Cook County Bureau of Health Services

John H. Stroger, Jr.
Hospital of Cook County

Case Presentations

Chicago Dermatological Society Meeting

March 21, 2007

Schedule for meeting at:
John H. Stroger, Jr. Hospital of Cook County
Wednesday, March 21, 2007

- **Derm Clinic – 2nd Floor, Clinic G**
  John H. Stroger, Jr. Hospital (new hospital)
  1901 W Harrison St, Chicago, IL 60612
  (Main entrance corner of Ogden & Damen)

- **Hektoen Institute Auditorium**
  627 S Wood St, 1st Floor

8:00 a.m. – 9:00 a.m. *Committee Meetings*	***Stroger Hospital, Room 4390, 4th Floor*** Main entrance, take Elevator #2
9:00 a.m. – 10:00 a.m. *Plans & Policy Committee Meeting*	***Stroger Hospital, Room 4390, 4th Floor*** Main entrance, take Elevator #2
9:00 a.m. – 10:30 a.m. *Registration*	***Dermatology Clinic G, 2nd Floor*** Main hospital entrance, take Elevator #1
9:00 a.m. – 10:00 a.m. *Resident Lecture*	***Hektoen Institute Auditorium, 1st Floor*** 627 S Wood Street
9:30 a.m. -11:00 a.m. *Patient Viewing*	***Dermatology Clinic G, 2nd Floor*** Main hospital entrance, take Elevator #1
9:30 a.m. -11:00 a.m. *Slide Viewing*	***Dermatology Clinic G, 2nd Floor*** Main hospital entrance, take Elevator #1
11:00 a.m. – 11:15 a.m. *Business Meeting*	***Hektoen Institute Auditorium, 1st Floor*** 627 S Wood Street
11:15 a.m. – 12:00 p.m. *Guest Lecture*	***Hektoen Institute Auditorium, 1st Floor*** 627 S Wood Street
12:00 p.m. – 12:30 p.m. *Lunch*	***Hektoen Institute Auditorium, 1st Floor*** 627 S Wood Street
12:30 p.m. – 2:00 p.m. *Case discussions*	***Hektoen Institute Auditorium, 1st Floor*** 627 S Wood Street

Guest Speaker
Timothy J. Rosio, M.D.
AnewSKIN Dermatology; Center for Dermatology, Mohs & Laser Surgery
Sacramento, CA

Residents' Lecture
10 tips, tools & techniques that will enhance your surgery

General Membership Lecture
"PLAN" Repairs: Selected Perioral, Lid, Auricular & Nasal Reconstructions
Amazing Tools to Keep Derms at the Therapeutic Forefront

The American Academy of Dermatology certifies that this educational activity has been recognized for 4 hours of AAD Category 1 and may be used toward the American Academy of Dermatology's continuing Medical Education Award (119-300)

Timothy Rosio, MD

Chicago Dermatological Society and Dermatology Foundation
Leadership Society Guest Lecturer

Dr Rosio's Lecture is funded by the
Chicago Dermatological Society

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Case #1

Presented by Jerry Feldman, MD and Michael Pomroy, MD

History of Present Illness:
In December 2005, this 31 year old Ecuadorian female presented to our clinic with a long history of biopsy proven psoriasis and was treated with triamcinolone ointment. She failed to appear for her follow up appointment and was next seen in our clinic in September 2006, five months pregnant, with a severe, painful pustular flare of her psoriasis.

Past Medical History:
None

Medications/Allergies:
Triamcinolone ointment, prenatal vitamins; No known drug allergies.

Family History:
Non-contributory.

Review of Systems:
Subjective fever, tender skin, fatigue.

Physical Exam:
Temperature: 99.9 degrees Fahrenheit
Bilateral arms, trunk, upper thighs: large, thin erythematous plaques with large colarettes and numerous pustules. Some of the plaques are annular.

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

Histopathology:
12/05: Trunk: There are mounds of parakeratosis with neutrophils and spongioform pustules in the stratum corneum. In addition there is psoriasiform hyperplasia, a diminished granular layer, and dilated blood vessels at the tips of the dermal papillae. These findings are consistent with psoriasis.

Diagnosis:
Pustular psoriasis flare during pregnancy.

Treatment and Course:
As noted above, the patient was originally started on triamcinolone 0.1% ointment in December of 2005 because of the localization of her disease. She failed to follow up in clinic until her widespread, serious flare in September of 2006.

At this time systemic treatment was required given her systemic symptoms and painful widespread eruption. We started the patient on Cyclosporine 100mg bid (3mg/kg/day) and continued her topical corticosteroids. Subsequently, she failed to improve, and her dosage was increased to 4mg/kg/day. At her 2 week follow-up, there was some improvement including a significant decrease in pain; however, she continued to get new lesions. Consequently, her dose was increased to 5mg/kg/day, which maintained reasonable control of her disease.

She delivered a healthy 5 lb. 6oz. baby via C-section at 36 weeks of gestation. The patient requested this procedure given her skin pain and distress. The baby is doing well and the mother noted a

decrease in the severity of her psoriasis after delivery. She is currently on Cyclosporine 100mg bid (3/mg/kg/day), triamcinolone 0.1% ointment, and 0.05% fluocinonide solution.

Discussion:

Pustular psoriasis of pregnancy is a rare form of psoriasis in which groups of sterile pustules arise at the edges of erythematous, sometimes annular patches of skin. It is a potentially fatal disease with a high incidence of fetal morbidity and mortality if left untreated. Systemic signs and symptoms tend to be present and include hypocalcemia, elevated leukocyte count, and fever. The onset is usually before the sixth month and the disease is progressive and unlikely to remit before delivery. The disease is not likely to recur with subsequent pregnancies; however, when it does, it tends to be more severe and presents even earlier. Pustular psoriasis of pregnancy presents significant problems given the teratogenic and cytotoxic nature of many medications commonly used in this entity. In general, severe pustular psoriasis flares require systemic treatment and these medications include methotrexate, acitretin, cyclosporine, the various biologic therapies, and prednisone, among others.

Methotrexate is pregnancy category X and is a known abortifacient given its effects as a folic acid antagonist. Treatment with methotrexate is absolutely contraindicated during pregnancy and a spectrum of effects have been observed in pregnancies exposed to methotrexate early in gestation including abortion to skeletal malformations to no abnormalities.

Systemic corticosteroids may often be required for a severe flare of pustular psoriasis during pregnancy and is one of the only times that systemic steroids are used for psoriasis. Systemic corticosteroids have been associated with various abnormalities in laboratory animals (e.g., cleft palate), but use of these medications in humans is more frequently associated with intrauterine growth retardation (IUGR) and low-birth-weight (LBW) infants.

The various biologic treatments for psoriasis, including etanercept, infliximab, adalimumab, efalizumab, and alefacept, can also be considered for cases of widespread psoriasis and, with the exception of eflaizumab (category C), all of them are category B. There is a paucity of data, however, regarding their safety in humans. Their use is generally not recommended in pregnant women unless the benefit-risk ration greatly favors their use.

Cyclosporine is pregnancy category C and pregnancy is considered a relative contraindication to its use. Of the oral agents available for severe psoriasis, cyclosporine may be the safest for women who become pregnant. There is no convincing evidence that cyclosporine acts as a teratogen; however, it has been associated with premature birth and LBW. Most reports of cyclosporine use in pregnancy come from its use in preventing allograft rejection, particularly in renal transplant patients. There have been at least 7 case reports documenting the effective use of cyclosporine for pustular psoriasis in pregnancy with none of the infants experiencing any birth defects.

References:

1. Lamarque V et al. Analysis of 629 pregnancy outcomes in transplant recipients treated with sandimmun. Transplanation Proceedings 1997;29:2480.
2. Oz BB et al. Pregnancy outcome after cyclosporine therapy during pregnancy: a meta-analysis. Transplantation 2001;71(8):1051-5.
3. Tauscher AE et al. Psoriasis and pregnancy. Jour Cutan Med Surg 2002;6(6):561-70.
4. Kapoor JR. Cyclosporine resolves generalized pustular psoriasis of pregnancy. Arch Derm 2006;142: 1373-5.

Case #2

Presented by Warren Piette, MD and Robert Lieberman, MD

History of Present Illness:
The patient is a 62-year-old woman who presented with a two-month history of lesions that began as mildly painful nodules which enlarged and evolved into minimally painful ulcers. One week prior to evaluation, the patient developed subjective fevers, chills, and fatigue, and painless swelling of her knees.

Past Medical History:
Hypertension

Medications/Allergies:
Enalapril, hydrochlorothiazide; No known drug allergies

Social History:
A frequent traveler, she developed ulcers shortly after a 2 month visit to Mexico.

Review of Systems:
She denied weight loss, night sweats and any respiratory, gastrointestinal, or urinary symptoms. She also denied photosensitivity, oral ulcers, seizures, sicca syndrome, or other eye complaints.

Physical Exam:
On her legs there were round, tender 3-4 cm ulcers with hemorrhagic eschar and an erythematous, indurated rim. Strong pedal pulses were palpated. No lymphadenopathy was present.

Laboratory Data:
Most Pertinent abnormal values:
White blood count 1.8 (neutrophils 20%, lymphocytes 51%, monocytes 28%, eosinophils 4%); smudge cells seen on smear; hemoglobin 9.4; mean cell volume 80.8; platelets 132K; erythrocyte sedimentation rate 108; high sensitivity C-reactive protein 0.72 (nl <0.5);
Bone marrow biopsy: hypercellular with lymphocyte predominance, but no abnormal population of cells detected by cytometric analysis

Serologies:
Antinuclear antibody >1:160, speckled
Anti-centromere antibody: negative
Anti-dsDNA antibody 26.27 (nl<50)
Anti-Smith antibody 0.33 (nl<0.9)
Anti-RNP/Smith antibody 0.39 (nl<0.9)
Anti-Ro antibody 3.96 (nl<0.9)
Anti-La antibody 2.21 (nl<0.9)
Anti SCL-70 Antibody 1.00 (nl<1.00)
C3 66 (nl 88-201)
C4 14 (nl 16-47)
Rheumatoid Factor 1120 (nl<20)
Anti-CCP antibody 106 (nl<20)
pANCA <1:10 (nl <1:10)
cANCA 1:80 (nl<1:10)
Anti-MPO 27 (nl<6)
Anti-PR3 <6 (nl<6)

Anti-phospholipid antibody profile
PTT, pre-mix 65.0 (nl 25.6-34.0)
PTT, post-mix 65.4
Beta-2-glycoprotein: positive
Anti-cardiolipin antibody: negative

Case #2 continued

Miscellaneous
Hepatitis C antibody positive; cryoglobulins negative
serum protein electrophoresis: gamma elevation; immunofixation: no M protein identified
IgG 3000 (nl 694-1618); IgA 440 (68-378); IgM 296 (77-220); kappa/lambda ratio of Ig 1.74 (nl 1.41-2.83)

The following additional values were normal or negative:
Comprehensive metabolic panel; liver function tests; PPD; urinalysis; wound culture; blood culture

Histopathology:
10/06 Right Leg: Ulcer with diffuse acute and chronic inflammation with a lobular and septal panniculitis. Stains for fungi and acid-fast bacilli are negative.

Radiology:
Chest x-ray: no infiltrate or hilar lymphadenopathy evident
CT chest/abdomen/pelvis: moderate splenomegaly, no lymphadenopathy

Diagnosis:
Lobular and septal panniculitis; clinical signs, symptoms, and serologies most consistent with lupus panniculitis

Treatment and Course:
The patient was started on hydroxychloroquine 400 mg po daily and prednisone 20 mg daily with subsequent resolution of ulcers. Her pancytopenia responded to Neupogen.

Discussion:
Based on this patient's presentation with fever, fatigue, pancytopenia, and painful skin ulcers on the distal extremities, we initially suspected a diagnosis of atypical Sweet's syndrome or pyoderma gangrenosum in the setting of an underlying myelodysplastic syndrome, myeloma, leukemia, or lymphoma with marrow invasion. A biopsy of the ulcer revealed a lobular and septal panniculitis, which supported neither a diagnosis of Sweet's syndrome nor pyoderma gangrenosum. Additionally, the patient did not have palpable or radiographically detectable lymphadenopathy, M protein detectable on immunofixation, or a clonal proliferation on bone marrow biopsy, all of which made an underlying hematologic malignancy unlikely. The finding of a hyperproliferative bone marrow in the setting of pancytopenia indicated peripheral destruction of these cells, suggestive of an autoimmune etiology. Given the patient's positive anti-nuclear antibody titer, positive lupus anticoagulant, leukopenia, thrombocytopenia and hypocomplementemia, in the setting of a nonspecific lobular panniculitis, a diagnosis of lupus was favored, and the cutaneous ulcers were believed to be a manifestation of the disease.

Lupus panniculitis is a chronic recurrent panniculitis that occurs in 1-3% of patients with cutaneous lupus erythematosus. Lupus panniculitis occurs more frequently in women with a median age of onset of 41 years. Clinically, the disease often presents as indurated, tender, subcutaneous nodules and plaques that develop on the face, proximal extremities, shoulders, hips, and trunk. More uncommonly, lupus panniculitis may present as ulcers. The overlying skin may or may not show classic features of discoid lupus erythematosus, as lupus panniculitis often occurs prior to other manifestations of lupus erythematosus.

