disease (based on reports of prior autoimmune phenomenon such as Raynaud's phenomenon, sicca symptoms, and photosensitivity), some had confirmed history of collagen vascular disease, and some patients had no preexisting symptoms or signs of collagen vascular disease.

The mechanism of terbinafine-induced SCLE is not clear, but is likely multifactorial and dependent on host factors. Terbinafine is highly lipophilic and keratophilic, and some have proposed that in predisposed persons, it is deposited in keratinocytes and may alter nuclear antigen structure, inducing autoantibody formation. Moreover, terbinafine may be involved in enhancing the cytotoxic reaction important in the anti-Ro antibody mediated cytotoxicity in photosensitive lupus. Another proposed mechanism implicates the build-up of arene oxide metabolites of terbinafine, which are thought to play a role in anticonvulsant hypersensitivity

syndrome and drug-induced lupus, and may become problematic in those with a genetic defect in drug metabolism.

Interestingly, in one recent report, 4 patients with terbinafine-induced SCLE were reported to have antihistone antibodies, which implies that terbinafine is capable of inducing ANA production with antihistone antibody specificity. As postulated by Callen, it is possible that SCLE is linked to the development of antihistone antibodies in patients who are anti-Ro positive and that the linkage is to the combination of antibodies, versus the induction of distinct antibodies in drug-induced LE. However, the significance of the presence of antihistone antibody is not known. In some reports, there are individual cases of antihistone positivity, some cases are negative, and in many cases, as in our patient, antihistone antibody was not tested.

Therapy for terbinafine-induced SCLE has included cessation of the drug in all cases, topical potent steroids, oral prednisone, oral dapsone, hydroxychloroquine, or no treatment at all depending on the severity of disease. In the reported cases, all patients improved. As recently reported in 4 cases by Bonsmann, after discontinuation of terbinafine, ANA titers decreased, antihistone antibodies became undetectable within 4 1/2 months in 3 of 4 patients; anti-Ro and anti-La antibodies persisted at 6 months. In general, however, there is no sufficient follow-up data for drug-induced SCLE. Lastly, previous studies have shown that planned or unintended rechallenge with the culprit drug has resulted in recurrence of the rash.

Although terbinafine has been added to the list of medications capable of inducing SCLE, terbinafine-induced SCLE is rare and in general it is a safe drug. We should be aware of this occurrence and advise those patients we deem at risk for this possible adverse event. Some authors recommend avoidance of its use in patients with known LE or in those with a history of a first degree relative with LE, known anti-Ro/anti-La antibodies, ANA positivity, or without a documented dermatophyte infection.

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Case #18

Case Presented by Sophie Worobec, MD
and Steven Mandrea, MD

History of Present Illness:
This 29-year-old African American female presented with an eruption on her right foot. She noted a "bug bite" one week earlier while on vacation in Jamaica (7/04). Over days, the involved area spread in a wavy pattern and lengthened along a track. It was very itchy, but not painful. The patient had been walking barefoot on a river walk along the ocean while on vacation.

Past Medical History:
None

Medications:
Norgestimate/ethinyl estradiol

Allergies:
No known drug allergies

Family History:
No known history of skin problems or chronic medical problems in her family

Social History:
Recent trip to Jamaica as above; does not have pets at home

Review of Systems:
Generally healthy; no recent fevers, chills, headaches, gastrointestinal upset or joint pain

Physical Examination:
There was a hyperpigmented serpiginous tract with mild erythema from the dorsal surface of the distal third digit of the right foot proximally to the third metatarsophalyngeal joint. The face, trunk, arms and legs were clear.

Diagnosis:
Creeping eruption (Cutaneous larva migrans)

Treatment and Course:
The patient was given a single dose of ivermectin 12mg orally. She did not return for follow up.

Discussion:
Cutaneous larva migrans is caused by hookworms that infect domestic dogs and cats (*Ancylostoma caninum* and *A. brasiliense*). It is most commonly seen in warm climates. When encountered in cooler climates, patients often have a history of recent travel to tropical areas. Children are affected more often than adults. The infection is acquired when larvae enter the skin of persons walking barefoot on ground contaminated with animal feces. As expected, the skin lesions are typically found on the distal lower extremity, although they may occur on the hands, buttocks and perianal area. There is often intense pruritus, edema and erythema associated with one or more inflammatory, serpiginous tracts, through which the larvae migrate at a rate of 1-2 cm per day. The larvae rarely progress beyond the skin; the only common systemic sign is a moderate peripheral blood eosinophilia. The diagnosis is usually made clinically. When biopsies

are performed it is common to find cavities left by the parasite in the stratum corneum with associated spongiosis. There is a mixed inflammatory infiltrate in the dermis, consisting of lymphocytes, histiocytes and numerous eosinophils. The treatment of choice is ivermectin 12 mg orally as a single dose, which has produced higher cure rates than single dose albendazole at 400 mg. Topical thiabendazole, 10-15% solution or ointment, is also effective for local disease. Cryotherapy has been used successfully in many instances as well. Untreated, the infection persists for weeks or months before resolving spontaneously.

