CHICAGO DERMATOLOGICAL SOCIETY

University of Chicago
Section of Dermatology
Chicago, Illinois

November 17, 2004

TABLE OF CONTENTS

PRESENTERS

Lucile E. White MD, Maria M. Medenica MD, Alan L. Lorincz MD, Vesna Petronic-Rosic MD

HISTORY OF PRESENT ILLNESS

A 23-year-old Caucasian man diagnosed with stage IVB Hodgkin's disease was referred to the University of Chicago oncology section after completing one and one-half cycles of chemotherapy. He had developed post-treatment complications of possible cellulitis and necrotizing fasciitis. At the University of Chicago, the patient was reluctant to resume chemotherapy because of his previous presumed skin infections. However, further PET scanning in August 2004 revealed disease progression, and adriamycin, bleomycin, dacarbazine, and prophylactic pegfilgrastim (Neulasta, Amgen) were administered. Vinblastine had been a component of his previous chemotherapy but was excluded from the new regimen due to its association with skin infections.

Shortly after chemotherapy and an injection of pegfilgrastim, the patient developed poorly defined, rapidly progressive, erythema, edema, and pain of his right forearm. He presented to the emergency room at the University of Chicago, was evaluated by the orthopedics service, and taken to the operating room for debridement of suspected necrotizing fasciitis. The dermatology service was consulted immediately and suggested a biopsy. The patient refused because a previous biopsy taken in February 2004 had exacerbated his presumed infection. When the dermatology consult service returned the following day, the patient's chest had developed an erythematous, edematous, tender plaque. After developing two more lesions, negative wound cultures, and treatment with imipenem, vancomycin, clindamycin, rifampin, and gentamycin, the patient consented to a skin biopsy.

PAST MEDICAL HISTORY

Previous skin infections: In January 2004, the patient received his first round of chemotherapy at an outside hospital. He was given post-chemotherapy pegfilgrastim to prevent neutropenia. Within a week of his chemotherapy the patient developed a red warm area on his shin. He was hospitalized and placed on antibiotic coverage for a suspected skin infection. The lesion continued to enlarge, ulcerate, and the wound was debrided. Cultures were negative. Biopsies taken at the time revealed a dense inflammatory infiltrate consistent with an abscess. Over the course of two months the lesion healed on systemic antibiotics.

Right upper extremity DVT: In January 2004, he developed a DVT at his PICC site and received three months of anticoagulation.

PAST SURGICAL HISTORY

Right lower extremity wound debridement: In February 2004, his leg wound was treated for suspected necrotizing fasciitis

MEDICATIONS

Magnesium oxide
Minocycline for acne
Oscal
Xanax

ALLERGIES

Ativan

FAMILY HISTORY

None

SOCIAL HISTORY

The patient is single and smoked one pack of cigarettes a day until he was diagnosed with Hodgkin's disease. He drinks occasionally. Until recently, he worked as a manager for a marketing company.

PHYSICAL EXAMINATION

At initial presentation, the patient was afebrile. He had a poorly-defined, firm, tender, 10 x 7.5 cm erythematous, edematous area on his right foreman.

By hospital day #3, the patient had become febrile. He had developed tender, 4x 6 cm poorly defined, erythematous, edematous plaques on his chest and left shoulder. The right upper arm had developed two ulcerations with peripheral erythema.

On hospital day #4, the patient's entire right arm was warm, erythematous, and edematous. His operative site, chest, and shoulder had multiple ulcerations with erythematous, hemorrhagic, undermined borders. His forehead and right thigh had developed erythematous pustules with peripheral erythema.

LABORATORY DATA

Relevant lab data at admission included:

White blood cells 15.3, absolute neutrophils 7.35 (1.12-6.72), absolute bands 4.28 (0-0.66), platelets 137
Quantitative levels of immunoglobulins A, G, and M were low
A complete metabolic panel was normal

Blood and wound cultures were negative.

DERMATOPATHOLOGY

The specimen revealed spongiosis of the epidermis, exocytosis of neutrophils, and mild edema in the papillary dermis. A dense, diffuse, neutrophilic infiltrate was present throughout the entire dermis. Special stains were negative for bacteria, fungi, and

mycobacteria. These findings suggested pyoderma gangrenosum or, less likely, Sweet's syndrome.

DIAGNOSIS

Pyoderma gangrenosum likely due to pegfilgrastim (Neulasta, Amgen)

TREATMENT & COURSE

Because of his low immunoglobulins, the patient received IVIG. Despite the IVIG, his skin lesions progressed.

High-dose oral prednisone resulted in rapid improvement. The lesions stabilized within 24 hours and started to granulate within 48-72 hours. Prednisone was tapered and discontinued over six weeks. The operative site continues to heal on doxycycline 100mg twice a day. Topically, the wounds were treated with clobetasol (for 3 weeks) and gentamycin ointments.

DISCUSSION

Granulocyte colony stimulating factors (G-CSFs) are commonly used to prevent neutropenia in patients receiving cytotoxic chemotherapy. Neutropenia typically develops five to ten days after chemotherapy and can increase susceptibility to infections, necessitate expensive antibiotic treatment, and, if fever develops, require isolation and hospitalization. Granulocyte colony stimulating factors stimulate proliferation and differentiation of the granulocytic progenitor cells in the bone marrow, thus, preventing neutropenia. These agents have infrequently been reported to cause Sweet's syndrome or pyoderma gangrenosum. [1,2,3,4]

The first generation of widely used stimulating factors includes filgrastim (Neupogen, Amgen). Filgrastim has a short half-life and is given daily for two weeks following chemotherapy. Filgrastim has been used in over 3 million patients. Skin eruptions and pruritus occur in less than 1% of treated patients.[5,6] Our patient received pegfilgrastim, a newer, pegylated G-CSF with a longer half-life, allowing dosing once monthly or once per chemotherapy cycle. [7] In clinical trials, the side effect profile of pegfilgrastim has been similar to filgrastim.

We can not rule out that our patient's Hodgkin's lymphoma contributed to his pyoderma gangrenosum, however, only one case of pyoderma gangrenosum associated with Hodgkin's disease has been reported. In this case, the pyoderma gangrenosum presented before the lymphoma was diagnosed. [8] Pyoderma gangrenosum is typically associated with ulcerative colitis, Crohn's disease, rheumatoid arthritis, hepatitis, monoclonal gammopathies, and hematologic malignancies. Reports of neutrophilic dermatoses with G-CSFs, although rare, are more common than with Hodgkin's lymphoma.

Our patient was diagnosed with Hodgkin's lymphoma in December 2003 and experienced cutaneous eruptions only after chemotherapy and pegfilgrastim, thus, implicating a drug from the treatment regimen. Case reports are elusive regarding neutrophilic dermatoses associated with adriamycin, bleomycin, or dacarbazine, suggesting neutrophilic dermatoses are not common with these agents.

In a patient receiving chemotherapy, the differential diagnosis of pyoderma gangrenosum includes acute infection. Infection must be ruled out before initiating immunosuppressive treatment. Blood and wound cultures should be sent and empiric treatment with antibiotics is prudent while a biopsy is pending. The pathology in neutrophilic dermatoses can be non-specific and mimic an abscess, as was seen in our patient's pathology performed at an outside hospital in February 2004. Thus, warm, edematous, erythematous lesions in a patient on chemotherapy and treated with pegfilgrastim should be followed closely.

Our patient also had low levels of immunoglobulins on admission and was treated with intravenous immunoglobulin. Quantitative immunoglobulins can be normal, increased, or decreased in pyoderma gangrenosum and, thus, are not diagnostically helpful.[9] Intravenous immunoglobulin has successfully been used to treat pyoderma gangrenosum in cases unresponsive to prednisone.[10] Our patient did not show a clinical response to IVIG, however, he received IVIG less than 48 hours before starting prednisone. It is possible that prednisone was started before a clinical improvement could be seen from the IVIG.

For neutrophilic dermatoses caused by older G-CSFs, treatment involved stopping the G-CSF with or without high-dose prednisone treatment. Lesions treated with systemic prednisone are reported to clinically improve with 48-72 hours.[4] We observed the same, rapid clinical improvement from prednisone in our patient who received a new, pegylated G-CSF, despite the drug's longer half-life.

REFERENCES

1. Glaspy JA, Baldwin GC, Robertson PA, et al. Therapy for neutropenia in hairy cell leukemia with recombinant human granulocyte colony-stimulating factor. Ann Intern Med 1988; 109: 789-795.

2. Ross HJ, Moy LA, Kaplan R, et al. Bullous pyoderma gangrenosum after granulocyte colony-stimulating factor treatment. Cancer 1991; 68:441-443.

3. Kumar G, Bernstein JM, Waibel JS, et al. Sweet's syndrome associated with sargramostim (granulocyte-macrophage colony stimulating factor) treatment. Am J Hematol 2004; 76: 283-285.

4. Johnson ML, Grimwood RE. Leukocyte colony-stimulating factors: A review of associated neutrophilic dermatoses and vasculitides. Arch Dermatol 1994: 130; 77-81.

5. Asano S. Human granulocyte colony-stimulating factor: its basic aspects and clinical applications. Am J Pediatr Hematol Oncol. 1991; 13: 400-413.

6. Horn TD, Burke PJ, Karp JE, et al. Intravenous administration of recombinant human granulocyte-macrophage colony-stimulating factor causes a cutaneous eruption. Arch Dermatol 1991; 127: 49-52.

7. Biganzoli L, Untch M, Skacel T, et al. Neulasta (pegfilgrastim): A once-per-cycle option for the management of chemotherapy-induced neutropenia. Semin Onc 2004; 31: 27-34.

8. Transactions of the Michigan Dermatological Society. Pyoderma gangrenosum and Hodgkin's lymphoma. Arch Dermatol 1974; 109: 269.

9. Schwaegerle SM, Bergfeld WF, Senitzer D, et al. Pyoderma gangrenosum. J Am Acad Dermatol 1988; 18: 559-68.

10. Dirschka T, Kastner U, Behrens S, et al. Successful treatment of pyoderma gangrenosum with intravenous human immunoglobulin. J Am Acad Dermatol 1998: 39: 789-90.

PRESENTERS

Mario E Lacouture MD, Christopher R Shea MD, Keyoumars Soltani MD

HISTORY OF PRESENT ILLNESS

A 28-year-old man presented with a 15 year history of pruritic, rust-colored 4-8 mm oval papules in a generalized distribution. The lesions had been present for about 15 years, and the patient indicated they decreased in intensity and color upon photoexposure. The patient also complained of systemic symptoms such as headache, dizziness, nasal congestion, abdominal cramping and diarrhea that had presented concurrently with the skin lesions, but had worsened over the past 2 years. There was no history of infection, BCG immunization, trauma, or arthropod bites.

PAST MEDICAL HISTORY

Unremarkable.

PAST SURGICAL HISTORY

Anal fistula repair.

MEDICATIONS

Multivitamin, acetaminophen prn, diphenhydramine prn.

ALLERGIES

No known drug allergies. Allergic to cat dander.

FAMILY HISTORY

Mother – cervical cancer. Grandfather – prostate cancer. Grandmother – lung cancer.

SOCIAL HISTORY

Patient works as a carpenter, social drinker, does not smoke.

PHYSICAL EXAMINATION

On physical exam, multiple (100-200) rust-colored, oval, well-defined, 4-8 mm papules and plaques were present on the trunk and proximal extremities. The face, distal extremities, including the palms and soles were spared. The lesions became edematous several minutes after they were rubbed (+Darier's sign). Abdominal exam was normal and no lymphadenopathies were present.

LABORATORY DATA

Serum tryptase was elevated at 66 ng/mL. A complete blood count and comprehensive metabolic panel were normal. A skin biopsy specimen was subjected to allele-specific polymerase chain reaction (PCR) targeting the codon 816 *c-kit* mutation. Products were consistent with a point mutation leading to Asp816Val, which has been shown to result in ligand-independent activation and autophosphorylation of the KIT receptor in mast cells.

A full-body CT scan showed one borderline left cervical lymphadenopathy (0.7 X 1.4 cm).

HISTOPATHOLOGY

A punch biopsy showed increased numbers of mast cells, both in around the vessels and in the dermal interstitium, confirmed by Giemsa staining. In addition, a superficial perviscular lymphocytic infiltrate was observed. A bone marrow aspirate showed an otherwise normocellular bone marrow, with multiple foci of CD117+ mast cells, some of which were accompanied by eosinophils. A high percentage of cells in the bone marrow (0.22%) showed high expression of CD117.

DIAGNOSIS

Systemic mastocytosis.

TREATMENT & COURSE

In spite of worsening systemic symptoms and bone marrow involvement, treatment with the Kit inhibitor Imatinib mesylate (Novartis, Switzerland) would be precluded due to *in vitro* and *in vivo* data showing lack of inhibition in mast cells harboring the Asp816Val mutation. Therefore, symptomatic treatment with antihistamines was initiated with cetirizine and ranitidine, as well as oral cromoglycate sodium, with partial symptomatic improvement.

DISCUSSION

Mastocytosis represents multiple distinct disorders in which mast cells infiltrate the skin and/or other organs. Clinical manifestations will depend on the number and extent of tissues involved. Whereas children have involvement limited to the skin, adults usually have extracutaneous involvement, which has been defined as systemic mastocytosis (SM). Mast cells represent a distinct myeloid cell lineage within lympho-hematopoietic tissues, and SM results from mutations in the *c-KIT* gene. Therefore, SM can be considered a myeloproliferative disorder. The prevalence is unknown, and distribution is equal between males and females. Over 40 cases of familial mastocytosis have been reported.

The skin is affected in >80% of patients, which facilitates the diagnosis of SM. Cutaneous lesions in adults consist of red-brown macules and papules-plaques measuring less than 1 cm, and the trunk and proximal extremities are affected most frequently. Darier's sign is usually present, and consists of the formation of an urticarial wheal after rubbing the lesions. This sign is more evident in younger patients, where lesional mast cell density is greater. Systemic symptoms associated with SM can be attributed to mast cell release of preformed and newly synthesized mediators, such as histamine. Cutaneous symptoms of mastocytosis include pruritus, flushing, urticaria, and dermatographism. Systemic symptoms include syncope, gastric distress, nausea and vomiting, diarrhea, bone pain, and neuropsychiatric symptoms. These symptoms may be exacerbated by heat, exercise or trauma to cutaneous lesions, and drugs (narcotics, non-steroidal antiinflamatories, salicylates, polymixin B, anesthetics, anticholinergics and alcohol).

The diagnosis of SM is based on the presence of one major criterion and one minor criterion or three minor criteria. Major criteria include the presence of multifocal dense infiltrates of > 15 mast cells in bone marrow and/or other extracutaneous organs. Four minor criteria include the presence of elevated serum alpha-tryptase levels > 20 ng/mL, the expression of CD2 and CD25 surface markers in c-kit-positive mast cells from bone

marrow or other organs, the presence of c-kit mutations on bone marrow and/or other tissue mast cells, and the presence of > 25% abnormal spindle-shaped mast cells in bone marrow and/or tissues.