Because this patient lacked the clinical criteria of systemic lupus erythematosus, it appeared that this patient's disease was still evolving. Anti-dsDNA and anti-Smith antibodies were negative in this patient, however their prevalence in the sera of patients with systemic lupus is only 60% and 30%, respectively. Additionally, autoantibodies typically manifest many years before the diagnosis of SLE; as

Case #2 continued

observed in patients with SLE who were followed prospectively in the years prior to their diagnosis, antinuclear antibodies, anti-Ro, anti-La antibodies, and anti-phospholipid antibodies all of which were positive in this patient, typically appear many years before diagnosis and precede, by an average of 2 years, the development of anti-dsDNA, anti-Sm and anti-ribonucleoprotein antibodies, which were negative in our patient.

Histopathologic features of lupus panniculitis are characteristic, though the diagnosis may be difficult in those cases involving only the subcutaneous fat. Classically, a lobular panniculitis with a predominantly lymphocytic infiltrate is identified, though concomitant septal involvement may be evident. Lymphoid follicles are characteristic, though not specific, for lupus panniculitis and show germinal centers with plasma cells at the periphery. The collagen bundles within subcutaneous septa may appear hyalinized and sclerotic, and necrosis of adipocytes is minimal to absent. Epidermal and dermal changes of discoid lupus erythematosus are present in over half of cases, and immunofluorescence studies commonly show linear deposition of IgM and C3 along the dermoepidermal junction. The lobular and septal panniculitis identified in our patient, while non-specific, supports the diagnosis of lupus panniculitis established by clinicopathologic correlation.

Our patient manifests a positive lupus anticoagulant, as indicated by the persistently elevated partial thromboplastin time upon 1:1 mixture with sera containing normal quantities of coagulation factors. Lupus anticoagulant is positive in approximately 15-34% of patients with systemic lupus erythematosus and is a risk factor for future thrombotic events. Additionally, this patient may be at increased risk of developing rheumatoid arthritis, as she has a high titer of rheumatoid factor in combination with a positive anti-cyclic citrullinated peptide antibody, the latter of which is associated with an odds ratio ranging from 28 to 64 for the development of rheumatoid arthritis in healthy subjects. She also manifested a cytoplasmic ANCA (cANCA) by indirect immunofluorescence, however, by ELISA, her ANCA was specific for anti-myeloperoxidase, which is classically associated with a perinuclear pattern (pANCA). Because high titers of rheumatoid factor may confound indirect immunofluorescence evaluation in the laboratory, ELISA confirms a perinuclear pattern. Follow-up titers three weeks later confirmed a positive titer of pANCA and negative cANCA. A positive ANCA, particularly pANCA, occurs in 15-20% of patients with lupus. As of yet, there is no proven clinical significance to this relationship.

Lesions of lupus panniculitis may respond to topical and intralesional corticosteroids, however often times systemic therapy with antimalarials is needed. Hydroxychloroquine is often used in this setting and may be required for several years due to the chronic nature of the disease. Dapsone has also been reported as effective therapy in some cases.

References:

1. Arbuckle M, McClain M, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526-1533.
2. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2006;65:845-51
3. Grossberg E, Scherschun L, Fivenson DP. Lupus profundus: not a benign disease. Lupus 2001;10:514.
4. Massone C, Kodama K, Salmhofer W. Lupus erythematosus panniculitis (lupus profundus): clinical, histopathological, and molecular analysis of nine cases. Journal of Cutaneous Pathology 2005;32:396-404.
5. Requena L, Yus ES. Panniculitis. J Am Acad Dermatol 2001;45:325-361.
6. Sen D, Isenberg DA. Antineutrophil cytoplasmic autoantibodies in systemic lupus erythematosus. Lupus 2003;12:651-658.

Case #3

Presented by Warren Piette, MD, Jane Kwan MD, and Sari Weinstein, MD

Patient A:

History of Present Illness:
This 39-year-old Hispanic woman presented with a 2-week history of painful purpura on her right inner thigh. About one month ago, she developed fatigue along with swelling and pain in the joints of her fingers and toes. Her review of systems was otherwise negative, notably for fever or chills, shortness of breath, gastrointestinal or genitourinary symptoms.

Past Medical History:
Two miscarriages at approximately 12 weeks
Splenic artery thrombus
Bleeding diathesis with thrombocytopenia

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory

Physical Exam:
There were non-blanching, sharply demarcated, retiform purpura present on the right medial thigh. The purpura appeared dusky and depressed centrally, and was bordered by an erythematous halo. Livedo reticularis was present proximally. The patient's fingers and toes were swollen; however, the joints were not warm, erythematous, or tender to palpation.

Laboratory Data:
The following were abnormal or positive:

ANA	Positive	[nl: Negative]
	Speckled 1:160	[nl: <1:80]
SSA	5.58	[nl: <0.9]
SSB	1.56	[nl: <0.9]
Rheumatoid Factor	34	[nl: <20]
C3	80mg/dL	[nl: 88-201mg/dL]
C4	<6mg/dL	[nl: 16-47mg/dL]
β2-glycoprotein	Positive	[nl: Negative]
Lupus anticoagulant	Positive	[nl: Negative]

The following were normal or negative:
CBC, basic metabolic panel, urinalysis, hepatitis B and C serologies, HIV serology, RPR, direct Coombs test, c-ANCA, p-ANCA, double-stranded DNA antibodies (Ab), anti-Smith Ab, anti-smooth muscle Ab, anti-parietal cell Ab, anti-endomysial Ab, anti-centromere Ab, anti-RNP, cryoglobulins, anticardiolipin antibodies, antithrombin III, protein C and S, Factor V Leiden, hand films showed soft tissue swelling without bony abnormalities

Pathology:
6/06 Right thigh: vasculitis with fibrin thrombi within small blood vessels and fibrin within vessel walls
DIF: weak IgA, strong IgM/C3 in blood vessels

Case #3 continued

Diagnosis:
Cutaneous infarction from occlusion secondary to antiphospholipid antibody syndrome, with late-stage vasculitis secondary to necrosis and recanalization of thrombus

Treatment and Course:
The patient was started on aspirin and hydroxychloroquine with resolution of the lesions and her symptoms. There is mild residual scarring present. Since the patient is doing well, anticoagulation has not been initiated at this time.

Patient B:

History of Present Illness:
This 24-year-old Mexican woman presented to the Cook County Emergency Department with a three-day history of exquisitely painful bleeding ulcers on her legs. Her ability to walk was limited by pain and acute leg swelling. She had noticed brown lesions on her legs and feet approximately one year prior to presentation; some of these had ulcerated three months prior. She also noted a prominence of veins on her right chest wall beginning approximately when she noted the marks on her legs.

Past Medical History:
None

Medications/Allergies:
Aspirin as needed for pain and a topical medication of unknown composition prescribed by an herbalist for the ulcers; No known drug allergies

Family History:
None

Review of Symptoms:
Review of systems was negative for fevers, chills, headaches, chest pain, cough, shortness of breath, abdominal or urinary complaints, or joint pains. She denied ever being, or trying to be, pregnant.

Physical Exam:
There was warm, tender erythema on both legs with well-circumscribed ulcers bilaterally on her medial and lateral malleoli, and retiform purpura with atrophie blanche-like changes on her distal legs and dorsal feet.

Laboratory Data:
The following were abnormal or positive:

Hemoglobin	9.8 g/dL	[nl: 11.7-15.2g/dL]
MCV	76 fl	[nl: 80-100fl]
PTT	77 sec	[nl: 20-40 sec]
ESR	117 mm/hr	[nl: <20 mm/hr]
Lupus anticoagulant	Positive	[nl: negative]
Anticardiolipin antibody	Positive	[nl: negative]
β-2 glycoprotein	Positive	[nl: negative]

Wound culture with methicillin-resistant Staphylococcus aureus and Klebsiella spp.

The following were normal or negative:
Basic metabolic panel, ANA, hepatitis panel, ANCA screen; X-rays without evidence of osteomyelitis

Case #3 continued

Pathology:
7/06 Left leg: There are fibrin thrombi within small blood vessels in the superficial dermis. A perivascular infiltrate of sparse lymphocytes and rare plasma cells and focally extravasated red cells are noted. There is no neutrophilic infiltrate.

Diagnosis:
Antiphospholipid Antibody Syndrome

Treatment and Course:
She was admitted for presumptive diagnosis of cellulitis and placed on IV antibiotics. Following our consultation, a diagnosis of Antiphospholipid Antibody Syndrome (with secondarily infected ulcers and cellulitis) was suggested. Following laboratory confirmation, she was sent home on aspirin 81 mg daily, oral antibiotics, and with instructions for local wound care. Because the right-sided venous dilatation on the upper trunk suggested chronic superior vena cava obstruction, an outpatient CT scan (pulmonary embolus protocol) was ordered. It revealed calcification of the superior vena cava consistent with old thrombus and a filling defect in the left lower lobe consistent with a new pulmonary embolus. She was readmitted to the hospital for IV heparin and initiation of warfarin. She is currently on a therapeutic dosage of warfarin with marked healing of her ulcers.

Discussion:
Not described until the 1980s, the antiphospholipid antibody syndrome (APS) marked the first association between antiphospholipid antibodies and hypercoagulability. Often correlated with venous thromboses (lower extremity deep venous thrombosis, pulmonary emboli), arterial thromboses (strokes, transient ischemic attacks, myocardial infarctions), and obstetric complications, in a substantial percentage of patients dermatologic manifestations are the presenting feature of the syndrome.

Skin manifestations have been reported in up to half of APS patients, and are often the presenting symptom (in 30.5%, according to one study). Livedo reticularis is the most frequent manifestation, observed in approximately a quarter of patients, with widespread involvement on the limbs, trunk, and/or buttocks. Investigation for possible correlations between livedo reticularis and other manifestations of APS has shown a statistically significant association with arterial thrombosis, cerebrovascular events, systemic hypertension and heart valve abnormalities. Necrotic ulcers are also frequently present, noted in 8%; post-phlebitic ulcers are observed in patients with recurrent phlebitis of the leg, whereas circumscribed skin necrosis is frequently an early feature of APS, often preceded by necrotizing purpura. Pseudovasculitis lesions mimic cutaneous vasculitis and warrant biopsy, which show fibrin thrombi in the small dermal vessels, dermal hemorrhage, and lack of vasculitis. Other reported cutaneous manifestations of APS include painful skin nodules, thrombophlebitis, livedoid vasculitis, subungual splinter hemorrhages, Degos' disease, and erythematous macules, papules, and purpura.

"Secondary APS," in patients with systemic lupus erythematosus (SLE) or another autoimmune disease, is an often-used term which the consensus committee advises against, since it is unknown whether APS and SLE are two diseases which may coincide, or if underlying SLE offers a setting for the development of APS, or if APS and SLE represent two elements of the same process.

Prophylactic treatment for APS, prior to a known thrombotic event, includes aspirin, hydroxychloroquine, and elimination of factors predisposing to thrombosis (hormonal contraceptives, estrogen therapy, COX-2 inhibitors). After a thrombotic event, treatment is warfarin. It is controversial if titration to an INR of 2-3 or >3 is optimal. Discontinuation, however, is associated with an increased risk of thrombosis.

Case #3 continued

2006 International Consensus Statement on Classification Criteria for APS
(diagnosis requires at least one clinical and one laboratory criterion)
Clinical Criteria
1. vascular thrombosis
in any tissue or organ
without significant evidence of inflammation in the vessel wall on histopathology
2. pregnancy morbidity, defined as at least one of the following
at least one unexplained death of a normal fetus at or beyond the 10th week
at least one premature birth of a normal neonate before the 34th week due to eclampsia, preeclampsia, or placental insufficiency
three or more unexplained consecutive spontaneous abortions before the 10th week
Laboratory Criteria, present on two or more occasions, at least 12 months apart
1. lupus anticoagulant (LA) present in plasma
2. anticardiolipin (aCL) antibody of IgG and/or IgM, present in medium or high titer
3. anti-β2 glycoprotein-I antibody of IgG and/or IgM

References:

1. Blume JE, Miller CC. Antiphospholipid syndrome: a review and update for the dermatologist. *Cutis*. 2006 June; 78: 409-415
2. Frances C et al. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. *Arthritis and Rheumatism*. 2005 June; 52(6): 1785-1793.
3. Miyakis S, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *Journal of Thrombosis and Hemostasis*. 2006 Feb; 4(2): 296-306.
4. Robson KJ, Piette WW. The presentation and differential diagnosis of cutaneous vascular occlusion syndromes. Advances in Dermatology. 1999; 15: 153-182.

Case #4

Presented by Warren Piette, MD and Carlos Rodriguez, MD

History of Present Illness:
A 24-year-old African-American female presented with oral erosions and bullous lesions on the trunk and extremities. Six days prior to admission she was seen in the emergency department for a sore throat of several days duration, and had been given chlorhexidine mouth wash. Two days later she developed a vesicular eruption on the face and erosions on the lips, followed by persistent fever, dysuria, watery diarrhea, eye and foot pain, and progressive blistering skin lesions.