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Case # 19

Case Presented by Iris Aronson, MD and Paul Storrs, MD and Madhuri Ventrapragada, MD

History of Present Illness:
This 6-week-old infant was diagnosed with a cystic hygroma by a prenatal ultrasound and followed closely with serial prenatal ultrasounds. Pt was delivered at 36 2/7 weeks due to the increasing size of the lesion. Pt presented to the emergency room at 6 weeks of age with fever and an increase in the size of the lymphatic malformation.

Past Medical History:
No significant past medical history

Medications:
None

Allergies:
No known drug allergies

Family History:
Noncontributory

Social History:
Diet: Similac with iron, approx 4 oz every 3 hours

Review of Systems:
Pt is able to use his left arm, and there has been no change in the color of the lesion.

Physical Examination:
The patient has an approximately 24 x 18 cm soft, mobile deep blue-colored tumor over the left anterior chest wall, left shoulder and left upper arm with a red plaque and patch centrally overlying the left anterior chest. There are some scattered small adjacent satellite lesions. The lesion is not warm to touch.

Laboratory Data:
The following laboratory studies were normal or negative:

Complete blood count
Urinalysis
Urine culture
Blood cultures

Diagnostic Procedures and Tests:
6/04 US of chest/abdomen: Hygroma over the left chest and abdomen
8/04 CT of thorax: Stable extensive lymphangiomatosis of left upper extremity and left hemithorax

Histopathology:
8/04 L arm (SP04-7156): There are several dilated spaces, most of which are devoid of red blood cells, lined with flattened endothelial cells. The stroma is hypercellular with proliferation of spindle shaped fibroblasts and fibrosis. Proliferation of newly formed

capillaries is observed. Focal mucinous degeneration is seen in the stroma. Collections of lymphocytes in the form of lymphoid follicles and aggregates of plasmacytoid cells are present. In other areas, fibrous tissue with loose stroma mixed with adipose tissue is present.

Diagnosis:
Lymphatic malformation

Treatment and Course:
The patient was treated with surgical resection of the lymphatic malformation when he was 9 weeks old. The surgery was performed as a joint venture with pediatric and plastic surgeons involved. The lesion was resected and the resulting defect closed with both a skin flap and a full thickness skin graft.

Discussion:
Lymphatic malformations can be split into two general categories, microcystic and macrocystic.

Microcystic lymphatic malformations can be present at birth or appear in childhood. These lesions appear as grouped small translucent papules, sometimes containing blood. These lesions can range from small to extensive plaques often with a deeper component that can appear as swelling or give the underlying tissues a bluish tone.

Macrocystic lesions (previously called cystic hygroma) are uncommon and can occur in the head and neck region, axilla, groin or chest wall. These lesions usually are present at birth or manifest by age 2 but rarely can develop suddenly in adolescents or adults. Complications of these lesions include infection, spontaneous bleeding and disfigurement. Previously, treatment options included surgical resection of lymphatic malformations but recently sclerotherapy has been tried with good results. Injection of sclerotherapeutic agents has resulted in decreased size or resolution of the lymphatic malformations. Lasers such as carbon dioxide, Nd-Yag and diode lasers have been used successfully to treat the vesicular component in microcystic or combined micro-macrocystic malformations.

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Case #20

Case Presented by Iris K. Aronson, MD, Paul Storrs, MD, and Alexander Berlin, MD

History of Present Illness:
This 82-year-old Middle Eastern man originally developed herpes zoster on the left thorax 2 years ago while in the Middle East, at which time an unspecified topical medication was used to treat the eruption. Following the resolution of zoster, the patient continued to have a burning sensation in the areas of involvement. Two months prior to presentation to our clinic, the patient developed increased burning, as well as darkening, of the previously erythematous lesions at the site of zoster. He was given betamethasone valerate cream by his primary care physician, which did not help. The patient was then seen in our clinic and was started on a course of oral acyclovir for 7 days.