Classification is based on either clinical criteria or the presence of mutations in the gene coding for the KIT receptor. Clinical classification is as follows: type Ia: indolent mastocytosis without systemic disease; type Ib: indolent mastocytosis with systemic disease; type II: mastocytosis associated with a myeloproliferative or myelodysplastic disease; type III: lymphadenopathic mastocytosis with eosinophilia; type IV: mast cell leukemia. The patient presented herein is classified as class Ib. Mast cells express the KIT receptor, which is encoded by the proto-oncogene *c-KIT*. The KIT receptor is a type III transmembrane tyrosine kinase whose ligand is stem cell factor, the major mast cell proliferation and differentiation factor. Classification can also be made based on *c-KIT* mutation status: childhod disease with or without an activating mutation, or those with an inactivating mutation; adult disease with the 816 activating mutation (the most frequent type, and that present in our patient), or those with the 560 or 820 activating mutation; and finally familial disease with or without activating mutations.

Documentation of mast cells in the skin or other organs by histopathology is essential for diagnosis. Mast cells can be more readily identified with the use of special stains: Giemsa and toluidine blue, as well as anti-tryptase and anti-CD117 monoclonal antibodies. We were able to identify the Asp816Val mutation in lesional skin from our patient using an allele-specific polymerase chain reaction technique. The most commonly involved extracutaneous sites are bone marrow, spleen, liver, lymph nodes, and gastrointestinal tract. A bone marrow biopsy and aspirate is the procedure of choice in cases of suspected SM.

Treatment for SM is dependent upon symptoms and degree of mast cell involvement and is aimed to either control symptoms and/or reduce mast-cell burden. For indolent disease (types Ia, Ib), treatment is directed towards controlling symptoms associated with mast cell degranulation. Antagonists of histamine type 1 and 2 receptors, have been used with success. Second-generation antihistamines (e.g. loratadine, fexofenadine hydrochloride, cetirizine hydrochloride) are preferable in the majority of instances due to decreased side effects. However, in cases where gastrointestinal symptoms relating to acid hypersecretion are present, H2 anithistamines (e.g. ranitidine, famotidine) may prove beneficial. Mast cell stabilizing agents, such as ketotifen fumarate and cromolyn sodium are also used when systemic symptoms are present. For cutaneous lesions and pruritus, psoralen plus UVA is effective, however systemic symptoms will be unaffected. Topical steroids are also effective for cutaneous lesions, and systemic steroids are beneficial when gastrointestinal symptoms and ascites are present.

For more agressive forms of SM, cytoreduction is desirable. Most experience has been obtained with the use of interferon-alpha, with an estimated 57% response rate in a meta-analysis including 14 patients. Anecdotal success has been reported with cladribine, a nucleoside analogue with myeolsuppressive and immunosuppressive properties. Allogeneic bone marrow transplantation is employed in patients with aggressive disease,

and the benefits appear to result from the immunotherapeutic effect of the donor bone marrow. The most promising therapy for the treatmend of SM is the use of the small molecule KIT inhibitor Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland). This drug inhibits wild-type and mutants of KIT bearing juxtamembrane activating mutations, but it does not inhibit mutants bearing the 816 mutation, as found in our patient. This is believed to be due to conformational changes in 816 mutants which interfere with drug association with the ATP-binding pocket, and patients harboring *c-KIT*^{816} will not benefit from this drug. The use of *c-KIT*^{816} inhibitors would therefore represent an ideal therapy for this disease.

REFERENCES

Longley BJ Jr, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu SZ, Heitjan D, Ma Y. Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci U S A. 1999;16:1609-14.

Tharp MD, Longley BJ Jr. Mastocytosis. Dermatol Clin. 2001;19:679-96.

Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, Bennett JM, Metcalfe DD. Diagnosis and treatment of systemic mastocytosis: state of the art. S. T. Holgate (chairman)G. W. Canonica, F. E. R. Simons, M. Br J Haematol. 2003;122:695-717.

Tharp MD. Mastocytosis. In Dermatology , Bolognia JL, Jorizzo JL, Rapini RP Eds. Mosby 2003.

Akin C, Brockow K, D'Ambrosio C, Kirshenbaum AS, Ma Y, Longley BJ, Metcalfe DD. Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit. Exp Hematol. 2003;31:686-92.

Tharp MD, Chan IJ. Taglialatela, M. Tharp, H. Timmerman, K. Yanai. Consensus group on new-generation antihistamines (CONGA): present status and recommendations. Clinical & Experimental Allergy. 2003;33:1305.

Pardanani A, Elliott M, Reeder T, Li CY, Baxter EJ, Cross NC, Tefferi A. Imatinib for systemic mast-cell disease. Lancet. 2003;16;362:535-6.

Castells M. Mastocytosis: classification, diagnosis, and clinical presentation. Allergy Asthma Proc. 2004;25:33-6.

Akin C, Metcalfe DD. Systemic mastocytosis. Annu Rev Med. 2004;55:419-32.

Akin C, Metcalfe DD. The biology of Kit in disease and the application of pharmacogenetics. J Allergy Clin Immunol. 2004;114:13-9.

PRESENTERS

Leslie E. Bernstein MD, Christopher R. Shea MD and Maria M. Medenica MD

HISTORY OF PRESENT ILLNESS

This 67-year-old man presented with a 2-day history of multiple, smooth, reddish-purple, asymptomatic lesions on his shins, ankles, and feet.

PAST MEDICAL HISTORY

Peripheral neuropathy
Transient ischemic attack with episodic quadrantanopsia

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

Atopic dermatitis

SOCIAL HISTORY

Non-smoker
Retired electrical engineer

PHYSICAL EXAMINATION

Shiny, violaceous, dome-shaped papules were symmetrically distributed on both anterior-inferior shins, ankles, and dorsa of feet. Many lesions appeared hemorrhagic and scaly. The papules were nontender.

LABORATORY DATA

The following results were within normal limits:
Electrolytes and glomerular filtration rate

The following were elevated:
24-hour total protein (2279), gamma region M spike (1662), serum total protein (8.4), protein electrophoresis gamma globulin (3.9), lupus anticoagulant (53), anticardiolipin M antibody (>150 units), quantitative cryoglobulin (1% volume), factor VIII (422), factor IX (102), serum viscosity (3.9), immune globulin M kappa (3182)

The following were decreased:
Hemoglobin/hematocrit (12.5/36.6), protein electrophoresis albumin (2.8), antithrombin III (81), immune globulin A (<5), immune globulin G (408)

Bone marrow core biopsy and aspirate demonstrated a lymphoplasmacytic lymphoma with extensive plasmacytic differentiation.

Abdominal ultrasound revealed hepatosplenomegaly.

Osseous survey showed no evidence of discrete myelomatous lesions.

DERMATOPATHOLOGY

Right shin: The epidermis was orthohyperkeratotic. Amorphous eosinophilic and PAS+ material was present in the dermal papillae and reticular dermis, including around vessels and appendages. Congo red stain was negative for amyloid. Anti-laminin labeled the DEJ basement membrane and dermal deposits including those around blood vessels and appendages. Anti-collagen type IV labeled basement membrane and amorphous deposits (weakly). Anti-CD34 labeled endothelial cells and highlighted the perivascular location of the dermal deposits. Direct immunofluorescence demonstrated deposits of IgA, IgM, C3, and fibrinogen on walls of and inside superficial dermal vessels. Transmission electron microscopy revealed superficial dermal capillaries surrounded by electron-dense finely granular deposits (without fibrils), consistent with immunoglobulin deposits.

DIAGNOSIS

Macroglobulinemia cutis, in the context of Waldenstrom macroglobulinemia

TREATMENT & COURSE

The patient received the following:
Prednisone
Chlorambucil
Allopurinol
Plasmapheresis x 2 cycles
Leucovorin
Rituximab x 2 courses

His cutaneous lesions resolved and his IgM level is declining.

DISCUSSION

Initially described in 1944, Waldenstrom macroglobulinemia is a rare, chronic, B-cell disorder, featuring a monoclonal proliferation of lymphoplasmacytes in the bone marrow and occasionally in the lymph nodes and spleen. The abnormal cells possess eosinophilic intranuclear inclusions, called Dutcher bodies, that are stained with PAS, indicating glycoprotein. The etiology of Waldenstrom macroglobulinemia is unknown, and there is a slight male predominance, particularly in the sixth and seventh decade. Circulating IgM is increased, causing a hyperviscosity syndrome. IgM may combine with coagulation factors or coat platelets, leading to a bleeding diathesis. The lymphoproliferative cells can infiltrate many organs. Patients often present with anemia, cachexia, lymphadenopathy, hepatosplenomegaly or weakness. One-third of macroglobulinemia patients develop cryoglobulinemia and this induces peripheral neuropathy.

The skin is affected in 5% of individuals with Waldenstrom macroglobulinemia. The most common lesion is a violaceous, indurated plaque, directly resulting from lymphoplasmactyoid infiltration of the reticular dermis and subcutaneous tissue. Invasive cells might contain intranuclear PAS-positive inclusions corresponding to IgM. Urticaria, purpura, purple discoloration of digits and ears, and ulcers develop less frequently, secondary to abnormalities such as cryoglobulinemia. Subepidermal bullae, associated with positive IgM immunofluorescence at the basement membrane zone, occur occasionally. IgM storage papules can appear on extensor surfaces of extremities, as well as the face, trunk and buttocks. These are generally asymptomatic, and may be hemorrhagic, umbilicated or crusted. Histology of these papules reveals homogeneous, PAS-positive eosinophilic material in the dermis, corresponding to IgM deposits. The amorphous material is not stained with Congo red or thioflavin T. Deposits of IgM (usually kappa) can be detected by direct immunofluorescence, including in the lamina lucida and subepidermal basement membrane. No correlation between IgM levels and the progression of cutaneous lesions exists. Treatment of the underlying Waldenstrom macroglobulinemia is the therapy for macroglobulinemia cutis, and chlorambucil is the preferred drug. A corticosteroid can be useful as an adjunctive medication. Melphalan and cyclophosphamide are alternatives. Hyperviscosity responds well to plasmapheresis. Chemotherapy and immunosuppression variably affect cutaneous lesions. Isolated, infiltrated skin plaques have been treated successfully with radiotherapy.

REFERENCES

Abdallah-Lotf M, Bourgeois-Droin C, Perronne V, Fouchard N, Michel S, Launay-Russ E, Granier F. Cutaneous manifestations as initial presentation of Waldenstrom's macroglobulinemia. Eur J Dermatol 2003; 13: 90-92

Hanke C, Steck W, Bergfeld W, Valenzuela R, Weick J, Young J, Gross E. Cutaneous macroglobulinosis. Arch Dermatol 1980; 116: 575-577

Libow L, Mawhinney J, Bessinger G. Cutaneous Waldenstrom's macroglobulinemia: Report of a case and overview of the spectrum of cutaneous disease. J Am Acad Dermatol 2001; 45: S202-S206

Mascaro J, Montserrat E, Estrach T, Feliu E, Ferrando J, Castel T, Mallolas J, Rozman C. Specific cutaneous manifestations of Waldenstrom's macroglobulinaemia. A report of two cases. Br J Dermatol 1982; 106: 217-222

Orengo I, Kettler A, Bruce S, Levy M, Rosen T, Tschen J. Cutaneous Waldenstrom's macroglobulinemia. A report of a case successfully treated with radiotherapy. Cancer 1987; 60: 1341-1345

Tichenor R, Rau J, Mantz F. Macroglobulinemia cutis. Arch Dermatol 1978; 114: 280-281

PRESENTERS

Amy Farmer MD, Christopher R. Shea MD and Sarah L. Stein MD

HISTORY OF PRESENT ILLNESS

The patient, a 16-year-old African-American female, was admitted to the inpatient Orthopedic surgery service for biopsy of a tibial mass discovered in a work-up for a one-year history of knee pain. Dermatology was consulted for evaluation of a mildly tender skin lesion that had been present for 11 months on the right chest wall and breast. The patient denied history of fevers, chills, night sweats, or weight loss.

PAST MEDICAL HISTORY

Obesity

PAST SURGICAL HISTORY

None

MEDICATIONS

Ibuprofen 1200 mg daily

ALLERGIES

None

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Non-contributory

PHYSICAL EXAMINATION

A 20 by 10 cm ill-defined plaque of coalescing, yellow-red nodules on a violaceous and hyperpigmented base with focal crusted ulceration was seen on the right chest wall and breast. No lymphadenopathy was noted. Ophthalmologic examination did not show evidence of uveitis.

LABORATORY DATA/IMAGING

The following laboratory tests were within normal limits: basic metabolic panel, thyroid stimulating hormone, anti-nuclear antibody, and urinalysis. Fungal, mycobacterial, and bacterial cultures of skin and bone were negative.

The following laboratory tests were abnormal: hemoglobin 10.8 (11.5-15.5), white blood cell count 13.4 (3.5-11), c-reactive protein 168 (nl <5), erythrocyte sedimentation rate 21 (0-20).

Plain film (right knee): A lucent epiphyseal lesion of the right tibial plateau abutting the articular surface was noted. There was no evidence of sclerosis. Impression was consistent with a giant cell tumor.
CT scan (chest/abdomen/pelvis): No pathologic lymphadenopathy.

DERMATOPATHOLOGY

From the chest wall lesion, a punch biopsy specimen was taken. The epidermis was thinned and exhibited crusting and focal erosion. In the dermis, a large cavity was noted containing foamy histiocytes with evidence of emperipolesis. Fite and gram stains were negative for organisms. Nearly all of the infiltrate expressed CD68 and S-100 protein. CD1a was negative. Pathology of the bone lesion revealed a similar infiltrate with identical immunostaining.

DIAGNOSIS

Cutaneous and osseous Rosai-Dorfman disease.

TREATMENT & COURSE

During her hospitalization, the patient received IV Cefazolin as well as antibiotic-impregnated bead (OsteoSet) placement during the bone biopsy. The patient was treated with topical mupirocin and betamethasone diproprionate ointment with improvement of ulcerations within the right chest wall mass. Subsequently, a nine-day course of radiation therapy (180 cGy/day, total dose 1440 cGy) was administered with some improvement in the thickness of the lesion. Post-radiation, the patient continues to use high-potency topical steroids.

DISCUSSION

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a benign, self-limiting histiocytic proliferative disorder typically involving the lymph nodes. Extranodal disease occurs in 40% of the cases, and sites involved include skin, nasal cavity, paranasal sinuses, eyelids, orbit, bone and CNS. Skeletal involvement is rare (<5% of reported cases), although it appears to be more prevalent in children. Eighty percent of cases present within the first two decades in life, more commonly in males. Etiology is uncertain, although HHV-6 has been investigated as a contributing factor. Systemic involvement typically presents as painless cervical lymphadenopathy, fever, anemia, elevated ESR, and a polyclonal hypergammaglobulinemia.