Past Medical History:
Systemic lupus erythematosus

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory

Review of Systems:
As above

Physical Exam:
At the time of consultation, the patient was febrile to 102.5F and had multiple vesicles and bullae on the face, with oral erosions and crusting on the lips and oral mucosa. She also had erythematous papules, some with central vesiculation, hemorrhage, or both (erythema multiforme-like) scattered on the neck, upper trunk and arms.

Laboratory Data:
The following were abnormal or positive:

WBC	2800/mm^3	[nl: 3900-10,000/mm^3]
Hgb	10.3 g/dL	[nl: 11.7-15.2g/dL]
Plt	124,000/mm^3	[nl: 140,000-390,000/mm^3]
ESR	74mm/hr	[nl: <20 mm/hr]
ANA	1:160	
Anti-RNP	+	
Anti-Ro	+	
Anti-La	+	
Urinalysis	+ leukocyte esterase, + nitrite, many bacteria	

The following were normal or negative:
Creatinine, liver function tests, blood cultures x 2, Chest X-ray, RPR, conjunctival swab, rheumatoid factor

Histopathology:
12/06 Chest/face: Interface dermatitis, vacuolar type, with numerous necrotic keratinocytes compatible with erythema multiforme or toxic epidermal necrolysis

Diagnosis:
Toxic Epidermal Necrolysis (TEN)-like Lupus Erythematosus

Case #4 continued

Treatment and Course:

Dermatology, Rheumatology, Ophthalmology and Infectious Disease services were consulted 3 days after admission. Prednisone was started at 60mg daily, which initially appeared to slow progression of her eruption. However, within 2 days her blisters worsened, and IVIG 0.7mg/kg/day was added for a total of 4 doses. She was also started on acyclovir 400mg PO 5 times daily and treated topically with emollients and local wound and eye care. Her electrolytes, fluid status and nutritional status were monitored closely. She became pancytopenic and her skin sloughing progressed further during the next few days, and she was transferred to the burn unit 5 days after admission. No active renal or joint involvement was seen at any time. Her cutaneous lesions slowly improved over several days in the burn unit, and prednisone was slowly tapered over the next 2 weeks.

Discussion:

Toxic epidermolysis (TEN)-like lupus erythematosus (LE) describes a rare clinical entity whose presentation combines features of TEN and LE, namely fulminate apoptotic epidermal cell injury in patients with cutaneous and laboratory findings indicative of lupus. TEN is an acute, rapidly-evolving life-threatening bullous disease of the skin and mucous membranes, generally seen as a result of drug hypersensitivity (80-95% of cases). However, a similar clinical presentation may be seen in other settings including lupus, acute graft versus host disease (GVHD) and pseudoporphyria. The clinical features of TEN-like lupus include TEN-like blistering lesions and denudation of skin in a photodistributed pattern, with or without mucositis, and an autoimmune serology consistent with SLE. Although some reported patients developed the syndrome after ingestion of different drugs, which include naproxen and other NSAIDS, most cases described patients in whom drug hypersensitivity was excluded or deemed very unlikely. All reported patients had biopsies consistent with TEN, and varying degrees of systemic involvement from lupus.

The diagnosis of TEN-like lupus is difficult to make due to its heterogeneous clinical presentation, a lack of formal diagnostic guidelines, and particularly since LE patients may have comorbid conditions for which they may be taking TEN-inducing medications. The first such case of erythema multiforme-like LE was described by Rowell in 1963. Subsequently, reports of TEN-like eruptions developing in LE patients were published by other authors, several of which described patients whose laboratory tests included positive antinuclear antibody (ANA), anti-double stranded DNA antibody, anti-La (SSB) antibody, rheumatoid factor, and in particular anti-Ro (SSA) antibody levels. Biopsies of these patients showed changes consistent with TEN, including full thickness epidermal necrosis and, at times, direct immunofluorescence consistent with LE. Some patients experienced a more subacute disease course, with development of TEN-like eruptions over weeks, without systemic features such as fever, gastrointestinal, respiratory, hematologic and renal symptoms. Mandelcorn and Shear suggested the possibility of TEN-like LE being a more severe variant of Rowell's syndrome (recurrent EM in LE patients). Most reported patients were treated with systemic corticosteroids and/or intravenous immunoglobulin (IVIG), and experienced immediate or eventual remission of their disease, although deaths have been reported. Some authors noted worsening of TEN while on steroids. One reported patient developed a deep venous thrombosis shortly after an episode of acute TEN-like lupus.

The classification of bullous skin disease in lupus patients has been focused primarily on immunopathogenetic characteristics including the antibodies involved and the clinical similarities with other known bullous diseases. Although useful, this scheme may be too narrow clinically, and Ting et al proposed a new classification method for bullous LE patients, divided into "LE-specific" and "LE-nonspecific" categories, based on the scheme originally described by Gilliam for cutaneous lupus erythematosus. LE-specific vesiculobullous disease includes those patients whose biopsies demonstrate an interface dermatitis, and whose cutaneous lesions are characteristic of lupus, including ACLE, SCLE, or SLE. LE-nonspecific patients lack an interface dermatitis and may demonstrate EBA-like, DH-like, BP-like, linear IgA-like or PCT-like skin lesions, which occur with their own distinct histologic and

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immunofluorescent patterns, with or without clinical or laboratory evidence of SLE. TEN-like LE falls into the former category. In addition, the term Acute Syndrome of Apoptotic Pan-epidermolysis (ASAP) was proposed by the authors to define a clinical syndrome of massive hyperacute sheet-like epidermal apoptotic injury which may result from multiple distinct etiologies. The acronym ASAP also reinforces the urgency with which the syndrome should be managed.

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Case #5

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

History of Present Illness:
This 19-year-old male presented to our clinic complaining of a several year history of minimally symptomatic nodules on his scalp, arms, and legs that were presumed to be lipomas. No biopsies or workup had been done in the past. He was scheduled for excision of lesions in uncomfortable locations.

Past Medical History:
None.

Medications/Allergies:
None; No known drug allergies.

Family History:
One brother with similar nodules.

Physical Examination:
Upon presentation to clinic, he was found to have firm fixed deep seated nodules on his scalp, left forearm and left leg. During surgery, these nodules appeared encapsulated, were located deep in the subcutaneous tissue, and attached to even deeper tissue. On removal, the lesions felt firmly gelatinous, almost cartilaginous in character. These changes prompted reexamination in the procedure room. He was noted to have multiple brown 2-3 mm macules in his bilateral axilla and multiple greater than 15 mm brown patches on his posterior neck, lower back, chest, abdomen and legs. He also had golden brown flecks in his bilateral irises, prompting referral to ophthalmology for a slit lamp examination.

Laboratory Data:
None.

Histopathology:
6/06: Posterior scalp, left forearm and left thigh: These three specimens show interconnecting bundles and fascicles of markedly expanded nerves surrounded by fibrous encapsulations. The individual fascicles display variable cellularity and often show edematous and mucinous changes. The fascicles are composed of proliferating delicate spindle cells and mast cells embedded in a myxoid to collagenous stroma. They were all found to be histologically consistent with plexiform neurofibroma. They were all positive for S100.

Diagnosis:
Neurofibromatosis type I

Treatment and Course:
Patient healed well after surgery, was referred to ophthalmology and for genetic counseling.

Discussion:
Neurofibromatosis I, formerly known as von Recklinghausen disease, is an autosomal dominant hamartomatous disease, affecting approximately 1 in 3500 individuals worldwide. Clinical criteria for diagnosis include two or more of the following: 6 or more café au lait macules larger than 5 mm before puberty or 15 mm after puberty, skinfold freckling, 2 or more neurofibromas or 1 plexiform neurofibroma, 2 or more Lisch nodules, an optic glioma, characteristic skeletal dysplasias such as tibial or sphenoid wing dysplasia, and an affected first degree relative. Although it is a classic autosomal

Case #5 continued

dominant disorder, approximately fifty percent of affected individuals have no affected parent indicating a new mutation.

The gene responsible for NF1 is located on chromosome 17 and encodes for neurofibromin, a GTPase activating protein which inactivates the intracellular signal transducer protein Ras. This is a tumor suppressor gene and is expressed in neurons, glial cells, and Schwann cells. Mutations result in loss of neurofibromin function and only Schwann cells in neurofibromas have been shown to have two mutated NF1 alleles. The other cells seen in neurofibromas, including fibroblasts, mast cells, and perineural cells are thought to be induced by cytokines. This disease is diagnosed using the previously described clinical criteria although molecular diagnostic methods are clinically available. However, molecular testing does not predict disease severity or specific complications.

Neurofibromas arise from cells of the nerve sheath. These can be focal growths or as in this case, extend along the length of the nerve involving multiple fascicles and can include nerve branches. Such lesions are referred to as plexiform neurofibromas and tend to occur on the trunk, extremities, head and neck. These are poorly circumscribed lesions and can grow very large and lead to deformity or compression of nerves and other structures. They are present in approximately 17% of NF1 patients and surgery is currently the only available means of treatment. Several clinical trials are currently studying antifibrotic drugs and Ras inhibitors for treatment of plexiform neurofibromas.

A 2-5% risk of malignant peripheral nerve sheath tumor development exists in patients with NF1. Early diagnosis is difficult as these malignancies tend to arise from preexisting benign lesions.

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Case #6

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

History of Present Illness:
This 37 year-old woman presented with multiple blue-red vesicular papules on her abdomen surrounded by a slightly indurated, erythematous plaque for 2 months. The patient states that the papules drain clear fluid at home when traumatized. She had been treated in the past with several rounds of antibiotics with only minimal resolution of the erythema. She has no fever, chills, or pain.

Past Medical History:
Hypertension, diabetes mellitus, obesity

Medications/Allergies:
Hydrochlorothiazide, enalapril, glucophage; No known drug allergies

Family History:
Non-contributory

Review of Systems:
Negative

Physical Exam:
This extremely overweight patient had a large abdominal pannus with multiple blue-red vesicular papules around her umbilicus. The papules were surrounded by an indurated, erythematous plaque with pitting edema. She has 1+ pitting of both legs.

Laboratory data:
The following were abnormal or positive:

CEA	8.31 mcg/l	[nl: <2.5 mcg/l]
CA 125	301.5 mcg.l	[nl: <35 kU/ml]
CA 19.9	171.8 U/ml	[nl: <40 U/ml]

The following were normal or negative:
Metabolic panel, CBC with differential

Histopathology:
8/06 Abdomen: Irregular dilated vascular spaces, with a branching and anastamosing pattern, thin walls, and lymphatic appearance involving the superficial dermis; compatible with benign lymphangioma. Vascular spaces positive for CD 34 and factor 8, negative for CD 68

Radiology:
CT abdomen: Lower abdomen and pelvic mass seen. This could possibly represent exophytic uterine fibroids. The presence of an ovarian tumor cannot be excluded. There is evidence of inguinal lymphadenopathy. There is a cystic fluid collection in the inferior and left anterior abdominal all. This could represent an abscess.

US pelvis: 14.7 X 10.2 X 13.4 cm right adnexal mass

Diagnosis:
Acquired Lymphangiectasis secondary to abdominal tumor.

Case #6 continued

Treatment and Course:

Initially the patient was encouraged to lose weight. Topical triamcinolone ointment was given for the stasis dermatitis of her abdomen. At the time of this write-up the patient was scheduled for an exploratory laparotomy to evaluate her abdominal tumor.

Discussion:

Acquired lymphangiectasis (AL) is a condition in which dilated superficial lymphatic vessels develop after damage and blockage of previously normal deep lymphatic vessels. It is often coexistent with lymphedema and frequently associated with cancer surgery and radiation therapy. It has also been reported to result from metastatic lymph node invasion and obstruction, scleroderma, and scrofuloderma. Acquired lymphangiectasis has been reported as clinically and histologically indistinguishable from congenital lymphangioma circuscriptum. The two names have often been used interchangeably in the literature. There has previously been one reported case of benign lymphangiomatous papules of the skin associated with ovarian fibroma. This may represent the second case of acquired lymphangiectasis described in association with an untreated tumor, without previous operation or radiotherapy.

Acquired lymphangiectasis and lymphangioma circuscriptum share similar clinical and histological features. Recently, however, the term acquired lymphangiectasis has been used to describe the defect arising in previously normal lymphatics, while lymphangioma circuscriptum describes the similar congenital defect.

Clinically AL consists of clusters of translucent vesicles that range from colorless to red to purple depending on the content of red cells in the lymphatic channels. The overlying skin may be hyperkeratotic, thickened, or verrucous in appearance.

Complications of AL include leakage of the vesicles, recurrent cellulitis, and pain. Although there is one reported case of a squamous cell carcinoma arising in lymphangioma circumscriptum.