Past Medical History:
Coronary artery disease
History of coronary artery bypass graft
Hypertension
Congestive heart failure
Post-herpetic neuralgia

Medications:
Betamethasone valerate cream to affected areas bid prn
Aspirin 81mg po qd
Furosemide 40 mg po bid
Lisinopril 40 mg po qd
Metoprolol 25 mg po qd
Atorvastatin 20 mg po qhs
Isosorbide mononitrate 60mg po qd
Nitroglycerin 0.4 mg sl prn
Ipratropium bromide/albuterol sulfate 2 puffs inh qid

Allergies:
No known allergies

Family History:
Noncontributory

Social History:
No smoking, occasional alcohol

Review of Systems:
No fevers, no chills, no nausea, occasional shortness of breath, no chest pain

Physical Examination:
The patient had multiple grouped purpuric macules on the left chest in a dermatomal distribution with a few macules extending beyond the midline. Examination of the back revealed hyperpigmented patches in the same dermatome with no purpuric lesions. The remainder of the exam was unremarkable.

Laboratory Data:

The following laboratory studies were abnormal or positive:

Platelets	117 thous/uL	[nl: 150-400]

The following laboratory studies were normal or negative:

White blood cell count
Hemoglobin

Histopathology:

5/04 L chest (SP-04-0003911): The epidermis shows hyperkeratosis, papillomatosis, and flattening of the rete ridges. Extravasated red blood cells are seen throughout the upper dermis. Capillaries show a prominent endothelium, but are otherwise unchanged.

Diagnosis:

Zosteriform purpura vs. atypical reactivation of herpes zoster

Treatment and Course:

Following treatment with oral acyclovir for 7 days, the condition improved significantly with fewer lesions and significantly decreased burning sensation. Patient was then started on topical capsaicin ointment for treatment of post-herpetic neuralgia.

Discussion:

Herpes zoster is a common disease caused by reactivation of latent varicella-zoster virus (VZV) infection. Typically dormant in a sensory ganglion, the virus may become reactivated in response to continuous or transient immunosuppression or injury to the skin. The virus frequently causes a prodrome of pruritus, burning, or pain, followed by characteristic vesiculobullous lesions in a dermatomal distribution. Disseminated zoster, as well as dermatomal pain without apparent cutaneous lesions (zoster sine herpete), have also been well documented.

Zoster occurs most frequently in adults and its incidence increases with age. Disease is most commonly self-limited; however, post-herpetic neuralgia (PHN) is a frequent sequela. PHN is estimated to occur in approximately 10% of patients, with a significantly higher incidence in older patients and rare occurrence in those under 40 years of age.

Since, in our patient, purpura developed in a dermatome previously affected by zoster and since it resolved completely following acyclovir treatment, it is reasonable to assume that the purpura was an atypical presentation of a reactivation of zoster in this case. Purpura is due to extravasation of red blood cells into the dermis. This may occur through several mechanisms, including (a) quantitative or functional platelet abnormalities or (b) leaky blood vessels secondary to capillaritis, vasculopathy, or frank vasculitis.

Severe quantitative platelet abnormalities (thrombocytopenia) are well known to occur in association with VZV and may take the form of idiopathic thrombocytopenic purpura (ITP), hemolytic uremic syndrome (childhood equivalent of thrombotic thrombocytopenic purpura or TTP), or disseminated intravascular coagulation and purpura fulminans.

Vascular damage with microthrombi and hemorrhage can sometimes be seen on histology, and eosinophilic inclusion bodies are occasionally observed in the nuclei of endothelial cells. Cases of leukocytoclastic, lymphocytic, and granulomatous vasculitis as well as Henoch-Schonlein purpura following VZV have been reported. Extravasated red blood cells with no histological evidence of vascular damage, as in our case, may represent capillaritis, also documented in some zoster patients.

When purpura is seen at the site of previous zoster involvement, other diagnostic possibilities also need to be entertained. These include reported cases of pseudolymphoma in zoster scars of patients with chronic lymphocytic leukemia, as well as leukemia cutis, and angiosarcoma. While these can usually be differentiated clinically, they may present with purpura within the lesions and, therefore, biopsy is critical in the evaluation of such patients.

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Case #9B

Case Presented by Iris K Aronson, 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
Hyperlipidemia

Medications:
Levothyroxine
Prednisone 10 mg qd
Plaquenil 200mg bid
Ezetimibe/simvastatin
Lisinopril
Alendronate
Sunblock SPF 30
Fish oil

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. She has recently restarted hydroxycholoroquine three months ago. Topically, she is using triamcinolone 0.1% ointment 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 for local wound care of the lesions on her cheeks.

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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