Purely cutaneous Rosai-Dorfman disease is rare. Cutaneous manifestations have clinical diversity with presentations including large nodules (erythematous or xanthomatous), plaques, pustules, acneiform lesions, pigmented macules, and a transient panniculitis or vasculitis. Osseous Rosai-Dorfman disease typically presents as multiple osteolytic lesions in long bones or the skull, and less commonly as solitary or sclerotic lesions. Histology reveals large foamy histiocytes and plasma cells in the dermis and often within dilated dermal lymphatics. Histiocytes exhibit emperiopolesis (phagocytosis of plasma cells, lymphocytes, or neutrophils). Xanthoma cells, fibrosis, increased vascularity, and focal necrosis may be present. The histiocytic infiltrate is S100-positive and CD1a-negative and expresses histiocytic markers such as CD68.

Rosai-Dorman disease has a benign, often protracted course. 70% to 80% of the patients have spontaneous resolution and treatment is reserved typically for disease that compromises organ function. Death has been reported as a result of organ infiltration or from immunologic disturbances. Patients with immunologic abnormalities, disseminated nodal disease, or liver or lung involvement have a worse prognosis. Reported treatments of cutaneous lesions include topical and intralesional corticosteroids, superficial radiation, cryotherapy, observation, chemotherapy, or surgical excision.

REFERENCES

Grote HJ, Mosenthin M, Foss HD, Kekow J, Roessner A. Osseous manifestation of Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy): a case report and review of the literature. Gen Diag Pathol 1998; 143: 341-5.

Ang P, Tan SH, Ong BH. Cutaneous Rosai-Dorfman disease presenting as pustular and acneiform lesions. J Am Acad Dermatol 1999; 41:335-7.

Stefanato CM, Ellerin PS, Bhawan J. Cutaneous sinus histiocytosis (Rosai-Dorfman disease) presenting clinically as vasculitis. J Am Acad Dermatol 2002; 46:775-8.

Brenn T, Leonard N, Grayson W, Fletcher C.D, McKee P. Cutaneous Rosai-Dorfman disease is a distinct clinical entity. Am J Dermatopathol 2002; 24:385-91.

Rodriguez-Galindo C, Helton KJ, Sanchez ND, Rieman M, Jeng M, Wang W. Extranodal Rosai-Dorfman disease in children. J Pediatric Hematol Oncol 2004; 26: 19-24.

UNKNOWN CASE

PRESENTERS

Michael J Welsch MD, Christopher R Shea MD

HISTORY OF PRESENT ILLNESS

Facial plaques in an African-American male

PRESENTERS

Lisa A. Carroll MD, Christopher R. Shea MD, Shail Busbey MD

HISTORY OF PRESENT ILLNESS

This 67 year-old African-American woman with a history of multiple medical problems was admitted to the University of Chicago Hospitals in July 2004 for chest pain and dyspnea. Dermatology was consulted due to the presence of an indurated, painful plaque located on the left inframammary chest wall. This lesion, which had been present for a number of years, reportedly was becoming more indurated and more painful. A biopsy was performed.

PAST MEDICAL HISTORY

Coronary artery disease
COPD
Diabetes mellitus
Congestive heart failure
Hypertension
Depression
Retinal detachment
Anemia
Stage IV non-Hodgkin lymphoma (follicular mixed cell type): diagnosed in 1992 after presentation with bilateral axillary lymph node enlargement and a breast mass detected on mammography; treated with radiation & chemotherapy; multiple recurrences with extranodal and solid organ involvement

PAST SURGICAL HISTORY

Coronary artery bypass graft
Retinal detachment repair
Right ureteral stent placement

MEDICATIONS

Furosemide
Aspirin
Lipitor
Paroxetine
Cozaar
Arinesp
Insulin
Cardizem

ALLERGIES

None

FAMILY HISTORY

MI, NIDDM

SOCIAL HISTORY

Divorced, lives alone, 2 grown sons, receptionist at drug abuse treatment center, 30-pack year history of tobacco (quit in 1985)

PHYSICAL EXAMINATION

There was a 3 x 5 centimeter, indurated, erythematous plaque composed of multiple papules & nodules fixed to the underlying tissue located under the left breast. Additionally, there were multiple indurated subcutaneous nodules in the groin, on the right shoulder, and on the abdomen.

LABORATORY DATA

8/04: normal complete metabolic panel, calcium, magnesium, complete blood panel except for slight anemia (hematocrit 34.6 [36-47]) & mild thrombocytopenia (114 [150-450])

8/12/04 pre & post-infusion brain MRI: no intracranial enhancement to suggest lymphoma; orbital lymphoma present bilaterally; probable lymphoma of left lateral pterygoid muscle

7/31/04 CT abdomen/pelvis: large, confluent, subcutaneous nodules involving both breasts and chest wall, new left upper rectus sheath hematoma, retroperitoneal nodes, subcutaneous infiltration present on lower back and in left groin, soft-tissue infiltrative nodules in bilateral ischiorectal fossae and in left posterior retroperitoneum consistent with known lymphoma

7/30/04 PET: diffuse increased activity affecting the subcutaneous regions around the chest and abdominal walls; active lesions with the para-aortic and retroperitoneal areas, uterus, pelvis

7/28/04 CT chest: axillary adenopathy, enhancing anterior and posterior subcutaneous lesions, mass effect on stomach by soft tissue density

10/20/92 breast ultrasound: hypoechoic 1.5 x 1.0 centimeter mass in upper outer right breast with speculated margins, other smaller hypoechoic nodules in bilateral breasts, bilateral enlarged axillary lymph nodes

DERMATOPATHOLOGY

7/29/04 biopsy of chest skin: slightly atrophic epidermis; nodular diffuse infiltrate of small lymphoid cells with moderate nuclear irregularities; immunolabeling as follows: CD20 strongly +, CD3 – (<10% of dermal lymphoid cells), lambda & kappa light chain -, PAX5 +, bcl2 strongly +, CD10 strongly +, CD5 – (<10% of dermal lymphoid cells) reported as lymphoma cutis with histologic and immunohistochemical features consistent with follicular lymphoma

6/30/04 bone marrow biopsy: small paratrabecular lymphoid infiltrates c/w marrow involvement by follicular lymphoma; immunolabeling as follows: CD20+, PAX5+, CD3-

11/09/99 bone marrow biopsy: lymph node architecture completely effaced by a high density of malignant lymphoma cells in a follicular pattern with varying follicle size and

lack of mantle zones, consistent with follicular lymphoma of mixed small cleaved and large cell type, grade 2; immunolabeling as follows: CD10+, CD20+, bcl-2 +, kappa -, lambda -

DIAGNOSIS

Secondary cutaneous follicular B-cell lymphoma

TREATMENT & COURSE

Patient is currently under the care of her oncologist.

DISCUSSION

Follicular B-cell lymphoma can present in the skin as a primary phenomenon, with disease limited to the skin for at least six months, or as a secondary phenomenon due to dissemination of nodal follicular B-cell lymphoma. Differentiation between primary and secondary follicular B-cell lymphoma has been hampered by successive changes in cutaneous lymphoma classification and by the lack of a definition of the morphologic and molecular features of these tumors. Both the prognosis and the treatment strategies differ significantly for secondary and primary cutaneous follicular B-cell lymphoma. As such, it is vital to differentiate between the two conditions, especially since cases of primary nodal follicular lymphoma have been reported to present initially with cutaneous manifestations.

Nodal follicular B-cell lymphoma rarely spreads to the skin, with cutaneous metastasis reported in <4% of cases. It tends to present as indurated nodules or plaques especially on the trunk. Disseminated follicular B-cell lymphoma is somewhat more aggressive than primary cutaneous follicular B-cell lymphoma, with a five-year survival probability of only 30-50%. On the other hand, follicular B-cell lymphoma is one of the most common primary cutaneous B-cell lymphomas. It tends to be indolent, with a five-year survival of approximately 97% and a ten-year survival above 90%. Patients present with solitary or grouped reddish papules or plaques. Lesions favor the head and neck, but may appear on the trunk. Recurrences occur in approximately 50% of cases, but dissemination internally is rare.

In general, primary and secondary cutaneous follicular B-cell lymphoma exhibit similar histopathology. Secondary cutaneous follicular B-cell lymphoma usually presents similarly to nodal disease, with follicle-resembling formations with ill-defined margins and little interfollicular tissue. There is usually relative monotony of cytologic features with rare mitoses, paucity of phagocytic histiocytes, and presence of neoplastic cells within the interfollicular regions. Primary cutaneous follicular B-cell lymphoma cases may present with a follicular architecture with similar cytologic features; however, it is usually characterized by a more diffuse growth pattern. Centroblasts and centrocytes predominate within the neoplastic infiltrate in both types of follicular B-cell lymphoma. A variable number of immunoblasts, small lymphocytes and histiocytes, and sometimes eosinophils and plasma cells, are admixed.

Both types of follicular B-cell lymphoma tend to express B-cell antigens such as CD19, CD20, and CD 79a. They do not tend to express CD5 and CD43. In general, CD10 and

bcl-2 are not expressed in primary cutaneous FCL, although there has been controversy regarding this. Early literature rarely demonstrated expression of bcl-2 by primary cutaneous follicular B-cell lymphoma. However, more recent studies have shown some cases of primary cutaneous follicular B-cell lymphoma that express bcl-2 and/or CD10. In systemic follicular B-cell lymphoma, approximately 85% of cases demonstrate a t(14;18) chromosomal translocation, which results in the juxtaposition of the bcl-2 gene on chromosome 18 with the Ig heavy chain region of chromosome 14. This results in overexpression of functionally normal Bcl-2 protein, which inhibits apoptosis of neoplastic cells. This translocation rarely, if ever, occurs in primary cutaneous follicular B-cell lymphoma. Detection of t(14;18) in cutaneous follicular B-cell lymphoma would suggest underlying nodal disease. Absence of both bcl-2 and t(14;18) makes primary cutaneous follicular B-cell lymphoma most likely; while presence of either one heightens suspicion of systemic follicular B-cell lymphoma.

Despite the controversy regarding the morphologic and immunophenotypic characteristics of primary and secondary FCL, one vital point is clear. When a patient presents with cutaneous follicular B-cell lymphoma, a full work-up for systemic disease is crucial. Although an immunophenotype that is CD10 and bcl-2 negative supports a diagnosis of primary cutaneous disease, primary disease may also be bcl-2 and/or CD10 positive. In general, systemic follicular B-cell lymphoma with cutaneous metastasis is bcl-2 and CD10 positive; however, it is possible for systemic disease to lack one or both of these markers. Thus, a full workup is necessary for every patients diagnosed with a follicular B-cell lymphoma in the skin.

REFERENCES

Aguilera NSI, Tomaszewski MM, Moad JC, Bauer FA, Taubenberger JK, Abbondanzo SL. Cutaneous follicle center lymphoma: a clinicopathologic study of 19 cases. Mod Pathol 2001;14:828-835.

Child FJ, Russell-Jones R, Woodlford AJ, Calonje E, Photiou A, Orchard G, Whittaker SJ. Absence of the t(14;18) chromosomal translocation in primary cutaneous B-cell lymphoma. Brit J Dermatol 2001;144:735-744.

Dabski K, Banks PM, Winkelmann RK. Clinicopathologic spectrum of cutaneous manifestations in systemic follicular lymphoma. Cancer 1989;64:1480-1485.

Franco R, Fernandez-Vazquez A, Mollejo M, Cruz MA, Camacho FI, Garcia JF, Navarrete M, Piris MA. Cutaneous presentation of follicular lymphoma. Mod Pathol 2001;14:913-919.

Hoefnagel JJ, Vermeer MH, Jansen PM, Fleuren GJ, Meijer CJLM, Willemze R. Bcl-2, bcl-6 and CD10 expression in cutaneous B-cell lymphoma: further support for a follicle centre cell origin and differential diagnostic significance. Brit J Dermatol 2003;149:1183-1191.

Lawnicki LC, Weisenburger DD, Aoun P, Chan WC, Wickert RS, Greiner TC. The t(14;18) and bcl-2 expression are present in a subset of primary cutaneous follicular lymphoma. Am J Clin Pathol 2002;118:765-772.

Prince HM, Yap LM, Blum R, McCormack C. Primary cutaneous B-cell lymphoma. Clin Exp Dermatol 2003;28:8-12.

Storz MN, van de Rijn M, Kim YH, Mraz-Gernhard S, Hoppe RT, Kohler S. Gene expression profiles of cutaneous B-cell lymphoma. J Invest Dermatol 2003;120:865-870.

Yang B, Tubbs RR, Finn W, Carlson A, Pettay J, Hsi ED. Clinicopathologic reassessment of primary cutaneous B-cell lymphomas with immunophenotypic and molecular genetic characterization. Am J Surg Pathol 2000;24:694-702.

PRESENTERS

Iris Kedar, M.D., Christopher R. Shea, M.D., Maria Medenica, M.D., Shail Busbey, M.D.

HISTORY OF PRESENT ILLNESS

This 62-year-old man presented with a two-year history of red areas that he first noticed on his forearm. The red areas slowly progressed to involve his penis, and both arms and legs. The lesions were asymptomatic and had not bled. He had no history of gastrointestinal bleeding. He had a history of a nose bleed that necessitated an emergency room visit a year and a half ago.

PAST MEDICAL HISTORY

Deep venous thrombosis, pulmonary embolism

PAST SURGICAL HISTORY

Appendectomy
Colonic polyp

MEDICATIONS

Warfarin

ALLERGIES

No known drug allergies

FAMILY HISTORY

No history of telangiectases or hereditary hemorrhagic telangiectasia.

SOCIAL HISTORY

Professor at University of Chicago. Married with one child.

PHYSICAL EXAMINATION

There were telangiectases on the penis, forearms, and thighs that were confluent in areas. Mucous membranes were normal.

LABORATORY DATA

The following were abnormal:

Beta2 glycoprotein IgA 23.9 (<20) (IgG, IgM negative)
Heterozygous for prothrombin G2010A mutation
Hct 35.8 (WBC 5.0, platelets 200)
INR 2.2 (on Warfarin)

The following were normal or negative:

Comprehensive metabolic panel, urinalysis, anticardiolipin antibodies, lupus anticoagulant, factor V Leiden, functional protein C, functional protein S, anti-thrombin 3, fibrinogen, homocysteine, hepatitis C antibody, urine porphyrins.

Normal colonoscopy 9/98

DERMATOPATHOLOGY

Left forearm: The epidermis was flat. The papillary dermis contained dilated blood vessels. Elastosis was present. There was a superficial perivascular lymphocytic infiltrate. The PAS stain demonstrated thickening and apparent reduplication of the basement membrane around dermal blood vessels. The epidermal basement membrane did not appear thickened. The Congo red stain was negative for amyloid. Anti-collagen IV and anti-laminin both strongly labeled the reduplicated basement membrane material around dermal blood vessels.