Treatment of AL can be problematic because the responsible lymphatic channels must either be excised or sealed to prevent recurrence. Compression, electrodessication, cryotherapy, sclerotherapy, surgical excision, as well as laser have all been tried. The argon, tunable dye, and CO2 laser have been moderately successful. Scarring and reccurrences are common with all treatments. In the other case of benign lymphangiomatous papules associated with ovarian fibroma, the unbilical papules resolved after excision of the tumor.

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Case #7

Presented By Warren Piette, MD and Meredith Stewart Reimer, MD

UNKNOWN

Case #8

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

History of Present Illness:
This seven-year-old girl was admitted to the hospital with an abdominal mass and painless hematuria. On prenatal ultrasound, an intra-abdominal cystic mass was discovered. This mass was resected when the patient was three years old, and histologic examination revealed it to be a lymphangioma. The child moved out of state and was lost to follow-up until reappearing in Chicago several weeks ago with a recurrence of the mass and the development of skin lesions around her surgical scar. She complains of occasional pain with micturation, but denies any other abdominal pain or symptoms.

Past Medical History:
Resection of abdominal lymphangioma at three years of age

Medications/Allergies:
None; No known drug allergies

Physical Exam:
There is a large, soft, palpable, right-sided abdominal mass. A long, linear scar is visible stretching from the right mid-back, across the flank, to the right lower pelvis. Numerous clear, skin-colored, erythematous and black verrucous papules are clustered in the area of the scar, some coalescing into plaques and others scattered singly around the periphery.

Laboratory Data:
The following were abnormal or positive:
Urinalysis with gross hematuria
The following were normal or negative:
CBC, BUN, creatinine

Radiology:
MRI Abdomen/Pelvis: There are extensive retrocrural, retroperitoneal, right lateral and posterior paraspinal, and abdominal wall lymphangiomas spanning from the level of T10 to the pelvis, displacing the urinary bladder to the left. The lesion infiltrates the right gluteal muscles and the overlying subcutaneous tissue. The lesion encases and displaces the inferior vena cava and abdominal aorta. Multiple lymphangiomas area also noted in the spleen, liver, and mid and lower poles of the right kidney. The lympangiomas extend into the right neuroforamina and ventral epidural space of T12 to L4. There is no spinal cord compression.

Diagnosis:
Lymphangioma circumscriptum overlying retroperitoneal lymphangioma

Treatment and Course:
The patient was observed in the hospital and her hematuria eventually resolved. She is awaiting possible surgical intervention at this time.

Discussion:
Lymphangiomas are benign, congenital malformations of lymphatic tissue that result from the sequestration of lymphatic vessels that fail to establish connections with the normal draining lymphatics. This developmental defect occurs during weeks 14 to 20 of intrauterine life. The exact incidence of lymphangiomas is unknown, although some estimate that it occurs in one out of every 6,000 live births. Fifty to sixty percent manifest by one year of age and 90% by age two years. Radiologically and histologically, lymphangiomas are classified as microcystic, macrocystic, or combined, depending on the size of the

Case #8 continued

endothelial lined spaces. They occur in the head and neck region in 75% of cases and the axillae in 20%; the remaining 5% develop in sites such as the mediastinum and the abdomen. Intra-abdominal lymphangiomas most commonly develop in the mesentery and omentum, with the retroperitoneum, spleen, liver and pancreas being less common sites.

Retroperitoneal lymphangiomas represent less than 1% of all lymphangiomas and are almost always of the cystic type. They usually present as a soft, painless, slowly growing abdominal mass. Although benign, they can cause complications by becoming locally invasive or compressing adjacent, vital structures. Rapid enlargement can occur with infection, hemorrhage, rupture or torsion, leading to symptoms of acute abdomen. The association of cutaneous lymphangiomas with deeper lymphatic involvement is unusual and has been described occasionally in the literature, with only one reported case of lymphangioma circumscriptum associated with retroperitoneal lymphangioma. Interestingly, the child in that case report also presented with painless hematuria from bladder wall involvement.

Diagnosis can be made radiologically using several modalities. Ultrasonography can identify multiloculated cystic masses that are anechoic with septations. On CT, lymphangiomas can appear as a homogenous, well-defined, multicystic lesion with a low attenuation value ranging between that of fluid or fat. On MRI, a mass with low signal intensity is seen on T-1 weighted images, while high signal intensity is seen on T-2 weighted images.

Lymphangiomas rarely undergo malignant change or spontaneous resolution. The treatment of choice is complete surgical resection. However, in some cases, it may be impossible to achieve complete extirpation of the lesion due to its proximity to and infiltration of vital organs. High recurrence rates also make surgery a less than ideal option. Radiotherapy was tried in the past, but soon abandoned due to complications. Chemotherapy is reserved for use in otherwise untreatable cases. Sclerotherapy with hypertonic saline has been used to treat cutaneous lesions; sclerosants used for deeper lymphangiomas include bleomycin, ethanol and acetic acid.

A promising sclerosing agent named OK-432 (Picibanil) is composed of a Group A Streptococcus pyogenes strain of human origin that has lost its streptolysin S-producing ability. This modified, low virulence strain is combined with penicillin G and works by causing a local inflammatory reaction. The resulting production of various cytokines leads to increased endothelial permeability, accelerated lymphatic drainage, and shrinkage of the cystic spaces without any scar formation of the overlying skin. This mimics the mechanism by which repeated lymphangiitis causes scarring of lymphatic vessels, with resultant lymphedema. In studies, it has been shown to have excellent results in the macrocystic type of lymphangioma, with a less favorable and more variable response in the microcystic type. It has been used to treat retroperitoneal lymphangioma and lymphangioma circumscriptum in case reports with good outcomes.

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Case #9

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

History of Present Illness:
This 33 year-old woman with a history of HIV infection and heroin addiction presented to the Cook County Emergency room with a two week history of worsening abdominal distension and fullness. She also reported the appearance of multiple, asymptomatic subcutaneous nodules on her abdomen, back, arms and axillae over the past two weeks. On extensive review of systems, she reported a recent history of subjective fevers with chills, drenching night sweats, and a 10 lb weight loss despite a normal appetite. She denied abdominal pain, nausea, vomiting, diarrhea, myalgias, arthralgias, headaches, dizziness or vision changes. She was sent to the dermatology clinic for biopsy of the subcutaneous nodules.

Past Medical History:
HIV infection-CD4 count unknown, Heroin Addiction, benign ovarian tumor excised 2000, arm fracture

Medications/Allergies:
Methadone; No known drug allergies

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

Physical Exam:
This was a thin woman in no acute distress. She was alert, oriented, and cooperative with a distended abdomen and cachectic extremities. Abdominal exam revealed a nontender, diffusely distended abdomen. The liver and spleen were not palpable and there was no fluid wave. There were multiple rubbery, movable subcutaneous nodules measuring 1-3 cm over the neck, submandibular area, shoulders, back and abdomen. There were larger 2-3 cm firm, fixed nodules in both axillae with no overlying skin changes.

Laboratory Data:
The following were abnormal or positive:

Hemoglobin	8.8 g/dl	[nl: 12.0-16.0 g/dl]
Hematocrit	28.1%	[nl: 35-45%]
Platelets	536,000/ mm^3	[nl: 150,000-450,000/mm^3]
AST	109mg/dl	[nl:10-40 mg/dl]
GGT	430 mg/dl	[nl: 3-60 mg/dl]
LDH	1781u/L	[nl: 50 - 150 U/L]
AlkP	504 u/L	[nl: 32 - 110 U/L]
Hepatitis C A	positive	[nl: negative]
CD3+/CD4+ cells	315/mm^3	[nl: 500-1500/mm^3]
CA-125	206kU/ml	[nl: <35 kU /ml]

The following were normal or negative:
AFP, CEA, ALT, WBC

Radiology:
CT Chest/Abdomen/Pelvis: There is a large mass, 11.2 cm x 7.2 cm, in the right lower abdomen which is extending to the right adnexa. Extensive lymphadenopathy is noted in the retroperitoneum and the subcutaneous tissues of the lower abdomen and pelvis. The liver is enlarged to 17 cm in length with multiple nodular densities throughout the liver. The spleen is enlarged to 14.5 cm in length. There are soft tissue densities encasing both kidneys and extending to the right renal hilum. There is a small amount of ascites. There are multiple nodular densities in both lower lung fields. There is no hilar or mediastinal lymphadenopathy. There are multiple subcutaneous enlarged lymph nodes noted in the thorax and bilateral axillary region.

Case #9 continued

Histopathology:

3/06: Skin Biopsy of nodule, Left axilla: The tumor is located in the dermis and subcutis and is composed of a diffuse infiltrate of monotonous medium-sized lymphoid cells showing round nuclei and clumped or fine chromatin with one or more large nucleoli. There are scattered macrophages with the appearance of a starry sky. Mitotic figures and apoptotic bodies are brisk. The tumor cells are positive for CD20 and CD10. Ki-67 immunostain shows a high index (>95%) of nuclear reactivity.

3/06: Bone Marrow Biopsy: negative for atypical infiltrates or abnormal population of cells

Diagnosis:

Burkitt's Lymphoma with metastases to skin, Stage IV BE

Treatment and Course:

The patient was initially started on HAART therapy for her HIV infection with Sustiva (efavirenz) and Combivir (zidovudine/lamivudine). She was then started on allopurinol before the commencement of aggressive chemotherapy. The first round of the hyperCVAD regimen which includes cyclophosphamide, vincristine, adriamycin and dexamethasone was given while she was an inpatient. The patient had an Ommaya intrathecal catheter placed and was given one dose of intrathecal methotrexate. She tolerated the first round of chemotherapy well and was discharged home with scheduled outpatient chemotherapy. The patient died at an outside hospital of unknown cause two weeks after discharge from the hospital.

Discussion:

Burkitt's lymphoma (BL) is a highly aggressive B-cell malignancy with endemic, sporadic, and immunodeficiency-associated clinical variants. Burkitt's lymphoma and Burkitt cell leukemia are classified as different manifestations of the same disease in the World Health Organization (WHO) classification of hematologic malignancies. In the WHO classification scheme, Burkitt's lymphoma is classified as a highly aggressive variant of Non-Hodgkin's lymphoma (NHL). BL is a B-cell neoplasm composed of monomorphic, medium-sized cells with basophilic cytoplasm and a high proliferation fraction, characterized by translocation and deregulation of the c-myc gene on chromosome 8. Histologically, the two characteristic features include the high proliferation fraction with frequent mitotic figures and a fraction of Ki-67+ cells approaching 100% and a "starry sky" pattern produced by numerous benign macrophages that have ingested apoptotic tumor cells. BL cells express monotypic surface IgM, pan-B-cell antigens, including CD19, CD20, CD22, and CD79a, and coexpresses CD10, Bcl-6, CD43, and p53 but not CD5, CD23, Bcl-2, CD138, or TdT.

The defining biologic feature of BL is c-myc protooncogene deregulation which results in tumor cells that are constantly in cycle demonstrated by the high proliferation fraction of the tumor cells. Genetically, BL cells demonstrate rearrangement of the immunoglobulin heavy and light chains leading to increased expression of c-myc gene, presumably by its proximity to the regulatory sequences of the immunoglobulin genes. In 90% of the cases studied, BL involves a translocation between the long arm of chromosome 8, the site of the c-myc oncogene (8q24), and one of three locations: the Ig heavy chain region on chromosome 14 [t(8;14)], the kappa light chain locus on chromosome 2 [t(2;80)], or the lambda light chain locus on chromosome 22 [t(8;22)]. The translocation between the c-myc gene and the Ig heavy chain region [t(8;14)] is found in the majority (80%) of cases. In addition, BL is closely linked to Epstein-Barr Virus (EBV) infection. The expression of CD21, the EBV/C3d receptor is dependent upon the EBV status of the tumor.

There are three distinct clinical variants of Burkitt's lymphoma: endemic, sporadic, and immunodeficiency-associated. The endemic or African form presents as a jaw or facial bone tumor that spreads to extranodal sites and is most commonly seen in African children, usually 4-7 years old, with a male:female ratio of 2:1. EBV is found in nearly 100% of cases. The sporadic form occurs worldwide and accounts for 1-2% of lymphoma in adults and up to 40% of lymphoma in children in the U.S. and

Case #9 continued

western Europe. It usually has an abdominal presentation with massive disease and neoplastic cells are EBV positive in only 15-30% of cases. The immunodeficiency-associated variant occurs mainly in patients infected with HIV but also occurs in allograft recipients and patients with congenital immunodeficiency. This variant often involves the lymph nodes, bone marrow, and extranodal sites, most often in the abdomen. BL accounts for 30-40% of NHL in HIV-positive patients. Compared with other HIV-positive patients with NHL, those with BL are younger and have higher mean CD4 counts (usually >200/µl). While only 25-40% of HIV-associated BL contain EBV genomes, this variant shares many pathogenetic features with the endemic variant. HIV infection leads to polyclonal B-cell activation and thus permits poorly controlled proliferation of EBV positive B cells which leads to a greater risk of c-myc rearrangement, and then to lymphoma. Endemic BL is exquisitely sensitive to chemotherapy, with a good prognosis. However, sporadic and immunodeficiency-associated BL is not as sensitive and patients have a poor prognosis and require short duration, high-intensity chemotherapy, usually with CNS prophylaxis.

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Case #10

Presented by Lissette Ortiz-Ferrer, MD and Giacomo Maggiolino, MD

History of Present Illness:
This is a 33 year old African American woman recently diagnosed with HIV with a CD4 count of 333 who was admitted to the hospital with complaints of painful oral erosions and genital lesions of 3 weeks duration. She complained of uncontrollable drooling. She had also noticed a clear discharge from both her genital lesions and vagina.
On admission to the hospital, she was started on oral Acyclovir for presumed herpes simplex viral infection. She was also treated with IV Fluconazole for thrush and given a stomatitis cocktail. She underwent an endoscopy for odonophagia which showed the entire esophagus appearing erythematous, friable, and edematous. ENT was consulted for a biopsy of an oral lesion.

Past Medical History:
Asthma, HIV

Medications/Allergies
Albuterol; No known drug allergies

Family History:
Non-contributory

Physical Exam:
The patient appeared very ill and uncomfortable. She had multiple oral erosions on her lips and oral mucosa. She also had two small erosions on the left labia majora which were extremely friable.

Laboratory Data:
The following were abnormal or positive:

CD3 + CD4:	262	[nl: 590-1060]
HIV RNA :	391	[nl: 0]
HSV ½ Antibody IgG:	Positive	[nl: negative]
Indirect Immunoflourescence:	Positive	
	1:40 Pemphigus antibody titer (substrate: monkey esophagus)	

The following were normal or negative:
Fungal culture, viral culture, HSV antibody IgM, complete blood count, basic metabolic profile.

Histopathology:
9/06: Oral mucosa: suprabasalar acantholysis
Oral mucosa: DIF negative

Diagnosis:
Pemphigus Vulgaris in an HIV positive patient

Treatment and Course:
The patient was started on oral Prednisone 80mg/day. Within a couple days, she immediately started feeling better. Both oral erosions and genital lesions started to clear. After one week of treatment, the Prednisone dose was decreased to 60mg/day, and Mycophenolate Mofetil (MMF) 500mg twice a day was started. She was subsequently discharged from the hospital and followed up one week later in clinic. At follow up, she no longer had anymore oral or genital lesions. Prednisone was continued to be tapered while continuing MMF at 500mg twice a day.

Case #10 continued

Discussion:

Pemphigus vulgaris is an autoimmune disease of the skin characterized by the development of relatively flaccid bullae on normal skin and mucous membranes. The disease is most commonly caused by autoimmune antibodies against Desmoglien 3, a transmembrane glycoprotein involved in cell adhesion. Autoantibodies against both Desmoglien 1 and 3 are found in patients with mucocutaneous disease.

There have been more than a few cases reported of HIV infected individuals developing autoimmune bullous diseases such as Pemphigus Vulgaris. Recent evidence has suggested that there is a loss of regulation of the immune system in early HIV disease that may account for the development of such autoimmune skin diseases. Several mechanisms have been proposed to explain how HIV leads to autoimmune diseases. One theory suggests that there is a nonspecific polyclonal B cell simulation secondary to IL-1 and IL-6 which are released by HIV infected macrophages. Another theory suggests that this polyclonal B cell simulation may also occur as a result of the loss of specific immunomodulatory T4 cells.

Treatment of Pemphigus Vulgaris in the setting of HIV infection remains a challenge. Hodgson et al. reported a rapid resolution of oral mucosal Pemphigus Vulgaris and a prolonged period of remission with cyclosporine therapy (which has also been shown to be beneficial in HIV by blocking T cell activation, reducing permissivity to HIV and preventing HIV viron maturation). However, Cyclosporine is not a safe drug to use in a patient on antiretroviral therapy. Mignogna et al. reported a case of an acute cyclosporine nephrotoxicity in a patient with Pemphigus Vulgaris and HIV on antiretroviral therapy. The report pointed out that there is a high risk of drug-to-drug interaction of Cyclosporine with protease inhibitors and HAART which is due to Cyclosporine's metabolism involving cytochrome p-glycoprotein and P450 enzyme system.

We decided to include Mycophenolate Mofetil (MMF) into the treatment of our patient based on a very recent placebo-controlled pilot study (Rupinderjeet et al.) which showed that the administration of MMF with HAART appeared to be safe, lead to decreased T cell activation, and was correlated with declines in viremia. Garcia et al. also found that MMF delayed viral load rebound and improved control of viral replication when patients stopped taking HAART . Because of its suggested safety in use with HAART antiretroviral therapy along with recent evidence of its own antiretroviral properties, we suggest that MMF be considered as a possible treatment of Pemphigus Vulgaris in HIV infected patients. Studies are still needed in evaluating MMF in the treatment of Pemphigus vulgaris in HIV patients.

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Case #11

Presented by Jerry Feldman, MD, and Giacomo Maggiolino, MD

History of Present Illness:
This is a 63 year old Hispanic male with a history of a "fungus infection" of his right foot for the past 17 years who has had two excisions of a soft tissue mass from the right foot at St. Mary of Nazareth Hospital Center 4 years ago. Over the past couple of years, he has developed increased swelling and pain within the same foot. He has been on Bactrim DS BID and Sporanox 100mg BID since December 2005 with improvement and now presents to Stroger Cook County Hospital in January 2006 for further evaluation.

Past Medical History:
Hypertension

Medications/Allergies:
Bactrim DS, Sporanox, Nabumetone, Toprol XL, Enalapril; No known drug allergies

Family History:
Non-contributory

Physical Exam:
+1 pitting edema of the right foot with multiple hyperpigmented brown and pink nodules with actively draining sinuses noted on the dorsom of the foot.

Laboratory Data:
The following were abnormal or positive:

Fungal Cultures (St. Mary's; 8/02): Aspergillus Fumigatus and Cladosporium isolated

The following were normal or negative:

Bacterial cultures (St. Mary's; 8/02), bacterial cultures (St. Mary's; 12/02), complete blood count, basic metabolic profile

Histopathology:
8/02 Right foot (St. Mary's): Granulomatous areas surrounding bacterial aggregates
12/02 Right foot (St. Mary's): Acute necrotic inflammation, multiple pieces of skin with focal hemorrhage. No malignancy and no granuloma seen. Cluster of actinomyces species identified within some of the pieces of the tissue.
12/02 Right foot (St. Mary's slide re-evaluated by Cook County Hospital): Fibrosis with abscess formation. A grain is identified within one of the abscesses.

Diagnosis:
Madura Foot

Treatment and Course:
The patient was treated for a total of one year on both Bactrim DS BID and Sporanox 100mg BID with improvement of both pain and swelling

Discussion:
Madura foot (also known as Maduramycosis) is a granulomatous inflammatory disease caused by a chronic infection of the skin and tissues with either bacteria (actinomycetoma) or fungi (eumycetoma). Worldwide, approximately 60% of mycetomas are actinomycetomas. They are occasionally seen in the South of the United States and are endemic in what is known as the Mycetoma belt which stretches between the latitudes of 15 degrees south and 30 degrees north.

Case #11 continued

Actinomycetomas may be caused by several pathogens. Both endogenous anaerobic bacteria (such as *Actinomyces israellii* and *Actinomyces bovis)* or aerobic bacteria (such as *Actinomadura sp*., *Nocardia brasiliensis*, and *Streptomyces sp.)* have been found to cause Actinomycetomas. These organisms are usually found in the form of grains which are present in the soil, where they may be accidentally implanted into the host tissue by a break in the skin.

Actinomycetomas are commonly characterized by the clinical triad of subcutaneous swelling, draining sinuses, and extrusion of grains. Early lesions present as painless papules surrounded by an indurated subcutaneous swelling; these papules may eventually turn into nodules that may suppurate and drain through multiple sinus tracts. The mycetoma may begin to spread and eventually involve and destroy nearby fascia, muscles, and possibly even bone. The lower limbs are usually affected, with the foot being the most common site (60%) followed by the hand. Adults aged 20 to 40 years are usually affected, and there is a predominance of males.

Diagnosis can be established by examination of the grains (drained through sinus tracts), culture of the lesions, fine-needle aspiration, and biopsy. Grains of Actinomycetoma are characterized by Gram-negative centers with Gram-positive fine radiating fringes. These grains are usually visualized histologically along with three possible tissue reactions which have been described. In Type 1 reactions, a layer of polymorphonuclear leukocytes is found surrounding the grains. In Type 2 reactions, macrophages and multinucleated giant cells are found to have engulfed grain material. Type 3 reactions show the formation of a well organized epitheliod granuloma with Langerhan's giant cells. Diagnosis can also be enhanced by radiologic imaging based on muscle and bone involvement.

Treatment of Actinomycetomas consists of antibiotic therapy with various combination of drugs. Common drugs in use include the combination of streptomycin and dapsone. If there is no response after a few months, then cotrimaxazole or rifampicin may be tried in substitution of dapsone. In resistant cases, sulfadoxine-pyrimethamine and sulphonamides have been shown to be effective. The average duration of treatment is about one year with cure rates between 60% and 90%. Surgery is indicated when Actinomycetomas do not respond to medical treatment.

Gunduz et al. recently published a case report of mycetoma successfully treated with itraconazole and co-trimoxazole in a patient who was found to have evidence of both a fungal and bacterial infection. Because our patient was also suspected of both a fungal and bacterial infection, he was treated with the same regimen of itraconazole (Sporanox) and co-trimoxazole (Bactrim DS).

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Case #12

Case Presented by Sidney Barsky, MD and Samantha Golden Stoler, MD

History of Present Illness:
This 27-year-old Syrian man presented to the Cook County Hospital with fever, chills, headache, and disseminated vesicles of 3 days duration. He chronically has extensive pruritic dermatitis for which he uses emollients alone for treatment. He has a history of recurrent umbilicated facial papules and currently has many on his forehead and face.

Past Medical History:
He has a lifetime history of severe eczema, recurrent infections and thrombocytopenia. His history is negative for spontaneous bleeding. He has received several courses of IVIG in the past, but has never had a bone marrow transplant.

Medications/Allergies:
None; No known drug allergies

Family History:
Younger brother with similar history. Deceased age 13.

Review of Sytems:
Negative for chest pain, SOB, bleeding, abdominal pain.

Social History:
He is a medical student in Syria.

Physical Exam:
He had extensive excoriated, erythematous, lichenified plaques on full body surfaces. His forehead was studded with many (>25) shiny, small, skin colored, umbilicated papules. His back and left axilla had vesicles, pustules, and many small papules with hemorrhagic crusts. There was extensive, generalized scaling.

Laboratory data:
The following were abnormal or positive:

Hemoglobin	10.6 gm/dl	[nl: 12.0-16.0 gm/dl]
Hematocrit	32.3%	[nl: 38.1-49.0 %]
MCV	75.7 fml	[nl: 83.2-97.0 fml]
Platelets	35,000/mm^3	[nl: 150,000-450,000/mm^3]
CD4+/CD3+ cells	376/ mm^3	[nl: 500-1500 cells/mm^3]

The following were normal or negative:
Metabolic panel, white blood cell count with differential, reticulocyte count, direct coombs test

Histopathology:
None.

Diagnosis:
Wiskott-Aldrich Syndrome with an atopic dermatitis-like skin eruption, disseminated herpes zoster, and molluscum contagiosum.

Case #12 continued

Treatment and Course:

Herpes zoster was treated with intravenous acyclovir and topical corticosteroids. Emollients were used for his severe eczema. IVIG was administered by the internal medicine team. Treatment of molluscum contagiosum was temporarily deferred.

Discussion:

The Wiskott-Aldrich syndrome (WAS) is an X-linked immunodeficiency disease that characteristically includes: thrombocytopenia with small platelets, eczema, and recurrent infections. Patients have an increased incidence of autoimmune manifestations and malignancies. There are variable clinical phenotypes that correlate with the type of mutations in the *WAS protein* (*WASP*) gene. WASP, a key regulator of actin polymerization in hematopoietic cells, plays a role in cell signaling, locomotion, and immune synapse formation. WASP facilitates the nuclear translocation of nuclear factor kappa β, enhancing lymphoid development and maturation and function of myeloid monocytic cells. Variable mutations in the WASP gene result in a clinical spectrum of disease including: classic WAS, X-Linked Thrombocytopenia, and congenital X-linked neutropenia. The incidence of the classic WAS phenotype has been estimated to be between 1 and 10 in 1 million individuals.

The severity of the immune deficiency can vary. Both T- and B-lymphocyte functions are affected, and lymphopenia is common. Serum IgG levels are generally normal, IgM levels may be moderately decreased, and IgA and IgE levels are often increased. Antibody responses are often insufficient. Thrombocytopenia associated with small platelets is a consistent finding in patients with mutations of the *WASP* gene. The absence or reduced quantity of WASP in lymphocytes is the best confirmatory test short of mutation analysis.

Eczema is common, and superinfection with molluscum contagiosum, herpes simplex, or bacterial infections can develop. Autoimmune diseases are frequent, most commonly reported is autoimmune hemolytic anemia. Malignant tumors can occur during childhood but are more frequent in adolescents and young adults with the classic WAS phenotype.