Left thigh: Similar findings as above. Anti-estrogen receptor was negative.
Transmission electron microscopy: The epidermis was unremarkable. Several capillaries in the upper layer of the dermis showed a single layer of unremarkable endothelial cells surrounded by six to ten layers of concentric basement membranes. Between the multilayered basement membranes were thin collagen fibers. The basement membranes appeared interrupted focally.

DIAGNOSIS

Generalized Essential Telangiectasia

TREATMENT & COURSE

The telangiectases had been slowly progressing. The patient recently started taking various vitamins and an herbal supplement called Noni. He notes that his thighs appear to be less red. Treatment has otherwise not been initiated.

DISCUSSION

Generalized essential telangiectasia (GET) is an uncommon condition that is characterized by widespread telangiectases that progress slowly over the course of years. Onset is usually in the thirties, and women are affected more than men. Telangiectases most often begin on the lower extremities, and may progress to the trunk or upper extremities. Lesions are usually asymptomatic, but may be associated with tingling, numbness, or burning. Dependent positions exacerbate the telangiectases. Lesions do not regress.

Involvement of other organ systems and hemorrhage are not commonly described. Mucous membranes are rarely involved. Clasically GET has not been associated with a systemic disease. Several case reports have described an association with autoimmune disease. Inheritance is usually sporadic; however, several familial cases with autosomal dominant inheritance have been described. The cause of GET is unknown. The diagnosis of GET requires ruling out underlying conditions associated with telangiectases and other primary causes of telangiectases, including hereditary hemorrhagic telangiectasia (HHT).

Histologically, thin-walled ectatic vessels in the upper dermis are seen. Alkaline phosphatase staining is negative, and vessels are therefore considered dilated venules. One report described the absence of estrogen and progesterone receptors. Multiple basement membranes in GET have been described in a case report by Shelly and Fierer. Multiple basement membranes have also been described in other disorders, including diabetes mellitus, porphyria, lipoid proteinosis, actinically damaged skin, and aging skin.

Treatment may be challenging with data limited to case reports. Tetracycline was successful in one case. Acyclovir was effective in a patient with GET and associated autoimmune disease. Ketoconazole was effective in one patient. Vascular lasers including the pulsed dye and Nd:YAG laser have been helpful.

REFERENCES

1. Buscaglia DA, Conte ET. Successful treatment of generalized essential telangiectasia with the 585-nm flashlamp-pumped pulsed dye laser. Cutis. 2001;67(2):107-108.

2. Checketts SR, Burton PS, Bjorkman DJ, Kadunce DP. Generalized essential telangiectasia in the presence of gastrointestinal bleeding. J Am Acad Dermatol. 1997;37(2):321-325.

3. Gambichler T, Avermaete A, Wilmert M, Altmeyer P, Hoffmann K. Generalized essential telangiectasia successfully treated with high-energy, long-pulse, frequency-doubled Nd:YAG laser. Dermatol Surg. 2001;27(4):355-357.

4. Green D. Generalized essential telangiectasia. www.emedicine.com. Last accessed 10/18/04.

5. Long D, Marshman G. Generalized essential telangiectasia. Australas J Dermatol. 2004;45(1):67-69.

6. McGrae JD, Winkelmann RK. Generalized essential telangiectasia: report of a clinical and histochemical study of 13 patients with acquired cutaneous lesions. JAMA. 1963;185(12):909-913.

7. Shelley WB, Fierer JA. Focal intravascular coagulation in progressive ascending telangiectasia: Ultrastructural studies of ketoconazole-induced involution of vessels. J Am Acad Dermatol. 1984;10(5):876-887.

8. Shelley WB. Essential progressive telangiectasia. Successful treatment with tetracycline. JAMA. 1971;216(8):1343-1344.

PRESENTERS

Arlene Molino, MD and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS

The patient is a right-handed 11-year-old Caucasian male who presented complaining of a 6 month history of nail changes involving both thumbnails and great toenails. He stated that it was somewhat painful when the tips of the digits were squeezed. The patient denied recent trauma or other growths adjacent to the nails. He and his mother repeatedly denied any picking at the cuticles or nails. Nail growth has not been affected. His hobbies include woodworking, but again he denies trauma to the nail unit related to this activity.

PAST MEDICAL HISTORY

Non-contributory

PAST SURGICAL HISTORY

Non-contributory

MEDICATIONS

None

ALLERGIES

None

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

The patient lives with his family and is a student. His mother denies any obvious psychological stressors on the patient.

PHYSICAL EXAMINATION

Parallel horizontal somewhat arciform ridges approximately 3mm wide were distributed down the midline of both thumbnails and great toenails. There was some debris apparent in the depressions on the right thumbnail, with greater prominence of the ridges in comparison to the left thumbnail. Mild erythema of the proximal nail fold and widening of the lunulae were noted on both thumbnails. Periungual hyperpigmentation was noted at the base of both great toenails. The remaining nails were unremarkable.

LABORATORY DATA

None performed

DERMATOPATHOLOGY

None performed

DIAGNOSIS

Habit-tic deformity versus median nail dystrophy

TREATMENT & COURSE

The patient is currently using halobetasol ointment 0.05% ointment to the proximal nail fold nightly. He and his family have been educated regarding the concern that these nail changes are most often secondary to habitual manipulation of the proximal nail fold and he has been strongly encouraged to be aware of this behavior and to avoid it.

DISCUSSION

Habit-tic deformity commonly manifests as a series of linear ridges, usually along the nail plate midline, extending from the cuticle to the free nail edge. A central depression may be present. There may also be hypertrophy of the lunula and evidence of trauma or inflammation of the proximal nail fold. This condition is usually found on the thumbnails. Patients often admit to manipulation of the nail plate or fold, and if bilateral, the abnormality may be more prominent on the dominant hand.

Median nail dystrophy bears clinical features resembling those of habit-tic deformity. Median canaliform dystrophy of Heller, also called dystrophia unguium mediana canaliformis, or median nail dystrophy, is typically described as a longitudinal groove at or near the midline of the nail plate with transverse fissures that extend from the groove at either side. The transverse deformities do not usually extend to the lateral edges of the nail plate, and have been reported both in an “inverted fir tree” or “arrowhead” pattern and as horizontal ridges. These findings are commonly symmetric, most often affecting bilateral thumbnails. Though rare, toenail involvement is usually of the great toes. In addition to the nail plate dystrophy, there may be enlargement of the lunula. It has been stated that the most remarkable feature of median nail dystrophy is the lack of inflammation or disruption of the proximal nail fold and periungual tissue. Accordingly, a history of trauma or nail picking habits has rarely been elicited. Histologic findings are rarely discussed as the lesion is seldom biopsied. Evidence of parakeratosis within the fissure, as well as clefts penetrating deeply into the nail substance has been reported.

The etiology of median nail dystrophy is not known. Proposed causes include repeated trauma, focal infections, and vascular malformations. Familial cases have been described. A recurrent case of median nail dystrophy has been reported with use of isotretinoin orally. The nail abnormality may resolve spontaneously over months to years. It is not uncommon for the condition to be recurrent. Reported treatment modalities have included topical steroids in ointment and tape form, nail wrapping, and radiation, with variable responses.

It has been proposed that habit-tic deformity and median nail dystrophy may be part of a spectrum of reaction patterns in response to nail matrix trauma. Both present with midline deformities and enlarged lunulae. In addition, several cases in which classic findings of both diseases presenting in a single individual have been reported, with simultaneous clinical resolution of the respective nail changes. It is believed by some that hypertrophy of the lunula is a consequence of trauma. Alternatively, others argue that a larger lunula may predispose one to nail changes from minor injury as it extends further out from protection by the proximal nail fold.

Our case is unusual in that the patient presents with involvement of both the thumbnails and great toenails. While the clinical morphology appears to be more consistent with habit-tic deformity, both the patient and family deny any manipulation of the cuticle or nail plate, prompting consideration of other possible etiologies or diagnoses.

REFERENCES

Bottomley WW, Cunliffe WJ. Median nail dystrophy associated with isotretinoin therapy. *Br J Dermatol* 1992; 127: 447-448.

Griego RD, Orengo IF, Scher RK. Median nail dystrophy and habit tic deformity: are they different forms of the same disorder? *Int J Dermatol* 1995; 34: 799-800.

Macaulay WL. Transverse ridging of the thumbnails. *Arch Dermatol* 1966; 93: 421-423.

Samman PD. A traumatic nail dystrophy produced by a habit tic. *Arch Dermatol* 1963; 88: 895-896.

Sweet RD. Dystrophia unguium mediana canaliformis. *Arch Dermatol Syphilol* 1951; 64: 61-62.

Van Dijk E. Dystrophia unguium mediana canaliformis. *Dermatologica* 1978; 156: 358-66.

Vittorio CC, Phillips KA. Treatment of habit-tic deformity with fluoxetine. *Arch Dermatol* 1997; 133:1203-1204.

PRESENTERS

Amy Farmer, MD, Vesna Petronic-Rosic, MD and Shail Busbey, MD.

HISTORY OF PRESENT ILLNESS

A 20 year-old African American female presented with a two-month history of discoloration and ulceration on both breasts. The lesions were tender and had a purulent discharge. Prior to presentation, the patient had received a short course of Keflex with no improvement.

PAST MEDICAL HISTORY

Secondary amenorrhea

PAST SURGICAL HISTORY

None

MEDICATIONS

DepoProvera (stopped 2/04)

ALLERGIES

None

FAMILY HISTORY

Mother died of breast cancer at age 31

SOCIAL HISTORY

Non-contributory

PHYSICAL EXAMINATION

Breasts were large and pendulous. The distal superior portion of both breasts had extensive reticulated erythema with several 0.5 to 2.0 cm shallow ulcerations. Atrophic white scars were present in the involved areas.

LABORATORY DATA

The following were within normal limits: complete blood count with differential, basic metabolic panel, anti-phospholipid antibodies, lupus anti-coagulant, prothrombin time/partial thromboplastin time, Factor V Leiden, anti-thrombin III, homocysteine, C-reactive protein, erythrocyte sedimentation rate, and anti-nuclear antibodies. Serologic testing for HIV, Hepatitis B, and Hepatitis C was negative.

DERMATOPATHOLOGY

A punch biopsy of the reticulated erythema was performed. The epidermis was unremarkable. In the dermis, there was a diffuse interstitial proliferation of endothelial cells forming vascular spaces filled with red blood cells. No signs of thrombosis or

vasculitis were present. There was no appreciable inflammatory cell infiltrate. CD31 and CD34 stained nearly all of the proliferating cells within the dermis. SMA stained numerous pericytes at their periphery. HHV-8 staining was negative. Colloidal iron stain revealed an increased amount of mucin in the vicinity of the vascular proliferations. PAS staining did not reveal thickening of the epidermal or vascular basement membrane. Staining with D2-40 did not reveal any lymphatic component to the vascular proliferation. Additional biopsies from ulcerated skin and atrophic plaques revealed similar histology with degenerative change, but no vaso-occlusive disease.

DIAGNOSIS

Diffuse Dermal Angiomatosis

TREATMENT & COURSE

The patient's ulcerations were treated with topical antibiotics to prevent secondary infection. Ibuprofen was started for pain relief. The patient awaits reduction mammoplasty by plastic surgery.

DISCUSSION

Diffuse dermal angiomatosis (DDA) is a variant of reactive angioendotheliomatosis (RAE) reported by Krel et al in 1994, with 7 cases reported in the literature to date. RAE is a benign vascular disorder in the skin characterized by intravascular and extravascular hyperplasia of endothelial cells and pericytes in the context of diverse types of coexistent systemic disease. DDA is characterized as an extravascular proliferation of endothelial cells located interstitially between collagen bundles within the full thickness of the dermis. The proliferation stains with anti-CD31 and anti-CD34 antibodies as well as with other endothelial markers. Scattered extravasated erythrocytes and hemosiderin deposits are also present. This entity differs from Kaposi sarcoma by the absence of atypical cells with frank spindling, diffuse slit-like lumen formation, and an inflammatory component. RAE and DDA have a variety of clinical presentations ranging from multifocal erythematous macules to ulcerated plaques. DDA has been reported to occur on the extremities as well as on the breasts. There are case reports of successful treatment of DDA using systemic corticosteroids, isotretinoin and vascular surgery. In RAE oral antibiotics and systemic steroids have been reported with a theoretical mechanism of suppressing either occult infection and/or neo-angiogenesis. Lesions may also resolve spontaneously.

REFERENCES

McLaughlin ER, Morris R, Weiss SW, Arbiser JL. Diffuse dermal angiomatosis of the breast: response to isotretinoin. J Am Acad Dermatol 2001; 45: 462-5.

McMenamin ME, Fletcher CD. Reactive angioendotheliomatosis. A study of 15 cases demonstrating a wide clinicopathological spectrum. Am J Surg Pathol 2002; 26: 685-697.

Rongioletti F, Robora A. Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. J Am Acad Dermatol 2003;49:887-96.

PRESENTERS

Miriam Hanson MD and Sarah Stein MD

HISTORY OF PRESENT ILLNESS

The patient is a 7-month-old Caucasian female who presented at 6 weeks of life for evaluation and treatment of a large plaque on her left face and thorax. The lesion began one week after birth as a rapidly enlarging discoloration that progressed into a red-purple vascular plaque involving a significant portion of her left face and thorax. The patient had been diagnosed with a large infantile hemangioma and started on oral prednisone (2 mg/kg/day) for one week prior to presentation.

PAST MEDICAL HISTORY

The patient was born via vaginal delivery at 40 weeks gestation. The pregnancy was complicated by maternal hyperemesis.

MEDICATIONS

Prednisone 2mg/kg/day at presentation

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Patient lives with mother, father, and three healthy siblings.

PHYSICAL EXAMINATION

Over the left face and scalp, encompassing the left ear, and extending onto the neck and upper chest and back, there was a cherry-red plaque. Within the plaque on the crown of the scalp, there was a 1x1.5 cm ulcer with a clean base.

Ophthalmologic exam demonstrated a left ptosis and mild astigmatism. Cardiac exam revealed a grade 2/6 systolic vibratory murmur at the left upper sternal border. ENT evaluation detected a small submucosal hemangioma at the level of the oropharynx with no evidence of airway obstruction.

LABORATORY DATA/IMAGING:

EKG (5/12/04): Normal sinus rhythm with biventricular hypertrophy.

Echocardiogram (5/12/04): Cardiomegaly, no structural abnormalities noted

MRI (brain; 6/1/04): Left sided cerebral atrophy.

MRA (brain;6/10/04): Right posterior meningeal artery malformation without extracranial abnormalities. No evidence of dural AV fistula, steal or left internal carotid artery stenosis.

U/S (abdomen; 6/11/04) : Within normal limits. No evidence of visceral hemangioma.