The *WASP* gene has been mapped to the region Xp11.22-Xp11.3, encoding a 502-amino-acid intracellular protein (WASP) expressed exclusively in hematopoietic cells. Molecular confirmation can now diagnose symptomatic male subjects, identify carrier female subjects, and reveal WAS-XLT in at-risk fetuses. Mutation analysis may be essential for establishing a final diagnosis of WAS.

Management of patients with WAS is very difficult. Early diagnosis is important for effective prophylaxis and treatment. Bacterial, viral, or fungal culture and appropriate antimicrobial therapy is of crucial importance. If antibody responses to protein or polysaccharide antigens are defective, prophylactic intravenous immunoglobulin (IVIG) infusions at full therapeutic dose are recommended. Eczema, if severe, requires aggressive therapy, including local steroids and, if indicated, short-term systemic use of prednisone. Autoimmune manifestations might require more aggressive immunosuppresion and might be refractory to conventional modalities. Autoimmune blood dyscrasias might respond to mAbs targeting the CD20 antigen (rituximab). Platelet transfusions are restricted to treat serious bleeding. Splenectomy, if performed, requires lifelong antibiotic prophylaxis. At present, the only curative therapy is HSC transplantation.

References:

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Case #13

Presented by Sidney Barsky, MD and Carlos Rodriguez, MD

History of present Illness:
A 29-year-old woman presented with fever and a six month history of red, edematous, painful breasts.

Past Medical History:
None

Medications/Allergies:
Cephalexin, metronidazole; No known drug allergies

Family History:
Non-contributory

Review of Systems:
+ fever and breast pain.

Physical Exam:
Febrile; Bilateral warm, tender, erythematous, edematous, indurated breasts with peau d'orange appearance. No nipple discharge, lymphadenopathy in the axillary or cervical nodes.

Laboratory Data:
The following was abnormal or positive:

Neutrophils	77%	[nl: 47.1-75.1%]

The following were normal or negative:
Complete blood count, AFB, fine needle aspirate

Histopathology:
2/06: Breast: Skin with fat necrosis, foreign body giant cells surrounding cystic spaces in the reticular dermis and subcutis, "Swiss cheese" vacuoles, fibrosis and foci of calcification, papillary clusters of neutrophils and debris and neutrophils in the intervening septae.

Diagnosis:
Silicone Granuloma

Treatment and Course:
The patient was admitted and treated with IV vancomycin and clindamycin and pain medications. Her biopsy specimen revealed industrial grade silicone which she admitted having had injected several times by a non-physician from 7 months to 1.5 years prior. She was seen by Gynecologic Oncology and Plastic Surgery to exclude malignancy and discuss possible bilateral mastectomy and reconstruction.

Discussion:
Silicone granuloma is an adverse reaction seen with the off-label use of injectable silicone (polydimethylsiloxane) for soft tissue augmentation. The widespread use of this cosmetic filler in dermatologic practice is partly due to its permanent, noncarcinogenic, and minimally antigenic properties. Different physical forms of silicone (i.e., elastomers, gels, and liquids), differing industrial and purity grades manufactured in various countries, the experience level of physicians, and the anatomical sites injected influence the likelihood of developing complications, including granuloma formation, migration of the filler, and disfiguring nodules.

Case #13 continued

The widespread use of injectable silicone became popularized in Germany, Switzerland and Japan during the 1940s, and later in the United States circa 1960, when improper injection of large volume, impure silicone formulas was more commonplace and produced poor results. Norman Orentreich later pioneered the microdroplet technique, in which very small amounts of medical grade silicone (pure, sterile, and of constant viscosity) was used to induce more gradual fibroplasia and reduce complications. Once injected, silicone is permanent, and as such must be placed at the precise deep dermal or subdermal plane to produce the desired effect.

Minor complications seen with silicone injection include bruising, erythema and edema, textural changes and bluish discoloration of the skin. Foreign body granuloma formation occurs particularly on the lips or sites prone to constant movement, and may manifest weeks to years after injection, as well as at sites distant from those initially treated. The exact pathogenesis of granuloma formation is uncertain, and may result from an aberrant host response, an infectious process, or a normal response to a contaminant in the filler. Silicone granulomas are quite similar to sarcoidal granulomas and may represent a response to chronic low-grade antigenic stimulation, associated with elevated levels of TNF-alpha. Histologically, silicone granulomas resulting from liquid or gel forms of the filler demonstrate round to oval cystic spaces resembling "swiss cheese," and a foamy infiltrate of macrophages and giant cells, whereas those due to elastomer (solid) forms produce more exuberant foreign body giant cell reactions. The silicone oil is eliminated during processing of specimens, which produces the vacuolated appearance. Fat stains (ie, Sudan) are negative.

Absolute contraindications to injectable silicone include use in breast augmentation, and treatment of horizontal forehead creases and mental creases. Injection into the penis, bones, tendons, and any cysts or blood vessels must also be strictly avoided. In addition, patients with chronic inflammatory diseases, history of multiple allergies, those with infections at sites close to treatment areas, and pregnant women may be at greater risk for developing adverse reactions. Dermatologists must carefully consider the medicolegal aspects of injecting silicone in patients previously treated by another physician, because in the event that a complication should arise, it may be impossible to determine whether the previous or current treatment is the culprit.

Treatment of silicone granulomas includes oral antibiotics such as minocycline, topical, intralesional and systemic steroids, excisional surgery, as well as retinoids and imiquimod. Allopurinol has been reported successful in treatment of local and distant silicone granulomas, presumably through its action as a free radical scavenger, as have pentoxifylline and etanercept, by decreasing TNF-alpha production. Liposuction and laser therapy have also been employed.

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Case # 14

Presented by Warren Piette, MD and Robert Lieberman, MD

History of Present Illness:
The patient is a 54-year-old man who presented with a four-month history of an enlarging painless nodule above his left knee. Two months prior to admission, he developed similar nodules in his thighs and arms.

Past Medical History:
Hypertension

Medications/Allergies:
Aspirin, hydrochlorothiazide, lisinopril, loratidine, multivitamin, sildenafil; No known drug allergies

Family History:
Non-contributory

Review of Systems:
The patient complains of recent fatigue, although he denies fevers, chills, appetite changes, weight loss, respiratory symptoms, joint pains, muscle aches, and eye complaints.

Physical Exam:
On his thighs, elbows, and forearms, there are numerous 1-2 cm firm subcutaneous nodules. No palpable joint effusions or lymphadenopathy are present. Muscle strength is intact.

Laboratory and Study Results:
The following were normal or negative:

Comprehensive metabolic panel; complete blood count; liver function tests; lipid panel; uric acid; urinalysis; thyroid stimulating hormone; free thyroxine; antinuclear antibody; rheumatoid factor; serum protein electrophoresis; chest radiography

Histopathology:
7/06 Right Thigh: Deep dermal and subcutaneous sarcoidal granulomas, consistent with sarcoidosis; PAS, AFB, and GMS stains were negative.

Radiology:
Chest x-ray: no active lung disease, lymphadenopathy, or gross abnormality.

Diagnosis:
Subcutaneous sarcoidosis

Treatment and Course:
The patient was referred to ophthalmology for evaluation of possible ocular involvement, and his ophthalmologic exam was within normal limits. At his next visit to dermatology, the patient reported new painful nodules in his buttocks, decreased appetite, worsening fatigue, and depressed mood. Due to the patient's underlying hypertension and his mood changes, he was started on steroid-sparing hydroxychloroquine 200 mg orally twice daily, and intralesional kenalog (5 mg/cc) was injected at two sites in buttocks for local relief of pain. Two months later, due to progressive growth of lesions, the patient was started on oral prednisone 40 mg daily to be tapered over 8 weeks. On follow-up one month later, he noted significant decreases in the size of most lesions, and he reported improved energy, appetite, and mood.

Case #14 continued

Discussion:

Sarcoidosis is an uncommon multisystemic granulomatous disorder of unknown etiology, characterized clinically by involvement of the lymph nodes, lungs, eyes, liver, spleen, and skin; and histologically by the formation of noncaseating granulomas in the involved organs. The disease peaks between the ages of 25 and 35 years with a second peak in women aged 45 to 65. Cutaneous involvement occurs in approximately 25 percent of patients and, while it may occur at any stage of the disease, it most often presents at the onset. Skin lesions are classified as specific when histologic examination shows sarcoidal granulomas and nonspecific when such findings are lacking. The most important nonspecific skin lesion is erythema nodosum. Specific lesions include papules, nodules, plaques, infiltrative scars, lupus pernio, and subcutaneous nodules.

Subcutaneous nodules are asymptomatic to slightly tender, firm, mobile nodules that measure between 0.5 cm and 2 cm. They most commonly occur on the extremities and trunk, may number from 1 to 100, and often co-exist with other cutaneous lesions of sarcoidosis. Subcutaneous disease is diagnosed histologically by identifying noninfectious sarcoidal or epithelioid granulomas with minimal lymphocytic inflammation that predominantly involves the panniculus. While older studies reported that specific skin lesions have no prognostic significance and are not associated with systemic disease, recent evidence suggests a strong association between subcutaneous sarcoidosis and systemic disease - most notably bilateral hilar adenopathy – although this finding may be an artifact of selection bias. For this reason, a workup for systemic sarcoidosis should be performed in patients diagnosed with subcutaneous disease and should include chest radiography, pulmonary function tests, ophthalmologic examination, and routine laboratory tests, including serum and urine calcium. Determination of serum angiotensin converting enzyme (ACE) levels are generally not a useful guide for disease progression or therapeutic response due to its positivity in only 60 percent of patients with sarcoidosis, its lack of correlation with cutaneous involvement, and the absence of systemic disease in some patients with cutaneous granulomas and increased ACE levels.

The mainstay of treatment of subcutaneous sarcoidosis is oral corticosteroids, to which the disease generally responds favorably. Steroid-sparing agents such as hydroxychloroquine and methotrexate have also been used successfully in some patients. Due to the association with subcutaneous sarcoidosis with systemic disease, the prognosis of subcutaneous disease largely depends on the extent of systemic disease observed.

References:

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Case #15

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

History of Present Illness:
This 23-year-old African American male was admitted to Cook County Hospital for left upper lobe pneumonia and dermatology was consulted for evaluation of multiple nodules on the patient's body. The first lesion occurred on the patient's upper lip approximately one week prior to admission; subsequently similar lesions began appearing widely distributed on the patient's body. He complained of tenderness and purulent drainage from multiple lesions. He denied any history of a previous similar eruption. He also complained of sore throat, cough with productive sputum, fever, chills, nausea, vomiting, diarrhea, night sweats and recent weight loss of ten pounds in the last 10 days. A PPD was negative 3 days ago.

Past Medical History:
Hodgkin's Lymphoma, stage IIB Nodular Sclerosing Type, diagnosed in January 2006 and treated with two cycles of systemic chemotherapy.

Medications/ Allergies:
Patient denied taking any outpatient medications. One week prior to his admission, he was given a one week course of doxycycline from the ED but only completed 4 days of the course. As an inpatient, he was receiving vancomycin and ceftriaxone intravenously at the time of consultation; No known drug allergies.

Family History:
Non-contributory.

Review of Systems:
No additional relevant information.

Physical Exam:
On admission, this patient was febrile and stable. He had many erythematous, tender, and sometimes fluctuant nodules ranging from less than 5 mm to greater than 2 cm diffusely on his lower extremities from his dorsal feet to his upper thighs, and bilateral arms extending from his dorsal hands to his shoulders. A large yellow crusted verrucous plaque was located on his left parietal scalp. A 1 cm erythematous crusted verrucous nodule was evident on his right upper lip. Smaller erythematous tender papules were scattered on his face and indurated nodules existed on his upper eyelids. His cervical lymph nodes were palpable and tender.

Laboratory Data:
The following were abnormal or positive:

WBC	18,900/mm^3	[nl: 4,000-10,000/mm^3]
Neutrophils	91.5%	[nl: 50-75%]
Lymphocytes	4.2%	[nl: 18-48%]

Wound fungal culture grew broad based budding yeasts.

The following were normal or negative:
Basic metabolic profile, urinalysis, liver panel, HIV screen, sputum AFB stain x 3, blood cultures.

Radiology:
Chest Xray: : Dense left upper lobe infiltrate and multiple nodules throughout both lung fields which are fairly well circumscribed.

Case #15 continued

CT chest: Irregularly defined soft tissue densities noted at the left lung apex and left perihilar region. Multiple small nodular densities, less than 5 mm in size are noted through the remaining lung fields.

Histopathology:

10/7 Left lower extremity: There is a mixed suppurative and granulomatous infiltrate predominantly in the deep dermis and subcutaneous fat, focally extending to the upper dermis. The infiltrate consists of sheets of neutrophils, scattered epithelioid histiocytes and multinucleated giant cells, as well as round to oval yeast forms with thick refractile cell walls. GMS stain further reveals single broad-based budding spores. These morphological features are characteristic of *Blastomyces dermatitidis.*

Diagnosis:

Disseminated Blastomycosis.

Treatment and Course:

At the time of consultation, this patient was receiving IV vancomycin and ceftriaxone. He was promptly started on liposomal amphotericin B 100 mg daily IV as we highly suspected a disseminated fungal infection with extensive skin and lung involvement. In addition, ceftriaxone was discontinued and imipenem was started. He continued spiking fevers up to 102.6 for the next five days and then began to improve symptomatically with resolution of lesions. He was transferred to another hospital on day 6 for an additional 10 days of IV amphotericin B and then switched to oral itraconazole.

Discussion:

Blastomycosis is a systemic pyogranulomatous disease that initially results from inhalation of conidia into the lungs to cause a primary pulmonary infection and frequently disseminates hematogenously to cause extrapulmonary disease. The skin, bones and genitourinary system are most commonly involved but almost any organ system can become infected.

Blastomyces dermatitidis, a thermally dimorphic fungus, is the causative organism. It is endemic to North America, particularly the southeast and southcentral states but can also be found in the Midwestern states bordering the Great Lakes. Cytology, histology, culture, and wet preparation with KOH digestion are used for diagnosis and identify yeast forms with characteristic broad based budding and thick, double contoured walls. With pulmonary disease, alveolar infiltrates, mass lesions that mimic bronchogenic carcinoma, and fibronodular interstitial infiltrates are the most common radiographic findings.

Infection in the immunocompromised host is more aggressive with frequent respiratory failure and dissemination to multiple organs. Mortality rates of 30-40% have been reported. Early and aggressive treatment with amphotericin B (0.7-1mg/kg/d) is indicated with a recommended total dose of 1.5-2.5g. Selected patients without CNS infection may be switched to oral itraconazole after clinical stabilization with amphotericin B.

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Case #16

Case presented by Sidney Barsky, MD and Jane Kwan, MD

History of Present Illness:
This 41-year-old woman and her 43-year old husband presented with hyperpigmented lesions on the trunk and legs. They had vacationed in Mexico two months prior, and while swimming in the Gulf of Mexico, reported feeling sudden stinging sensations on their skin. Finding themselves surrounded by jellyfish, they quickly exited the water and noticed erythematous, linear wheals on their bodies. They denied any systemic symptoms after the incident occurred, including abdominal pain, nausea, diarrhea, diaphoresis, paresthesias, dizziness, muscle cramps or convulsions. They were unable to describe the jellyfish in detail and did not seek medical attention at that time. The lesions were quite painful initially, but the redness, swelling, and symptoms resolved within a week, leaving persistent post-inflammatory hyperpigmentation. They deny any contact exposure to substances such as lime or perfumes.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies

Family History:
Non-contributory

Physical Exam:
There is linear and flagellate hyperpigmentation on the abdomen, flank, back, and legs of both patients.

Diagnosis:
Persistent flagellate hyperpigmentation secondary to jellyfish envenomation (Portuguese man-of-war)

Discussion:
Jellyfish belong to the Phylum Cnidaria, formerly Coelenterata, and are characterized by the possession of stinging cells, or nematocysts. Hundreds to thousands of these cells line the tentacles of the jellyfish, and when disturbed, evaginate and inject venom into the victim. The venom is a neurotoxin composed of histamine, indoles, kinins, catecholamines, quaternary ammonium compounds and short-chain polypeptides. All of these are capable of producing local tissue damage.

Of the marine fauna, jellyfish are the most frequent cause of aquatic dermatoses. The response to jellyfish venom is a mixture of an irritant and allergic reaction. Usually, skin reactions are mild and consist of acute inflammatory lesions characterized by burning pain, erythema, edema, and sometimes vesicles. The severity is related to the species, localization and extent of lesions, and host response; in most cases, resolution of symptoms occurs after 72 hours. Rarely, severe cutaneous toxicity can occur with hemorrhagic or necrotic lesions. Delayed or recurrent reactions may be due to delayed type hypersensitivity and can present as granulomatous papules and nodules that develop several days after the sting. Chronic or persistent cutaneous reactions are rare and include hyperpigmentation, subcutaneous fat atrophy, keloidal scarring, granuloma annulare, and erythema nodosum. The pattern of the sting may provide a clue to the guilty species. An annular or ladder-like pattern is suggestive of a box jellyfish sting, while a linear or flagellate-like pattern, as in our patients, is more characteristic of Portuguese man-of-war stings.

The Portuguese man-of-war, *Physalia physalis* or *utriculus*, is found in the Atlantic Ocean, particularly in the Gulf of Mexico, the Caribbean, and off the coast of Florida. Although it is actually a hydroid, it is commonly regarded as a jellyfish. It possesses a float, which is a long, gelatinous multi-colored tail that floats on the surface of the ocean. Numerous tentacles armed with nematocysts trail below in the water, some up to 150 feet or more. *Physalia physalis* can cause major systemic symptoms, while *P.*

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utriculus does not. While some species of jellyfish are potentially lethal, systemic manifestations of toxicity are rare. These vary from diaphoresis, paresthesias, muscle cramps, abdominal pain, nausea and diarrhea to ataxia, convulsions, anaphylaxis and cardiopulmonary distress. The most lethal of the jellyfish is the Australian sea wasp or *Chironex fleckeri*.

Management of jellyfish stings consists of first neutralizing the toxin and inactivating the nematocysts with dilute acetic acid. Fresh water should not be used, nor nematocyst or tentacle removal attempted, until this is done, since osmotic changes or mechanical perturbation can trigger the firing of undischarged nematocysts. Antihistamines, oral or topical analgesics, and ice packs can be helpful in managing symptoms. Immersion in hot water between 104 to 113 degrees Fahrenheit for 30 to 90 minutes can denature heat sensitive toxins, reducing pain and vasospasm in the wound site. There has been a case report of resolution of persistent hyperpigmentation from jellyfish envenomation using topical hydroquinone.

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Case #17

Presented by Jerry Feldman, MD and Sari Weinstein, MD

History of Present Illness:
This 61 year old African-American man presented to our clinic with an approximately 10 year history of asymptomatic telangectasias on his hands, chest and back and prominent telangiectasias on his conjunctiva and oral mucous membranes.

Past Medical History:
Epistaxis requiring nasal vessel ablation approximately 10 years ago; hypercholesterolemia, hypertension, depression, emphysema

Medications/Allergies:
Verapamil, hydrochlorothiazide, Q-VAR, albuterol, fluoxetine; No known drug allergies

Family History:
The patient denies any family history of similar lesions or epistaxis.

Review of Symptoms:
He complained of headaches, shortness of breath, nosebleeds, and joint pains; he denied chest pain, nausea, vomiting, diarrhea, melena, or hematuria

Physical Exam:
Palms with multiple erythematous 2-3 mm telangectasias; back, chest with poorly defined erythematous macules; oral membranes with telangiectasias; Left conjunctiva with telangiectasias

Laboratory Data:
Complete Blood Count; Liver Function Test; all within normal limits

Histopathology:
None

Diagnosis:
Hereditary Hemorrhagic Telangiectasia

Treatment and Course:
The patient was referred to pulmonary and gastrointestinal clinics for screening for arteriovenous malformations.

Discussion:
First described by doctors Osler, Weber, and Rendu in the late 19th century, hereditary hemorrhagic telangiectasia (HHT) is a disease of the vascular system, characterized by epistaxis, telangiectasias, and multiorgan vascular dysplasia or arteriovenous malformations (AVM). It is inherited as an autosomal dominant trait, but about 20% of cases appear to be sporadic. A prevalence rate has been estimated to be at most 1 in 10,000 and higher in certain geographically isolated regions. Individuals with HHT present with a wide range of symptoms and with great variability between and within families. Spontaneous recurrent nosebleeds from telangiectasias of the nasal mucosa is the presenting sign in more than 90% of patients; the increasing severity and frequency seen with advancing age can lead to chronic anemia. Also common are multiple, often subtle, telangiectasias on the face, lips, oral cavity (especially the tongue), and fingers, thought to appear in the 3rd decade of life, which have also been reported to

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become hemorrhagic. With a peak incidence in the 5th decade of life, telangiectasias can develop in the gastrointestinal tract, especially in the stomach and small intestine, and may present with GI hemorrhage and iron deficiency anemia in 15% of patients. Liver involvement, reported in up to 40% of HHT patients, is often asymptomatic and reflects intrahepatic telangiectasias leading to the formation of shunts between the major vessels of the liver. Pulmonary AVMs have been reported in up to 50% of patients; the right to left shunt between the pulmonary artery and pulmonary vein can lead to hypoxemia, stroke, and brain abscess. Cerebral involvement in 10-20% of patients may also be associated with telangiectasias, cerebral AVMs, aneurysms, or cavernous angiomas which can lead to seizures or hemorrhagic stroke.

HHT is a genetically heterogeneous disorder. HHT type 1 is caused by mutations in the *ENG (endoglin)* gene, whereas HHT type 2 is caused by mutations in the *ACVRL1* (*activin receptor-like kinase* or *ALK-1*) gene. The corresponding endoglin and ALK-1 proteins are specific endothelial receptors of the transforming growth factor β superfamily essential for maintaining vascular integrity. Over 155 *ENG* and 123 *ALK-1* mutations have been identified. The two types of HHT are difficult to distinguish clinically, as all reported manifestations are known to occur in both disease types, and knowing the genotype does not allow the clinician to rule out any specific organ involvement or predict severity. Generally, however, cerebral AVMs and pulmonary AVMs are more common in HHT1, and a later onset and lower penetrance with predominantly GI bleeding and liver involvement seem to be more common in HHT2 . It remains to be determined how a reduction in endoglin or ALK-1 predisposes to HHT, and what causes vascular lesions to develop selectively in limited vascular beds. A new locus for HHT3 was recently mapped to chromosome 5, although the causative gene remains unidentified. A subset of patients with a combined syndrome of juvenile polyposis and HHT display mutations in the *MADH4* gene.

The diagnosis of HHT is generally made clinically, according to the Curaçao criteria. An individual is considered to have HHT if three of the following four diagnostic criteria are met: recurrent spontaneous epistaxis; mucocutaneous telangiectasia; visceral involvement (pulmonary AVM, cerebral/spinal AVM, GI bleeding, or intrahepatic shunting); and a family history of HHT. The presence of two criteria warrants a probable or suspected diagnosis, while a single criterion renders the diagnosis unlikely. Many signs are age-dependent and do not manifest until later in life and thus careful consideration is essential when evaluating children. Signs and symptoms of concern include epistaxis, skin bleeding, cyanosis, clubbing, bruit, migraine, stroke, headache, subarachnoid hemorrhage and GI bleeding.

The Nd:YAG laser, estrogen therapy, cautery, embolotherpy and septal dermoplasty have been shown to be effective treatments for epistaxis in HHT, and laser treatment can be offered to individuals with HHT if telangiectasias are perceived as undesirable. Screening tools may include obtaining a detailed medical and family history, genetic linkage analysis, blood gas measurement, oximetry, and chest radiography. Diagnostic methods include high-resolution computed tomography and magnetic resonance imaging of the lung, CNS, and GI tract.

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Case #18

Presented by Warren Piette, MD and Carlos Rodriguez, MD

History of Present Illness:
A 54-year-old Hispanic male presented to our clinic with a 6-month history of a painful ulcer on his right posterior leg, and a similar lesion on his left leg.

Past Medical History:
Chronic Gout

Medications/Allergies:
Allopurinol (previously); No known drug allergies.

Family History:
None

Review of Systems:
Pain at ulcer sites; denied fevers, chills, night sweats, weight loss

Physical Exam:
His posterior right leg demonstrated a large, very firmly indurated, slightly erythematous subcutaneous plaque in which a 3.5 cm punched-out ulcer was situated. In addition, firm red-to-yellow papules were noted on his dorsal hands, left elbow and right knee.

Laboratory Data:
The following was abnormal or positive:

Uric Acid	7.7mg/dL	[nl: 4-6mg/dL]

The following were normal or negative:
Complete blood count, serum chemistry, liver enzymes, fasting lipid panel

Histopathology:
6/06: Right posterior leg: deep dermal deposits of amorphous eosinophilic material consistent with tophaceous gout.

Diagnosis:
Gouty panniculitis

Treatment and Course:
Allopurinol was restarted at 200mg daily, and later increased to 300mg daily, combined with topical wound care. Slow resolution of the ulcers was seen. Consideration was given to adding a uricosuric agent such as probenecid, but the patient was soon lost to follow-up.

Discussion:
Gout progresses through four basic stages which include asymptomatic hyperuricemia, acute gout, interval or intercritical gout, and chronic tophaceous gout. Asymptomatic hyperuricemia, in which serum uric acid level is generally > 7 mg/dL, does not require treatment; elevated levels may be found in 5% of normal adults, and only a fraction of those with hyperuricemia develop clinical gout. Uric acid levels are generally elevated for > 20 years prior to the onset of clinical disease. Gout may result from metabolic errors that cause uric acid overproduction, or from underexcretion of urates by the kidneys, both classified as primary gout. Alternatively, it may result from hyperuricemia induced by coexisting diseases or

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medications (secondary gout). Primary gout more commonly affects men, with the first attack occurring typically between the ages of 40 and 50 years. Secondary gout most commonly develops secondary to diuretic therapy, and may also occur in PUVA patients.