The following laboratory data were within normal limits: platelets, basic metabolic panel, iron, magnesium

Abnormal data included WBC 18.3 (6-17.3) with 51% neutrophils, 39% lymphocytes, 8% monocytes, 1% eosinophils, Hb 8.1 (10.3-13.2) with MCV 83.1 (69-85), % reticulocyte count 3.2 (range 0.1-1.7), absolute reticulocyte count 83.5 (25-75), ferritin 622 (10-220), total protein 5.6 (6-8.3), albumin 3.4 (3.5-5)

Urine fibroblast growth factor 30,000 (normal <4000)

DERMATOPATHOLOGY:

None performed

DIAGNOSIS

Large segmental ulcerated hemangioma of infancy in the setting of probable PHACE syndrome

TREATMENT AND COURSE

The dose of prednisone was initially increased to 3 mg/kg/day . The patient's course was complicated by further ulceration, bleeding, and secondary infection of the hemangioma despite continued systemic corticosteroids, meticulous wound care, becaplermin gel, systemic and topical antibiotics and pulsed dye laser treatments. After 10 weeks of prednisone, Vincristine 0.5 mg/kg q week) was initiated. Prednisone was weaned to 2.5 mg/kg/day. The patient was followed weekly, and the ulcerations have slowly begun to heal. After 6 injections of Vincristine, the dosage was tapered to every other week. Topical mupirocin ointment, becaplermin gel, metronidazole gel, clobetasol ointment have been used during the course. The patient has had significant retardation of normal growth and development. She has required nasogastric feeding due to failure to gain appropriate weight. She is receiving physical therapy regularly.

DISCUSSION

Hemangiomas of infancy are benign vascular proliferations that have a characteristic clinical course with early proliferation followed by spontaneous involution. For the majority of lesions, no intervention is necessary. However, treatment may be required if the hemangioma becomes life-threatening, is complicated by significant ulceration, interferes with critical function, causes cosmetic disfigurement and/or is associated with extracutaneous systemic manifestations.

The association of large facial hemangiomas with underlying cerebral and arterial abnormalities has been well documented. The acronym "PHACE" was first proposed in 1996 to describe a neurocutaneous syndrome with the following features: posterior fossa brain malformations, large facial hemangiomas, arterial anomalies, cardiac and aortic defects, and eye abnormalities. In the literature, 70% of children diagnosed with PHACE have only one extracutaneous finding and the manifestation is highly variable, which suggests that PHACE represents a spectrum of anomalies. The pathogenesis of PHACE syndrome is not known but evidence points to a developmental error expressed between 6 and 8 weeks of gestational age. Children at risk with large plaque-like facial hemangiomas should have a careful ophthalmologic, neurologic, and cardiac evaluation.

The management of complicated and life-threatening hemangiomas continues to be an area of considerable challenge. Systemic corticosteroids are the most accepted first line of therapy but response rates vary from 30-60% depending on the dose, duration, and age at initiation of treatment. The mechanism of action of corticosteroids is not fully understood but appears to be due to an increased sensitivity of the vasculature to other physiologically occurring vasoconstrictive agents. The recommended dosing of corticosteroids is 2-3 mg/kg/day and the treatment may take weeks before a response is observed. Potential side effects in infants include irritability, gastrointestinal reflux, hypertension, adrenal suppression, growth retardation, immune suppression and osteoporosis. Most of the side effects are reversible with cessation of treatment.

In corticosteroid-resistant hemangiomas, the use of interferon alpha 2a and vincristine has been reported. The mechanism of action of interferon is inhibition of endothelial cell migration and proliferation growth factors, including vascular endothelial growth factor and basic fibroblast growth factor. Unlike steroids, interferon does not need to be administered during the proliferative phase to be effective. However, its use has been limited by the side effect profile, which includes fever, neutropenia, anemia, elevated liver enzymes, and irreversible spastic diplegia that develops in up to 20% of cases.

The use of vincristine is an emerging treatment option for complicated and life-threatening hemangiomas that have failed to respond to steroids. Vincristine is a vinca alkaloid that arrests cell mitosis in metaphase by preventing tubulin polymerization and inducing microtubule depolymerization. It has been hypothesized that endothelial cells have higher tubulin content and in combination with the active angiogenesis of the hemangioma forms the basis for the treatment with vincristine. The side effect profile of vincristine has been well studied given its considerable use in the treatment of malignancies in infants and children. The main short-term side effects in children are alopecia, nausea, emesis, constipation, hyponatremia and neurotoxicity. Rare side effects include thrombocytopenia, elevated liver enzymes, hypertension and seizures. Patients are examined and laboratory data are monitored on a weekly basis.

REFERENCE

Fawcett S, Grant I, Hall P, Kelsall A, Nicholson J. Vincristine as a treatment for a large haemangioma threatening vital functions. Brit Assoc of Plastic Surgeon 2004;57:168-71.

Frieden I, Reese V, Cohen D. PHACE syndrome: The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. Arch Dermatol 1996;132:307-11.

Grosso S, deCosmo L, Bonifazi E, Galluzzi P, Farnetani, MA, Loffredo P, Anichini C, Berardi R, Morgese G, Balestri P. Facial hemangioma and malformation of the cortical development: A broadening of the PHACE spectrum or a new entity? Am J Med Gen 2004; 124A: 192-5.

Haisley-Royster C, Enjolras O, Frieden I, Garzon M, Lee M, de Laat P, Madern G, Gonzalez F, Frangoul H, Le Moine P, Prose N, Adams D. Kasabach-Merritt phenomenon: A retrospective study of treatment with vincristine. J Ped Hem Onc 2002:24;459-62.

Metry D, Dowd C, Barkovich J, Frieden I. The many faces of PHACE syndrome. J Pediatr 2001;139:117-23.

Moore J, Lee M, Garzon M, Soffer S, Kim E, Saouaf R, del Toro G, Yamashiro D, Kandel J. Effective therapy of a vascular tumor of infancy with vincristine. J Pediatr Surg 2001;36:1273-6.

Perez J, Pardo J, Gomez C. Vincristine – An effective treatment of corticoid-resistant life-threatening infantile hemangiomas. Acta Oncologica 2002;41:197-9

PRESENTERS

Yaohui Gloria Xu MD, Maria M. Medenica MD, and Sarah Stein MD

HISTORY OF PRESENT ILLNESS

A 13-year-old African American male presented for evaluation of nodules in the skin of 1-2 years' duration. These nodules were slightly tender, occasionally itchy and non-draining. Similar new nodules had developed over time. Review of systems was negative.

PAST MEDICAL HISTORY

Infantile asthma

PAST SURGICAL HISTORY

None

MEDICATIONS

None

ALLERGIES

None

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Non-contributory

PHYSICAL EXAMINATION

Multiple, discrete, firm, bluish-colored, subcutaneous nodules, ranging from 0.5 to 2 cm in diameter, were located on the right shoulder, left arm, left thorax and posterior occipital scalp.

LABORATORY DATA

None

DERMATOPATHOLOGY

A punch biopsy of a representative nodule on the thorax revealed mild epidermal acanthosis with a modest superficial perivascular infiltrate of lymphocytes and histiocytes. In the mid and deep dermis, there was a collection of relatively large cells with granular cytoplasm and centrally located round nucleus. These large cells were arranged in strands between the collagen fibers as well as arranged in large sheets within the dermis.

DIAGNOSIS

Multiple acquired granular cell tumors

TREATMENT & COURSE

The nature of granular cell tumor as well as treatment options, observation versus excision, was discussed with the patient's mother.

DISCUSSION

Granular cell tumor (GCT), initially described as granular cell myoblastoma by Abrikossoff in1926, consists of a heterogeneous group of neoplasms featured by distinctive granular cytoplasm histologically. It is a relatively uncommon benign tumor seen mainly in adults (age 30-50 years), although in the literature over 400 cases have been reported, with the youngest age of acquired GCT being 4-years-old. Additionally, there are roughly 10 reported cases of congenital GCT. It is more common in women and African-Americans. The tumor can occur anywhere, usually presenting in the skin, soft tissue and aerodigestive tract with a predilection for the head and neck, particularly the tongue. Clinically, it presents as a solitary nodule that is asymptomatic or occasionally tender or pruritic. Multiple lesions are found in approximately 10% of cases.

Histology reveals an ill-defined, infiltrative, dermal neoplasm composed of polygonal cells with characteristically abundant, granular, faintly eosinophilic cytoplasm and round, dark nuclei. The cytoplasmic granules represent phagolysosomes, which are PAS positive and diastase resistant. Pseudoepitheliaomatous hyperplasia of the epidermis is often seen, while a perineurial or plexiform growth pattern is uncommonly observed.

Although granular cell change is reported in a variety of epithelial and mesenchymal neoplasms including basal cell carcinomas, leiomyomas, and leiomyosarcomas, it is generally accepted that the GCT is derived from Schwann cells of nerve sheath. Immunohistochemically, the tumor stains positive for S-100 protein and CD68. Recently, other markers suggestive of neural origin, such as neuron-specific enolase, protein gene product 9.5, and inhibin-alpha are positive in some cases.

The prognosis of GCT is good, but very rare malignant cases (3%) are documented. The presence of necrosis and increased mitosis may favor aggressive behavior; however, there are no reliable criteria to predict malignant behavior prospectively. Immunohistochemical staining has no proven prognostic value.

The treatment is complete excision. A high local recurrence rate is noted if the excision margin is positive.

REFERENCES

Gross VL, Lynfield Y. Multiple cutaneous granular cell tumors: a case report and review of the literature. Cutis 2002; 69:343-6.

Le BH, Boyer PJ, Lewis JE, Kapadia SB. Granular cell tumor: immunohistochemical assessment of inhibin-alpha, protein gene product 9.5, S100 protein, CD68, and Ki-67 proliferative index with clinical correlation. Arch Pathol Lab Med 2004; 128: 771-5.

Mentzel T, Wadden C, Fletcher CD. Granular cell change in smooth muscle tumors of skin and soft tissue. Histopathology 1994; 24:223-31.

Miracco C, Andreassi A, Laurini L, De Santi MM, Taddeucci P, Tosi P. Granular cell tumor with histological signs of malignancy: report of a case and comparison with 10 benign and 4 typical cases. Br J of Dermatol 1999; 141:57.

Zaenglein AL, Meehan SA, Orlow SJ. Congenital granular cell tumors localized to the arm. Pediatr Dermatol 2001; 18: 234-7.

PRESENTERS

Mario E Lacouture MD, Christopher R Shea MD, Keyoumars Soltani MD

HISTORY OF PRESENT ILLNESS

A 38-year-old Caucasian male presented for a 6 month history of a lesion on the ventrolateral aspect of the tongue. The lesion was asymptomatic, and there was no history of previous infection, trauma or surgery of the tongue.

PAST MEDICAL HISTORY

Squamous cell carcinoma of the right index finger.

PAST SURGICAL HISTORY

Mohs surgery for squamous cell carcinoma of the right index finger.

MEDICATIONS

None.

ALLERGIES

No known drug allergies.

FAMILY HISTORY

Noncontributory.

SOCIAL HISTORY

Patient is a carpenter, social drinker and does not smoke.

PHYSICAL EXAMINATION

On physical exam, a filiform, 0.5 x 1.0 cm verrucous papule was obsrved on the left lateral aspect of the tongue. The rest of the oral cavity was unremarkable. There was no cervical or axillary lymphadenopathy.

LABORATORY DATA

Fluorescent in situ hybridization studies showed that high-risk HPV type 16 probes hybridized abundantly to the specimen, thus making this lesion equivalent to a high-grade squamous intraepithelial lesion of the lower genital tract.

DERMATOPATHOLOGY

Biopsy of the affected area on the tongue showed a verruciform lesion with areas of parakeratosis, abundant dyskeratinocytes, numerous mitotic figures, and hyperchromatic nuclei, diagnostic of a condyloma with dysplasia.

DIAGNOSIS

Dysplastic condyloma of the tongue.

TREATMENT & COURSE

Mohs Micrographic surgery (MMS) was indicated given the location of the lesion and the poorly defined tumor margins. The first stage showed keratinocyte dysplasia, consistent with the initial biopsy findings. The second stage of excision showed margins free of tumor, and the residual 2.5 x 1.0 cm defect was closed primarily with interrupted 4-0 silk.

DISCUSSION

HPV infection has been linked to the development of both benign cutaneous and mucosal lesions such as verruca and condyloma, being present in 45-100% and 75% of these lesions in the oral mucosa, respectively. Similarly, HPV DNA has been found in 38% of oral verrucous carcinomas and 75% of oral squamous cell carcinoma (OSCC). The oncogenic potential of HPV depends upon the viral subtype as well as the immune status of the host. Oral verruca harbors types 2 and 57 most commonly, whereas types 6 and 11 are usually present in condyloma of the oral cavity. Whereas HPV types 6 and 11 are the most common in verrucous carcinoma, type16 is the most frequent in OSCC. However, other HPV subtypes traditionally considered benign, such as HPV 6,7,33,35, and 59 have also been identified in patients with OSCC. Epithelial cancer cells express HPV oncoproteins E6 and E7, which are critical to their malignant behavior, through the inhibition of tumor suppressors p53 and RB. In the patient here presented, HPV 16 DNA was identified in the dysplastic condyloma of the tongue, a finding that is uncommon in condylomas in immunocompetent hosts.

While HPV infection has been correlated with the development of SCC, alcohol and tobacco have been the two factors most commonly associated with the development of OSCC. The tongue is the most common site for intraoral carcinoma, especially the lateral tongue, as was the lesion present in our patient. SCC of the tongue typically affects elderly males over 60 years of age and is rare in patients under 45.Our patient, being 38 years of age, was in an age group in which OSCC occurs infrequently.

However, our patient did not have invasive SCC but rather condyloma with dysplasia of the tongue, which is a precursor lesion to SCC. SCC is thought to arise from dysplastic lesions which progress to SCCIS, which eventually may develop into invasive SCC. There have been conflicting findings reported in the literature regarding the behavior of oral SCC in young adults. Some have reported no difference in the clinical course of the disease in younger patients whereas others have suggested that oral SCC is more aggressive in the younger age group. A recent study suggests that while the overall outcome among older and younger patients with oral SCC is similar, in younger patients the disease may follow one of two distinctive courses, aggressive or uniform, while in elderly patients it typically follows a uniform course.

Surgical excision is one of the options for the removal of dysplastic lesions and the definitive treatment for invasive OSCC. MMS allows for maximal tissue sparing adjacent to the tumor and in certain instances has cure rates superior to conventional surgical techniques. With potential for aggressive growth in a young patient and a notable risk of recurrence of SCC of the tongue, MMS should be considered as a treatment option. In addition, mucocutaneous SCC has a greater tendency for metastasis

compared with primary cutaneous SCC, another indication for MMS. In our patient, MMS was employed in the excision of a condylomatous dysplasia of the tongue harboring a high-risk HPV type, a potential precursor lesion to OSCC. Dr Mohs reported 5 cases of intraoral carcinoma treated with MMS, yielding an 80% cure rate. To our knowledge, this is is one of the few cases of MMS of the tongue reported in the literature, underscoring the importance of this technique in intraoral premalignant lesions.