In acute gout, hyperuricemia causes the precipitation of uric acid crystals in tissue from supersaturated extracellular fluid. A brisk inflammatory response ensues, causing erythema, pain and swelling, commonly at night or in the early morning hours. Local inflammation may be accompanied by fever, leukocytosis, and an elevated erythrocyte sedimentation rate. Interval gout describes the period between acute episodes of gout, during which patients are asymptomatic. Chronic tophaceous gout is seen with prolonged hyperuricemia and repeated acute episodes of gout, and tophi may develop in the skin and soft tissues, synovial membranes, tendons, cartilage, and bone. Tophi usually manifest 10 years or more after the onset of gout, but more rapid development may be seen in myeloproliferative diseases and with certain enzyme deficiencies. They generally resolve 6-12 months after normalization of uric acid levels. Interestingly, dermal and subcutaneous tophi demonstrate less inflammation than do epidermal tophi.

Deposition of urate crystals in the subcutaneous fat is quite rare. Previously reported cases of gouty panniculitis presented patients with very similar clinical manifestations and laboratory findings. Most were middle-aged men who presented with longstanding tender ulcerated nodules on the lower legs which drained opaque to brown colored liquid. Biopsy specimens revealed subcutaneous deposits of urate crystals and a granulomatous response with histiocyes and giant cells, as well as a polymorphonuclear leukocytic infiltrate with predominant involvement of the fat lobules causing necrosis. When examined under polarized light, biopsies demonstrated negatively birefringent needlelike crystals. Of note, other lobular panniculitides in which crystal formation may be seen include sclerema neonatorum, subcutaneous fat necrosis of the newborn, post-steroid panniculitis, facticial panniculitis, and hemorrhagic panniculitis. Some of the previously reported patients had established diagnoses of gout, while in others the skin lesions were the initial manifestation of the disease. Several patients had been on diuretic therapy for treatment of hypertension and/or congestive heart failure. Prior damage to the subcutis by trauma or elevated amylase/lipase levels as seen in patients with pancreatitis, in addition to peripheral vascular disease, may also have contributed to the subcutaneous deposition of urate crystals.

Treatment of gouty panniculitis is challenging. In previously reported cases, patients received standard therapies for acute and/or chronic gout, which helped normalize uric acid levels and limited the development of new lesions, but did not necessarily induce resolution of existing ulcers. The management of acute gout is aimed at prompt reduction of inflammation and pain, including protection from trauma, NSAIDs including indomethacin, corticosteroids, and colchicine. Colchicine in particular has been used with success in treatment of other deep panniculitides. Intramuscular ACTH and triamcinolone acetonide are also effective. The management of chronic gout includes a uricosuric drug (ie, probenecid) in those with low urate clearance, and a xanthine oxidase inhibitor (ie, allopurinol) in patients with urate overproduction and for gout prophylaxis. Many patients, however, have both low urate clearance and high purine intake or urate overproduction. One patient with gouty panniculitis experienced complete remission of skin lesions following 2 months of treatment with allopurinol at 600mg/day.

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Case #19

Case Presented by Sidney Barsky, MD, Alyssa Nash, MD and Michael Pomroy, MD

History of Present Illness:
This 7 year old male presents with a five day history of a pruritic eruption which began on his cheeks and ears. He denied any systemic symptoms, history of any similar rash, and had no history of varicella. After further questioning it was noted that this eruption coincided with the first sunny and clear weekend of the spring season.

Past Medical History:
None

Medications/Allergies:
None; No known drug allergies.

Family History:
Non-contributory

Review of Systems:
Negative

Physical Exam:
On the bilateral cheeks, nose, and lips there are symmetrically distributed, discrete, circular crusted erosions and papules, some of which are umbilicated. On the bilateral helices of the ears there are umbilicated vesicles and flaccid bulla with hemorrhage, and on the dorsal hands there are a few scattered erythematous papules.

Lab Data:
None

Histopathology:
5/06 Right ear lobe: Intraepidermal vesiculation with reticular degeneration, necrosis, and a superficial mixed infiltrate composed of lymphocytes and a few neutrophils, consistent with hydroa vacciniforme.

Diagnosis:
Hydroa Vacciniforme

Treatment and Course:
At the time of consultation the patient was advised to wear sunscreen and to have constant photoprotection. He was seen in follow-up at our clinic for one subsequent visit and appeared to have resolution of some of the lesions with scarring. Since then, the patient has been lost to follow-up.

Discussion:
Hydroa vacciniforme (HV) is a rare, sporadic, idiopathic photodermatosis that was first described by Bazin in 1862. This seasonal eruption is characterized by the formation of tender itchy vesicles and papules on a background of erythema and edema. The acute eruption is followed by a phase of crusting and healing with vacciniform scarring. The lesions are usually distributed on the cheeks, nose, and ears and less frequently on the upper chest and forehead. It has only rarely been reported on the oral mucosa. The seasonal onset of the eruption is usually in the spring or summer but some patients have symptoms throughout the year. Presentation is usually in childhood with spontaneous resolution during adolescence.

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Histologically, the principal abnormality is intraepidermal vesiculation and reticular degeneration leading to epidermal necrosis. The vesicles are filled with fibrin and acute inflammatory cells. There is a dermal infiltrate composed of perivascular neutrophils and mononuclear cells, particularly T lymphocytes.

The most recent large study was composed of 17 Scottish patients. The mean age of onset was 7.9 years with a bimodal distribution of 1-7 years and 12-16 years. Spontaneous clearing occurred in 60% of patients and there was a mean duration of disease of about 9 years. This study confirmed that there is a tendency for the disease to have an earlier onset as well as a shorter duration in females.

Over the past several years there have been implications that latent EBV infection may play a role in hydroa vacciniforme, and that in certain severe HV eruptions there is a significant risk of future EBV-related malignancies. These reports of severe, atypical HV and malignancy have been noted only in Japan, Korea, and Mexico.

The largest, and most recent study regarding this new association included Japanese patients with HV or severe HV-like eruptions and showed that 28 out of 29 patients with hydroa vacciniforme had evidence of latent EBV infection within the dermal infiltrate on histopathology.
The group with severe HV had markedly increased levels of EBV DNA and was associated with a NK cell lymphocytosis. Five out of 11 patients in the severe group died of EBV-associated NK/T cell lymphomas or hemophagocytic syndrome between 2 and 14 years of the onset of the eruption. Because of this increased risk of malignancy, it is very important to differentiate typical HV from severe HV in Asia. Severe HV patients typically have more facial swelling, a high fever and liver damage, as well as a lack of spontaneous resolution with age.

Treatment of HV is primarily focused on photoprotection as it has been shown that UV light, particularly UVA, is responsible for the eruption and resultant scarring. Sunscreen, photoprotective clothing, and even Museum 200 plastic film (prevents penetration of wavelengths <380nm; SunGuard) for car and home windows can be recommended to patients. Approximately 60% of patients can respond with this management alone. There are scattered reports regarding the use of PUVA, β-carotene, fish oil, chloroquine, hydroxychloroquine, azathioprine, thalidomide and cyclosporine in this disease; however, none of these have been shown to have consistent benefit. Some have shown that narrowband UVB can offer photoprotection for some patients and can increase tolerance to sunlight. Three out of five patients in one study reported increased tolerance to sunlight and a decrease in severity of disease. In general, the majority of patients experience spontaneous improvement during adolescence.

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Case #20

Case presented by Lisette Ortiz, M.D., Shelley Halper, M.D., and Meredith Stewart Reimer, M.D.

History of Present Illness:
This 49 year-old woman presented to an outside dermatologist for evaluation and treatment of skin tags and multiple asymptomatic papules on her face, neck and chest. The skin tags began to appear on her neck in her early 30s and gradually increased in number over the years**.** The papules on her face began to appear in her mid-30s and also gradually increased in number and eventually spread to involve her neck and chest. These lesions were initially thought to be milia but when extraction of these lesions was attempted, no cystic contents could be produced, so a biopsy was performed.

Past Medical History:
None

Medications/Allergies:
No medications; No known drug allergies

Family History:
Paternal grandomother: deceased with unknown kidney disease; Father: deceased age 80 metastatic oral cancer, no skin lesions or kidney disease; Brother: healthy age 62, similar facial papules not yet biopsied, possible history of spontaneous pneumothorax; Sister: healthy age 63, similar facial papules not yet biopsied; Daughter: healthy age 23, acrochordons on neck; Son: healthy age 21, no similar skin lesions

Physical Exam:
There are hundreds of white to skin-colored smooth, dome-shaped, firm papules, 1-4 mm in size, scattered on her forehead, eyelids, cheeks, nose, chin, neck, behind her ears, and upper chest. There is no punctum evident on any of the papules. There is no scale, erythema, crust, telangiectasia, or dyspigmentation associated with these lesions. She also had multiple skin-colored, soft, pedunculated papules on her neck, axillae, and under her breasts.

Laboratory Data:
None

Histopathology:
6/06: Shave biopsy cheek: Within the dermis there is a net-like proliferation of the follicular outer root sheath epithelium surrounded by a dense fibrous connective tissue sheath consistent with a fibrofolliculoma.
1/05: Shave biopsy (multiple) neck: multiple fibroepithelial polyps (acrochordons)

Radiology:
CT scan Chest/Abdomen/Pelvis: There is a small cystic bleb within each lung. There are small 4mm areas of low-attenuation with each kidney that may represent renal cysts. There is minimal atherosclerotic calcification of the abdominal aorta. Otherwise the CT exam is unremarkable.

Diagnosis:
Fibrofolliculomas and acrochordons associated with Birt-Hogg-Dubé Syndrome

Treatment and Course:
The patient has been referred to a renal specialist for evaluation and serial screening for kidney pathology. The patient was educated on the associated risks of pulmonary and renal pathology in Birt-Hogg-Dubé syndrome and it was recommended that her family members be screened by a dermatologist for evaluation and biopsy of suspicious lesions to evaluate for the presence of the syndrome.

Case #20 continued

Discussion:

Birt-Hogg-Dubé (BHD) Syndrome is an uncommon autosomal dominant condition classically characterized by a triad of fibrofolliculomas, trichodiscomas, and acrochordons. This genodermatosis is also associated with an increased risk for renal neoplasia, lung cysts, and spontaneous pneumothorax. Recently, the gene responsible for the clinical manifestations of BHD syndrome has been cloned and characterized and is located on chromosome 17p12q11. The function of the BHD gene product, called folliculin is speculated to be a tumor suppressor gene. To date, 23 different germline mutations have been identified in the BHD gene and the majority these are protein-truncating mutations. Folliculin has widespread tissue expression including the kidney, lung, and skin.

The most common cutaneous manifestation of BHD syndrome is a fibrofolliculoma which histologically appears as a circumscribed proliferation of fibrous tissue around distorted keratin-plugged hair follicles from which strands of basaloid cells protrude into the stroma. Fibrofolliculomas and trichodiscomas cannot be distinguished clinically and both appear as ivory or skin-colored, discrete, smooth, firm, 2-4mm papules predominantly on the forehead, nose, and cheeks. Histologically, trichodiscomas are sharply defined fibrovascular tumors in the superficial dermis with abundant mucin surrounding the lesion. Most dermatopathologists contend that fibrofolliculomas and trichodiscomas are different names for a single pathologic process at different stages of development. Acrochordons are also commonly described in BHD syndrome. The classic skin findings in BHD syndrome generally become clinically evident in the third or fourth decades and increase in number over time.

Birt-Hogg-Dubé syndrome has been reported in association with a variety of renal tumors including clear cell, papillary, and chromophobe types of renal cell carcinoma as well as oncocytomas and hybrid variants. The most predominant type of renal tumor is chromophobe renal cell carcinoma. In the largest study of patients with BHD syndrome, the odds ratio for developing renal tumors in BHD syndrome-affected family members was 6.9. Kidney tumors in BHD syndrome usually occur earlier than sporadic tumors, and are usually multiple and bilateral. Other important manifestations of BHD syndrome include pulmonary cysts and pneumothorax. Pulmonary cysts are characterized by dialated alveolar spaces and when they bulge into the pleural surface, they may rupture under the pressure of inhalation causing a pneumothorax. It was previously thought that intestinal polyps were seen more frequently in patients with BHD syndrome but recent epidemiologic studies show no increased incidence.

Clinical diagnosis of BHD syndrome requires a minimum of ten skin lesions clinically compatible with fibrofolliculomas and at least one histologically proven fibrofolliculoma. While cutaneous tumors appear in the third and fourth decades, renal pathology can occur as early as 20 years of age. It is recommended that patients undergo abdominal computed tomography and/or renal ultrasound at the time of diagnosis and every 3-5 years thereafter. Siblings and family members should be screened with physical examination and biopsy of suspicious lesions beginning in their 20s. Treatment of fibrofolliculomas and trichodiscomas is difficult although some success has been reported with carbon dioxide and Er:YAG resurfacing and treatment for renal cell carcinoma is generally resection..

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