REFERENCES

Syrjanen SM, Syrjanen KJ, Happonen RP. Human papillomavirus (HPV) DNA sequences in oral precancerous lesions and squamous cell carcinoma demonstrated by in situ hybridization. J Oral Pathol 1988;17:273-8.

Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin 2002;52:195-215.

Understanding the biology of oral cancer. Med Sci Monit. 2002 Nov;8(11):RA258-67.

Kiviat NB. Papillomaviruses in non-melanoma skin cancer: epidemiological aspects. Semin Cancer Biol 1999;9:397-403.

Harwood CA, McGregor JM, Proby CM, Breuer J. Human papillomavirus and the development of non-melanoma skin cancer. J Clin Pathol 1999;52:249-53.

Palme CE, Gullane PJ, Gilbert RW. Current treatment options in squamous cell carcinoma of the oral cavity. Surg Oncol Clin N Am. 2004;13(1):47-70.

Shriner DL, McCoy DK, Goldberg DJ, Wagner RF. Mohs micrographic surgery. J Am Acad Dermatol 1998;39:79-97.

zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342-50.

Popovtzer A, Shpitzer T, Bahar G, et al. Squamous cell carcinoma of the oral tongue in young patients. The Laryngoscope 2004;114:915-17.

PRESENTERS

Miriam Hanson, MD, Christopher R. Shea, MD, Keyoumars Soltani, MD, Maria Medenica, MD, and Vesna Petronic-Rosic, MD

HISTORY OF PRESENT ILLNESS

The patient is a 36-year-old African American woman who presented with a complaint of "dark spots" on her distal tongue since childhood. In the last six months the lesions had increased in number and size and become occasionally pruritic. She denied a history of trauma or infection. The patient was a nonsmoker. There was no relevant family history of similar oral lesions or gastrointestinal disease. On review of systems, she denied any changes in bowel habits.

PAST MEDICAL HISTORY

Asthma

MEDICATIONS

Singulair
Advair inhaler
Albuterol inhaler

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

No history of tobacco use
Works as a building inspector

PHYSICAL EXAMINATION

On examination, there were numerous, well-defined, brown macules, 2-5 mm diameter, on the upper and lower vermilion border of the lips, soft and hard palate, and buccal mucosa. Ocular sclera, conjunctivae, perineal skin, acral surfaces, and nails were unremarkable.

LABORATORY DATA

All laboratory data, including BMP and CBC with differential, were within normal limits.

DERMATOPATHOLOGY

Punch biopsies were performed on hyperpigmented and normal mucosa. In the hyperpigmented mucosa, there was an increase in basal layer melanin deposits and an increase in the number of normal-appearing melanocytes. Superficial pigmentary incontinence was seen within the dermis. Fontana-Masson staining and

immunohistochemistry for S-100, melan-A, and gp100 (HMB-45) confirmed an increased number of melanocytes. In normal-appearing mucosa, there was no melanin pigment observed in the epithelial basal layer, and the number of melanocytes was not increased.

DIAGNOSIS

Laugier and Hunziker mucocutaneous pigmentation

TREATMENT AND COURSE

A complete medical evaluation did not reveal signs of systemic disease. Additionally, a colonoscopy was performed and was normal. The patient's lesions have stabilized in number and are no longer symptomatic.

DISCUSSION

Laugier-Hunziker pigmentation is an acquired disorder of macular discoloration that was first described in 1970 to involve the lips and oral mucosa and, less frequently, the fingernails. The concept was later broadened to account for mucocutaneous pigmentation that occurred at other sites, including the palms, soles, genital and anal mucosa, and esophagus. The skin lesions in the disorder manifest as irregular, hyperpigmented, slate-colored to dark-brown macules from 2-5 mm in diameter, with either well defined or indistinct margins. These lesions can occur singly or as multiple groups that are confluent. The nail changes involve three main types: 1-2 mm longitudinal streaks, wider streaks of 2-3 mm pigmentation along the lateral aspects of the nails plate, and/or homogeneous staining of one-half of the nail. All of these findings can be found in one or more fingernails; toenails are less frequently involved.

The macular pigmentation of Laugier and Hunziker follows a chronic course with a progressive increase in lesions over time. There are no associated systemic diseases and no evidence to suggest a genetic transmission. Several conditions must be considered in the differential diagnosis such as adrenal insufficiency, Peutz-Jeghers syndrome, McCune-Albright syndrome, melanoma, pigmentation from exogenous systemic agents, and physiologic melanoplakia.

Histopathological and ultrastructural findings confirm that this condition is benign. Most published reports describe an accumulation of melanin in the basal keratinocytes and a normal number and morphological appearance of melanocytes in the areas of hyperpigmentation. In our case, the patient presented with typical clinical findings of Laugier and Hunziker pigmentation but on histopathological examination, the pigmented mucosal lesions demonstrated a proliferation of intraepidermal melanocytes. Melanocytosis has been reported in only two other cases in the literature and in one of the two reports, cellular atypia in the intraepidermal melanocytes was described. The significance of these findings is not known, but given the possible risk of malignant transformation, we propose long-term observation of the affected patients.

We present our case today for discussion of the diagnosis, histopathological findings, and management of this patient's disease.

REFERENCE

Fisher D, Field EA, Welsh S. Laugier-Hunziker syndrome. Clin Exp Dermatol 2004; 29:312.

Gutiérrez JV, Romero AM, Martínez G, Torrero MV, López de Juan M. Hyperpigmentation mimicking Laugier syndrome, levodopa therapy, and Addison's disease. JEADV 2003; 17:324-7.

Lampe AK, Hamptom PJ, Woodford-Richens K, Tomlinson I, Lawrence CM, Douglas FS. Laugier-Hunziker syndrome: an important differential diagnosis for Peutz-Jeghers syndrome. J Med Genet 2003; 40:e77-83.

Lenane P, Sullivan DO, Keane CO, Louglin SO. The Laugier-Hunziker syndrome. JEADV 2001; 15:574-7.

Makhoul EN, Ayoub NM, Helou JF, Abadjian GA. Familial Laugier-Hunziker syndrome. J Am Acad Dermatol 2003; 49:S143-5.

Moore, RT, Chae M, Rhodes, AR. Laugier and Hunziker pigmentation: A lentiginous proliferation of melanocytes. J Am Acad Dermatol 2004; 50:S70-4.

PRESENTERS

Amy L. Priess MD, Christopher R. Shea MD, Sarah L. Stein MD

HISTORY OF PRESENT ILLNESS

This is a healthy, fourteen-month-old African American boy who presented for evaluation of a lesion on the right arm that had been present for 2 months. The lesion began as an asymptomatic red papule that continued to grow and darken over two months. The family denied any precipitating event or trauma to the area.

PAST MEDICAL HISTORY

The patient was born at full term via normal spontaneous vaginal delivery, and had met normal developmental milestones.

PAST SURGICAL HISTORY

None

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Non-contributory

PHYSICAL EXAMINATION

This was a well-appearing, well-developed African American boy. On the right forearm there was a 2 x 2 centimeter irregular blueish- nodule with surrounding hyperpigmentation that was slightly tender to palpation.

LABORATORY DATA

None

DERMATOPATHOLOGY

Sections were of skin with prominent, slightly dilated vascular spaces in the superficial and deep dermis. Occasional vessels had hobnail endothelium. Hemorrhage was noted around the vascular proliferation. There was a perivascular infiltrate composed of lymphocytes and rare eosinophils. Hemosiderin was also noted.

Anti human herpes virus eight (KSHV) was negative. Anti CD31 labeled the endothelial cells of the normal dermis and the vascular proliferation. Anti CD34 labeled mainly the dermal blood vessels, while the vascular proliferation was less strongly labeled

DIAGNOSIS

Hobnail hemangioma (targetoid hemosiderotic hemangioma)

TREATMENT & COURSE

The patient was referred to plastic surgery for excision.

DISCUSSION

Hobnail hemangioma (targetoid hemosiderotic hemangioma) is a term used to describe a histologically distinct entity with a clinically benign course.

Targetoid hemosiderotic hemangioma was first described by Santa Cruz in 1988. Clinically it was described as a small violaceous papule with an ecchymotic ring that expands peripherally then disappears. It is generally a solitary lesion occurring on the trunk or limb of young to middle-aged persons. The histology of targetoid hemosiderotic hemangioma varies with the age if the lesion. Early lesions exhibit a characteristic biphasic growth pattern. Dilated vascular channels in the superficial dermis are lined with a single layer of epithelioid-appearing endothelial cells with scanty cytoplasm and large, hyperchromatic nuclei. These cells protrude into the vascular lumen creating a hobnail or matchstick appearance. In the reticular and deeper dermis, the vascular structures appear to dissect between the collagen bundles. Mature lesions contain collapsed vascular spaces and cellular intervascular spaces with spindle-shaped cells and hemosiderin deposition. Little or no cytological atypia is present.

Multiple subsequent descriptions of these lesions have demonstrated that the clinically targetoid appearance as well as the hemosiderin deposition are inconsistent, variable features. The term hobnail hemangioma has been adopted to describe this clinical entity. However, some authors distinguish targetoid hemosiderotic hemangioma and hobnail hemangioma based on the clinical presence of the targetoid ring.

Hobnail hemangioma is a rare vascular tumor. It is most common in young adults with age of onset ranging from birth to 72 years of age. However, presentation before age 5 has been rarely noted in the literature.

Clinically, the differential diagnosis of hobnail hemangioma includes benign and malignant melanocytic lesions, dermatofibroma, solitary angiokeratoma, and non-specific hemangioma. Histologically, hobnail hemangiomas must be differentiated from patch-stage Kaposi sarcoma, well-differentiated angiosarcoma, retiform hemangioendothelioma, and malignant endovascular papillary angioendothelioma (Dabska tumor). Each of these entities shares histologic similarities with hobnail hemangioma, including the finding of a hobnail appearance of the endothelium.

Immunohistochemical analysis reveals these lesions are moderately to strongly CD31 and *Ulex europeus* positive. Variable expression of CD34 and Factor VIII related antigen has

also been demonstrated. Unlike Kaposi sarcoma, human herpes virus 8 DNA has not been demonstrated in hobnail hemangioma.

The etiology and origin of this lesion is uncertain. Both vascular and lymphatic derivations have been proposed. Many authors have suggested trauma as a possible etiology. Excision is curative.

REFERENCES

Carlson A, Daulat S, Goodheart H. Targetoid hemosiderotic hemangioma-a dynamic vascular tumor: Report of 3 cases with episodic and cyclic changes and comparison with solitary angiokeratomas. J Am Acad Dermatol 1999;41:215-24.

Cotell S, Silverman A, Katta R. What is your diagnosis? Targetoid hemosiderotic hemangioma. Cutis 2003;72:24,51-2.

Guillou L, Calonje E, Speight P, Rosai J, Fletcher C. Hobnail hemangioma: A pseudomalignant vascular lesion with a reappraisal of targetoid hemosiderotic hemangioma. Am J Surg Pathol 1999;23:97-105.

Gutzmer R, Kaspari M, Herbst R, Kapp A, Kiehl P. Absence of HHV-8 DNA in hobnail hemangiomas. J Cutan Pathol 2002;29:154-8.

Mentzel T, Partanen T, Kutzer H. Hobnail hemangioma ("targetoid hemosiderotic hemangioma"): clinicopathologic and immunohistochemical analysis of 62 cases. J Cutan Pathol 1999;26:279-286.

Santa Cruz D, Aronberg J. Targetoid hemosiderotic hemangioma. J Am Acad Dermatol 1988; 19: 550-8.

Santonja C, Torrelo A. Hobnail hemangioma. Dermatol 1995;191:154-6.

PRESENTERS

Michael Jude Welsch MD, Allan L. Lorincz MD, and Maria Medenica MD

HISTORY OF PRESENT ILLNESS

This patient is a 43-year-old male who was referred for removal a large lesion on his right buttock. The patient denied history of familial cancers. He was not aware of any cutaneous lesions on his forehead or behind the ears.

PAST MEDICAL HISTORY

History of idiopathic spontaneous pneumothorax x 2 and subsequent collapsed lung.

PAST SURGICAL HISTORY

Thoracotomy and chest tube placement for the pneumothoracies

MEDICATIONS

None.

ALLERGIES

No known drug sensitivities

FAMILY HISTORY

His father had previous pneumothorax.

SOCIAL HISTORY

6 siblings, no children

PHYSICAL EXAMINATION

There are small (1-5 mm), ivory-white, papules over the superior forehead and posterior auricular areas. A large, soft compressible nodule was present on the right buttock. A large pink scar was present on the right thorax.

DERMATOPATHOLOGY

Biopsy from the right postauricular neck demonstrated an infundibulocentric lesion with thin cords of epithelial cells projecting into the dermis and producing a fenestrating pattern. Stroma showed fibrin-like appearance of collagen bundles proliferating around the epithelial cords, parallel to each other and perpendicular to the epidermis. The findings were consistent with fibrofolliculoma.

Biopsy the buttock disclosed findings consistent with nevus lipomatous superficialis.

DIAGNOSIS

Birt-Hogg-Dubé syndrome

Nevus lipomatous superficialis

TREATMENT AND COURSE

The patient underwent a CT scan of abdomen and pelvis that revealed a small renal cyst in the right kidney

DISCUSSION

Birt-Hogg-Dubé syndrome (BHDS) is an autosomal dominant multisystem disorder first recognized by the cutaneous triad of fibrofolliculomas (FF), trichodiscomas (TD) and acrochordons (AC) appearing in early adulthood. The condition predisposes to renal cancers and spontaneous pneumothorax.

Clinically, FF and TD are indistinguishable and present in all patients as multiple, smooth skin-colored to grayish-white papules ranging from 1 to 5 mm in size. Rarely they may appear as small cysts, comedonal papules or coalesce into plaques. The lesions are mostly confined to the face (nose, cheeks, forehead and auricles) but may extend to the neck and upper trunk. The number of FFs and TDs ranges from several up to 100 lesions. Multiple skin tags distributed on the eyelids, periocular area, groin, neck, and axilla are also common. Other skin lesions described include perioral and intraoral soft papules, atrophic papular collagenomas, large-plaque type collagenomas, and lipomas.

Histopathological findings of thin aberrant follicular structures surrounded by well-demarcated, mucin-rich stroma define FF-type lesions. On the contrary, TDs usually manifest thickened collagenous stroma with lamellar fibroplasia adjacent to a hair follicle. Elastic fibers are scant or absent. Proliferation of small, thickened blood vessels can be seen at the base of the tumor, with the term “perivascular fibroma” having been used for these changes. Recent studies disclosed that FFs and TDs, although quite distinct at the first glance, might actually represent the different stages in the development of the single entity. Both tumors are believed to be hamartomas deriving from perifollicular mesenchyme or “mantle” of the follicular epithelium. Hence, the term “mantleoma” has also been used for these tumors.

Kidney tumors were first reported in the context of BHDS in 1993, and subsequent studies confirmed this association. They occur much later than skin lesions and, among families with recognized clustering of renal cancers, BHDS may account for up to 6% of cases. The histological description of BHDS-associated renal tumors has been inconsistent and has been reported as clear cell adenocarcinoma, oncocytoma, chromophobe adenocarcinoma, and papillary renal cell variants.

The full clinical spectrum of BHDS is yet to be determined. Lung cysts and/or spontaneous pneumothorax seem convincingly associated, as do lipomas and oral papules. Other lesions reported but with less evidence for true association include malignant melanoma, prostate cancer, basal cell carcinomas, intestinal adenomatous polyps, and parathyroid adenomas. Medullary carcinoma of the thyroid in one family with BHDS was associated with germline mutation of the RET proto-oncogene.

Linkage studies identified the gene product named folliculin to chromosome 17p11.2 chromosomal locus. Based on the analogy to other similar familial tumor syndromes (tuberous sclerosis, neurofibromatosis, multiple endocrine neoplasia type 1 and Cowden's syndrome) BHDS may present another example of the inactivation of a tumor-suppressor gene resulting in the development of cutaneous hamartomas and internal neoplasia.

The treatment of disfiguring skin lesions is limited. Systemic isotretinoin and copper vapor laser have been tried with variable outcome. The vaporization with CO2 or Erbium laser has produced temporary successful ablation of facial lesions in several cases.

REFERENCES

Birt AR, Hogg GR, Dubé WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977;113:1674-1677.

Chung JY, Ramos-Caro FA, Beers B, Ford MJ, Flowers F. Multiple lipomas, angiolipomas, and parathyroid adenomas in a patient with Birt-Hogg-Dubé syndrome. Int J Dermatol 1996;35:365-367.

Toro JR, Glenn G, Duray P, Darling T, Weirich G, Zbar B, Linehan M, Turner ML. Birt-Hogg-Dubé Syndrome: A novel marker of kidney neoplasia. Arch Dermatol 1999;135:1195-1202.

Lindor NM, Hand J, Burch PA, Gibson LE. Birt-Hogg-Dubé Syndrome: an autosomal dominant disorder with predisposition to cancers of the kidney, fibrofolliculomas, and focal cutaneous mucinosis. Int J Dermatol 2001;40:653-656.

Schulz T, Ebschner U, Hartschuh W. Localized Birt-Hogg-Dubé syndrome with perivascular fibromas. Am J Dermatopathol 2001;23:149-153.

Zbar B, Alvord WG, Glenn G, Turner M, Pavlovich CP, Schmidt L, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dubé syndrome. Cancer Epidemiol Biomarkers Prev 2002;11:393-400.

Ackerman AB, Reddy VB, Soyer HP. Fibrofolliculoma/Trichodiscoma. In: Neoplasms with follicular differentiation. United States of America: Ardor Scribendi Publishers, 2001:221-244.

Collins GL, Somach S, Morgan MB. Histomorphologic and immunophenotypic analysis of fibrofolliculomas and trichodiscomas in Birt-Hogg-Dube syndrome and sporadic disease. J Cut Pathol 2002;29:529-533.

De la Torre C, Ocampo C, Doval IG, Losada A, Cruces MJ. Acrochordons are not a component of the Birt-Hogg-Dubé syndrome. Does this syndrome exist? Case reports and review of the literature. Am J Dermatopathol 1999;21:369-374.

PRESENTERS

Lisa A. Carroll, MD, Christopher R. Shea, MD, Keyoumars Soltani, MD, and Shail Busbey, MD

HISTORY OF PRESENT ILLNESS

This 22 year-old Caucasian male presented with a one-day history of 3 clustered, slightly tender, erythematous papules on the shaft of his penis that coalesced and developed a central "blood-blister" overnight. This blister then broke down into an ulceration with brown-black crust and increasing peripheral erythema and tenderness. Due to concern for HSV with secondary cellulitis, the patient was admitted to the hospital for intravenous antibiotics and acyclovir as well as for further evaluation. The patient's condition worsened despite IV antibiotics and acyclovir. Review of symptoms was otherwise negative. Two biopsies were performed.

PAST MEDICAL HISTORY

Hypothyroidism
Episode of abdominal pain without diarrhea (spring 2003)

PAST SURGICAL HISTORY

Tonsillectomy
Inguinal hernia repair
Parathyroidectomy

MEDICATIONS

Synthroid

ALLERGIES

None

FAMILY HISTORY

Diabetes mellitus (I & II)
Asthma

SOCIAL HISTORY

1st year law student
Monogamous relationship with a female x 4 months prior to presentation
No use of condoms with partner

PHYSICAL EXAMINATION

There was an approximately 1x1cm mildly indurated erythematous plaque with central overlying hemorrhagic crust and surrounding macular erythema on proximal shaft of penis. Additionally, there was a 2mm pustule with central overlying scale and an erythematous halo on distal shaft of penis. Mild inguinal LAD was noted.

LABORATORY DATA

The following studies were normal/negative: CMP, CBC, ESR, HIV, RPR, HSV IgM, HSV 2 IgG, HSV culture, viral culture, tissue culture for fungus, tissue culture for AFB

The following studies were abnormal: TSH 4.3 (0.3-3.8), many pan-sensitive Staph aureus present on tissue culture

DERMATOPATHOLOGY

Penile ulcer edge: neutrophilic dermatosis, c/w pyoderma gangrenosum

Neutrophils were present below a parakeratotic stratum corneum. The epidermis exhibited spongiosis as well as infiltration by neutrophils. A dense infiltrate of neutrophils was present in the dermis. Hemorrhage was noted but a primary vasculitis was not identified. The PAS and GMS stains were negative for fungi. The gram stain was negative for bacteria. Special stains did not identify any microorganisms.

Distal pustule on penis: subcorneal pustule with gram-positive bacteria

A pustule containing numerous neutrophils was present under the stratum corneum. The epidermis exhibited slight, reactive hyperplasia and spongiosis. The superficial dermis contained an infiltrate of lymphocytes and neutrophils. The PAS and GMS stains were negative for fungi. The gram stain demonstrated gram-positive cocci within the subcorneal pustule.

DIAGNOSIS

Pyoderma gangrenosum

TREATMENT & COURSE

Upon diagnosis of penile pyoderma gangrenosum, the patient was treated with IV decadron 14mg qAM. Due to the presence of secondary infection with *Staphylococcus aureus*, the patient continued on IV antibiotics. The lesions quickly ceased further progression and the erythema resolved. The patient was discharged from the hospital on prednisone (1mg/kg) and Augmentin. Further work-up to rule out underlying conditions included protein electrophoresis and immunoelectophoresis, urine immunoelectrophoresis, ANCA, cryoglobulins, beta 2 glycoprotein antibodies, and anticardiolipin antibodies. These studies were within normal limits. Previous gastrointestinal studies performed for at an outside institution in the spring of 2003 due to abdominal pain included an upper GI with small bowel follow-through and a colonoscopy. The colonoscopy revealed mild nodularity of the terminal ileum with nonspecific chronic inflammatory changes, unlikely to represent inflammatory bowel disease. As an outpatient, prednisone was gradually tapered over 2 months. The patient also was treated with topical gentamycin ointment to the ulcer bed and clobetasol ointment to the area surrounding the ulcer. Minocycline 100mg bid was started after the patient's course of Augmentin was finished. The lesion healed with an atrophic scar.

DISCUSSION

Pyoderma gangrenosum (PG) is a destructive, ulcerative neutrophilic dermatosis with an unclear etiology. Clinically, PG is characterized by centrifugally enlarging necrotic ulceration with a violaceous, undermined border and an erythematous halo. Often, lesions start as discrete pustules or papules with an erythematous border that rapidly break down into gangrenous ulcers. Lesions tend to heal with atrophic, cribriform scars.

Visceral involvement by PG is possible, with reported cases of death with pulmonary disease.

PG is associated with systemic disease in 50-70% of cases. Associations include inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, hematologic malignancy, monoclonal IgA gammopathy, and chronic active hepatitis. Inflammatory bowel disease (IBD) is the most common co-morbid condition, affecting 30-60% of patients. Although early reports suggested a stronger association with ulcerative colitis, more recent reports support a stronger association with Crohn's disease. Hematologic associations include acute lymphoid and myeloid leukemia, polycythemia vera, myeloid metaplasia, Waldenstrom's macroglobulinemia, and other paraproteinemias (especially IgA paraproteinemia). Additionally, medications, such as interferon-alpha, GM-CSF, isotretinoin, and the antipsychotic sulpride have been associated with PG. When a patient is diagnosed with PG, it is important to look for associated systemic conditions.

In adults, PG typically occurs on the lower extremities, though it may affect any area of the body. PG of the external genitalia in adults is rare. Involvement of the vulva, penis, or perineal area can result in severe mutilation, thus it is vital to diagnosis and treat the condition as early as possible. PG of the genitalia has also been associated with systemic disease. In one case of genital PG in association with ulcerative colitis, the cutaneous ulceration was the first clinical manifestation of disease. Patients with genital PG usually have typical PG lesions elsewhere on the body. Few cases of isolated penile lesions have been reported. Cases of genital PG may resemble Fournier's gangrene, a necrotizing polymicrobial infection of the perineum and genitalia. It is important to differentiate between these two conditions given that their treatments are radically different. Fournier's gangrene responds to surgical debridement and broad-spectrum antibiotics. In PG, on the other hand, surgical debridement may lead to further tissue destruction via pathergy. Treatment of PG requires immunosuppression.

Since there are no specific serologic or histologic markers for PG, PG is a diagnosis of exclusion. Pathology usually demonstrates a dense dermal infiltrate of neutrophils, sometimes with extensive ulceration and necrosis. The advancing edge of lesions may demonstrate a lymphohistiocytic infiltrate. Vasculitis is usually absent. Cultures of early lesions are usually negative, but lesions of longer duration may yield positive cultures for staphylococci or streptococci. These cultures may reflect colonization or wound superinfection.

Treatment of PG consists of immunosuppression and local wound care. Early, aggressive treatment is often crucial since PG tends to spread rapidly, with extensive tissue destruction. High-dose systemic corticosteroids have been the gold standard for treatment; however, cyclosporine has recently been put forth as first line treatment for PG. The rapid improvement of PG with cyclosporine therapy suggests a role for T-lymphocytes in the pathogenesis of PG. Cyclosporine, unlike other immunsuppressants, does not cause bone marrow suppression, but other side effects such as hypertension, renal damage, anaphylaxis, hyperkalemia, and hyperuricemia may occur. Other

treatments that have been helpful in individual cases have included cyclophosphamide, mycophenolate mofetil, systemic FK-506, minocycline, thalidomide, dapsone, azathioprine, and plasmapheresis.

REFERENCES

Lee LK, Hinshaw M, Cripps D, Jarrard DF. Pyoderma gangrenosum of the penis. J Urol 2003;170:185-186.

Crowson AN, Mihm Jr MC, Magro C. Pyoderma gangrenosum: a review. J Cutan Pathol 2003;30:97-107.

Mlika RB, Riahi I, Fenniche S, Mokni M, Dhaoui MR, Dess N, Dhahri ABO, Mokhtar I. Pyoderma gangrenosum: a report of 21 cases. International J Dermatol 2002;41:65-68.

Blitz NM, Rudikoff D. Pyoderma gangrenosum. Mount Sinai Journal of Medicine 2001;68:287-295.

Park H-J, Kim Y-C, Cinn Y-W, Yoon T-Y. Granulomatous pyoderma gangrenosum: two unusual cases chowing necrotizing granulomatous inflammation. Clin Exp Dermatol 2000;25:617-620.

Gungor E, Karakayali G, Alli N, Artuz F, Lenk N. Penile pyoderma gangrenosum. J Eur Dermatol Venereol 1999;12(1):59-62.

Farrell AM, Black MM, Bracka A, Bunker CB. Pyoderma gangrenosum of the penis. Brit J Dermatol 1998;138:337-340.

Baskin LS, Dixon C, Stoller ML, Carroll PR. Pyoderma gangrenosum presenting as Fournier's gangrene. J Urol 1990;144:984-6.

Sanusi ID, Gonzalez E, Venable DD. Pyoderma gangrenosum of penile and scrotal skin. J Urol 1982;127:547-9.

PRESENTERS

Arlene Molino MD, Allan Lorincz MD, and Maria Medenica MD

HISTORY OF PRESENT ILLNESS

The patient is a 57-year-old Bosnian/Yugoslavian female who presented with an 18 month history of oozing nodules on her left posterior calf. The patient denied recent cough, fever, or chills. The patient reported a history of tuberculosis during childhood; however, the details regarding treatment were not known. There was no history of recent travel or sick contacts. The patient did not recall receipt of a bacillus Calmette-Guerin (BCG) vaccination at any time.

PAST MEDICAL HISTORY

Childhood tuberculosis infection

PAST SURGICAL HISTORY

Non-contributory

MEDICATIONS

Multivitamin
Calcium supplement

ALLERGIES

None

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

The patient lives with her daughter. She emigrated from Bosnia to the United States in 2000.

PHYSICAL EXAMINATION

Several erythematous to violaceous papules and plaque were distributed over the left posterior calf. On the mid-calf, there was a 1.5 cm ulcer with serosanguineous discharge. There was evidence of atrophic scarring.

LABORATORY DATA

The following were within normal limits: CBC with differential, CMP, C-reactive protein, anti dsDNA, RPR, and UA.

The following were abnormal: ANA value, speckled (normal<1:160), PPD 22 mm (normal <10mm)

RADIOGRAPHS

CXR: Scar-like opacity in the left upper lung. No evidence of active tuberculosis.

DERMATOPATHOLOGY

An elliptical excision from the left calf was performed. Histology revealed an unremarkable epidermis. A modest perivascular infiltrate of lymphocytes and histiocytes was seen in the superficial dermis, with a denser perivascular infiltrate in the mid and deep dermis. In addition, an area of necrosis containing cellular debris of red blood cells and neutrophils was found within the lower dermis and subcutaneous fat. Collections of lymphocytes, histiocytes, epithelial cells, and multinucleated foreign body giant cells surrounded the necrotic area. There were occasional foamy histiocytes and lipid-laden multinucleated foreign body giant cells. In the deep dermis, endothelial cells swelling with vessel occlusion was noted. Focally, the vessel walls contained inflammatory cells consisting of neutrophils, few lymphocytes, and histiocytes. Fite stain did not reveal acid fast organisms.

DIAGNOSIS

Erythema induratum of Bazin

TREATMENT & COURSE

The patient was started on isoniazid 300mg daily and pyridoxine 50mg daily. Improvement in skin lesions was noted after 2 months of therapy. Compression stockings and ammonium lactate cream were added after 3 months of anti-tuberculosis therapy. The patient received one year of therapy with progressive resolution of the lesions.

DISCUSSION

In 1861, Bazin described a form of panniculitis associated with tuberculosis, manifesting as subcutaneous indurated plaques located primarily on the posterior lower extremities of middle-aged women. Erythema induratum of Bazin (EIB) typically presents with tender, erythematous nodules and plaques distributed on the lower extremities, with predilection for the calves. Lesions often appear during colder months, are persistent, and may ulcerate. EIB predominantly affects females, with a mean age of 30-40 years, although peaks at early adolescence and at perimenopause have been reported. Patients are often obese, with evidence of venous insufficiency in the lower extremities. Patients may also report symptoms of tuberculosis infection, a positive PPD, or have chest radiographs consistent with an active infection. The erythrocyte sedimentation rate and c-reactive protein may be elevated.

Histologically, EIB most often presents as a lobular panniculitis with a mixed cell infiltrate. In early lesions, a neutrophil predominant infiltrate is seen. In older lesions, a granulomatous infiltrate predominates and fibrosis may be present. Small and medium vessel vasculitis is noted. In the subcutaneous fat, areas of necrosis with rare caseation can be demonstrated. Ziehl-Neelson stains are typically negative for acid-fast bacilli. Detection of M. tuberculosis DNA by PCR from paraffin-embedded skin specimens has been reported in 25 to 77% of patients diagnosed with EIB.

The existence of erythema induratum of Bazin (EIB) as a tuberculid and separate entity from nodular vasculitis has been debated. Some authors have suggested that EIB is a subtype of nodular vasculitis that is associated with *Mycobacterium tuberculosis*

infection. Others argue that the evidence supports a tuberculid origin secondary to the following: a markedly positive purified-protein-derivative (PPD) reaction in most patients, clinical response to anti-tuberculosis medications, and recent detection by PCR of low amounts of M. tuberculosis DNA in lesions. Investigators have proposed that EIB is a reactive immune complex mediated vasculitis leading to fat necrosis and inflammation. A type IV cell-mediated immune hypersensitivity to mycobacterial antigen has also been hypothesized.

The course of EIB is typically chronic and recurrent. Spontaneous healing with scarring has been reported. Although there is debate regarding the use of anti-tuberculosis medications, treatment with these medications is considered standard. The 1997 World Health Organization treatment recommendations recommend a 6 month minimum course of combination therapy with rifampin, isoniazid, and streptomycin or ethambutol. Studies have shown both a decreased relapse rate and clearance time for those treated on combination therapy, although success has been reported using single or double agent therapy. Long term follow-up is recommended as relapse may occur after several years of remission.

REFERENCES

Baselga E, Margall N, Barnadas MA, Coll P, de Moragas JM. Detection of Mycobacterium tuberculosis DNA in lobular granulomatous panniculitis. Arch Dermatol 1997; 133: 457-462.

Barbagallo J, Tager P, Ingleton R, Hirsch RJ, Weinberg JM. Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol 2002; 3: 319-328.

Lebel M, Lassonde M. Erythema induratum of Bazin. J Am Acad Dermatol 1986; 14:738-742.

Rademaker M, Lowe DG, Munro DD. Erythema induratum (Bazin's disease). J Am Acad Dermatol 1989; 21: 740-745.

Requena L, Yus ES. Panniculitis Part II. Mostly lobular panniculitis. J Am Acad Dermatol 2001; 45: 325-361.

Yen A, Fearneyhough P, Rady P, Tyring S, Diven D. Erythema induratum of Bazin as a tuberculid: confirmation of Mycobacterium tuberculosis DNA polymerase chain reaction analysis. J Am Acad Dermatol 1997; 36: 99-101.

PRESENTERS

Leslie E. Bernstein, MD, Anne E. Laumann, MBChB, MRCP, and Christopher R. Shea, MD

HISTORY OF PRESENT ILLNESS

This 52-year-old woman had a 10-year history of untreated asymptomatic bumps on her face and hands. She also had tingling in her hands.

PAST MEDICAL HISTORY

Castleman's disease, dilated cardiomyopathy, pulmonary hypertension, hypothyroidism, cirrhosis, splenomegaly, chronic renal failure/hemodialysis, anemia, gout and pulmonary embolism

MEDICATIONS

Prednisone
Allopurinol
Prevacid
Nephro-caps
Phoslo
Bextra
Coumadin
Synthroid

ALLERGIES

No known drug allergies

FAMILY HISTORY

Father died of cirrhosis

SOCIAL HISTORY

Remote history of intravenous drug use

PHYSICAL EXAMINATION

There are firm, violaceous, dome-shaped papules and nodules on the patient's face and dorsal hands. She has enlarged cervical, axillary and inguinal lymph nodes, and a palpable spleen tip. She has a II/VI cardiac systolic ejection murmur.

LABORATORY DATA

The following values were negative or within normal limits:
Serum protein electrophoresis, rheumatoid factor, ANA, hepatitis B surface antigen/hepatitis C antibody (nonreactive)

The following values were abnormal:

ferritin 540, thyrotropin 12
Chest x-ray: cardiomegaly
Abdominal x-ray: splenomegaly
Abdominal CT scan: cirrhotic liver, partially calcified splenic hilar mass, splenomegaly and atrophic kidneys
Axial skeletal survey: sclerotic lesions in the calvaria, bilateral radial and ulnar areas and left tibia. Lucencies in the frontal bone, left proximal humerus and right clavicle. Iliac crest proliferative change.
Renal biopsy: thrombotic microangiopathy
Previous skin biopsy: acanthosis. Upper and mid-dermis capillaries arranged in small islands. Negative Congo red stain. Suggestive of tufted angioma.
Lymph node biopsy: effacement of lymph node. Regressively transformed germinal centers with "onion-skinned" appearance. Angiofollicular lymph node hyperplasia, consistent with Castleman disease, hyaline vascular type.

DERMATOPATHOLOGY

Chin biopsy: The epidermis is unremarkable. The dermis contains a lobular collection of blood vessels, most with thin walls. No significant atypia is identified. An unusual fibrotic stromal response surrounding vascular lobules is identified. Several luminae have slender, crescentic profiles. There is hemosiderin in the surrounding stroma. PAS strongly highlights the basement membrane around the vascular proliferation. PAS-positive deposits are not identified.

DIAGNOSIS

Hemangioma, suggestive of glomeruloid hemangioma, an unusual vascular proliferation associated with POEMS syndrome

TREATMENT & COURSE

Therapeutic alternatives for the hemangiomas were discussed with the patient. These included excision, cryotherapy, electrodessication and the use of the pulsed-dye laser. Two have been excised from her nose and she would like more excised. Her systemic diseases are being treated with the medications listed above.

DISCUSSION

POEMS syndrome is a multisystem disorder manifested by polyneuropathy, organomegaly, endocrinopathy, a monoclonal paraproteinemia or M-spike, and skin lesions. It is known also as Crow-Fukase syndrome, Takatsuki's disease, and PEP (polyneuropathy, endocrinopathy, and plasma cell dyscrasia) syndrome. In 1968 Shimpo et al. first described POEMS and Bardwick and colleagues later coined the acronym. Renal as well as osseous disease is associated with POEMS. The classic bone lesions are spinal spiculated proliferations seen on radiographs.

The cutaneous findings in POEMS include angiomas, hyperpigmentation, hypertrichosis, hyperhidrosis, sclerodermoid features, digital clubbing, multiple seborrheic keratoses, acquired icthyosis, livedo reticularis and purpura. Angiomas occur in 24-44% patients. The histology of these vary, and usually reflect cherry-type capillary hemangiomas, with middle to lower dermis haphazard, branching vascular luminae lined by flat endothelial

cells. Glomeruloid hemangiomas are specific for POEMS disorder. As in our patient, they usually present as multiple, firm, dome-shaped reddish-purple papules and nodules on the trunk or proximal extremities. Pathology reveals ectatic dermal vascular spaces containing aggregates of capillaries, resembling renal glomeruli. Sinusoidal-like spaces also fill the irregular vascular luminae. The capillary-type endothelial cells contain large vesicular nuclei, open chromatin and abundant cytoplasm, and are CD31, CD34 and Ulex europaeus agglutinin-1 positive and CD68 negative. The sinusoidal-like cells possess small basal nuclei with dense chromatin and sparse cytoplasm, and are CD31 and CD68 positive and CD34 and UEI negative. Between capillary loops are stromal cells with pale to clear, vacuolated cytoplasm often with eosinophilic PAS-positive hyaline globules, which might represent immunoglobulins or proteins absorbed from the circulation. These cells are factor VIII-related antigen positive, suggesting endothelial origin. The lesions do not appear to be neoplastic, but rather reactive, possibly to serum-derived immunoglobulins deposited in the cytoplasm of dermal microvascular endothelial cells. Features of cherry angiomas, glomeruloid hemangiomas and tufted angiomas have been detected in single biopsy specimens from patients with POEMS, perhaps reflecting different stages in an individual lesion. The tufted angioma-like pattern is considered the most primitive, with collections of immature polygonal cells surrounding irregular vascular channels lined by flat endothelium.

Microscopic examination of lymph nodes in 63% of patients with POEMS reveals characteristics of Castleman's disease, a rare entity of unknown origin marked by angiofollicular lymphoid hyperplasia in lymph nodes. Characteristics of Castleman's disease also include hepatosplenomegaly, central nervous system disturbances, hypergammaglobulinemia, renal dysfunction, and anemia. Castleman's disease and POEMS syndrome appear to be overlapping entities.

The etiology of POEMS is unknown. A particular autoantibody role of the M protein is not established. Neural and kidney abnormalities result from thrombotic microangiopathy, possibly secondary to increased vascular endothelial growth factor. Elevated vascular endothelial growth factor/vascular permeability factor, IL-6 and estrogens may mediate angioma formation.

Treatment of patients with POEMS includes chemotherapy to target any underlying paraproteinemia, immunosuppression, hormone replacement and symptomatic therapies.

REFERENCES

Bardwick P, Zvaifler N, Gill G, Newman D, Greenway G, Resnick D. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes: The POEMS syndrome. Medicine 1980; 59: 311-322

Chan J, Gletcher C, Hicklin G, Rosai J. Glomeruloid hemangioma. A distinctive cutaneous lesion of multicentric Castleman’s disease associated with POEMS syndrome. Am J Surg Pathol 1990; 14(11): 1036-1046

Tsai C, Lai C, Chan H, Kuo T. Glomeruloid hemangioma-a specific cutaneous marker of POEMS syndrome. Int J Dermatol 2001; 40: 403-406

Kingdon E, Phillips B, Jarmulowicz M, Powis H, Vanderpump J. Glomeruloid haemangioma and POEMS syndrome. Nephrol Dial Transplant 2001; 16: 2105-2107

Kishimoto S, Takenaka H, Shihagaki R, Noda Y, Yamamoto M, Yasuno H. Glomeruloid hemangioma in POEMS syndrome shows two different immunophenotypic endothelial cells. J Cutan Pathol 2000; 27: 87-92

Rongioletti F, Rebora A. Cutaneous reactive angiomatoses: patterns and classification of reactive vascular proliferation. J Amer Acad Dermatol 2003; 49(5)

Scheers C, Kolivras A, Corbisier A, Ghaaraert P, Renoirte C, Theunis A, de Saint-Aubain N, Andre J, Sass U, Song M. POEMS Syndrome Revealed by Multiple Glomeruloid Angiomas. Dermatology 2002; 204: 311-314

PRESENTERS

Iris Kedar, M.D., Nadera J. Sweiss, M.D., Maria Medenica, M.D., Vesna Petronic-Rosic, M.D.

HISTORY OF PRESENT ILLNESS

This 40-year-old African-American woman presented with bilateral painful leg lesions of 2 weeks duration, significant weight loss, and dyspnea. Physical examination revealed extremely painful, dusky, necrotic plaques above the medial malleoli. At follow-up 2 weeks later the lesions had progressed to deep necrotic ulcers. One ulcer had eroded an artery, requiring ligation to stop bleeding. A newly developed facial lesion was present.

PAST MEDICAL HISTORY

Gastroesophageal reflux disease
Asthma

PAST SURGICAL HISTORY

Ectopic pregancy

MEDICATIONS

Albuterol
Lansoprazole

ALLERGIES

No known drug allergies

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Current tobacco use. Recreational drug (cocaine, heroin) use in the past. Denies intravenous drug use.

PHYSICAL EXAMINATION

There are deep necrotic ulcers with eschars at the base and irregular borders on the lower legs above the medial malleoli. An indurated erythematous plaque is present on the left cheek.

LABORATORY DATA

The following were abnormal:

WBC 12.8, platelets 461, SGOT 92, SGPT 130, alkaline phosphatase 1190, ESR 81, C-reactive protein 14, ACE 97, Beta 2 glycoprotein IgG 95.8 (<20), anticardiolipin G Ab 20 (1-19.2), hepatitis C antibody positive with viral load <3200 copies/ml

The following were normal or negative:

Hematocrit, basic metabolic panel, calcium, albumin, PT, PTT, ANA, lupus anticoagulant, factor V Leiden, antithrombin 3, cyroglobulin, cryofibrinogen, ANCA, TSH, RPR, HIV, rheumatoid factor, hepatitis B consistent with immunization

STUDIES

Chest x-ray: lymphadenopathy, diffuse bilateral fine interstitial process, consistent with sarcoidosis.
CT chest/abdomen/pelvis: extensive lymphadenopathy in the chest, some lymphadenopathy in the abdomen, pelvis; diffuse interstial honeycombing of the lung bilaterally.
Liver ultrasound: hepatomegaly, no hepatic artery thrombosis.

Transbronchial lung biopsy and percutaneous liver biopsy revealed changes consistent with sarcoidosis.
Lymph node transbronchial needle aspiration: benign lymphoid tissue.

DERMATOPATHOLOGY

Leg (skin adjacent to ulcer): The epidermis showed moderate acanthosis with spongiosis. The upper, mid, and lower dermis housed a granulomatous infiltrate with islands of epitheloid cells. Fite and GMS stains did not reveal microorganisms.

DIAGNOSIS

Ulcerative sarcoidosis

TREATMENT & COURSE

Our patient had evidence of sarcoidosis in the lung and liver. She also had a positive Hepatitis C antibody with viral load <3200 copies/ml, limiting the use of potentially hepatotoxic therapies. Treatment with prednisone was initiated at a dose of 20mg BID, which led to slow but progressive improvement of all lesions. Prednisone was decreased to 10mg QD several weeks later due to severe hyperglycemia. Mycophenolate mofetil (500mg TID) and pentoxifylline were started. Her ulcers continue to epithelialize. The patient's dyspnea and liver enzymes abnormalities are improving as well.

DISCUSSION

Sarcoidosis is a chronic granulomatous disorder of unknown etiology, characterized by noncaseating granulomas that affect multiple organ systems. The lung and lymph nodes are most frequently involved. The skin is involved in approximately 25% of patients. Specific cutaneous lesions are characterized by granulomas microscopically, and appear as papules, nodules, plaques, lupus pernio, or infiltrative scars. Erythema nodosum is the most common nonspecific, or reactive, skin manifestation, and is associated with a better prognosis. Ulcerative sarcoidosis is one of several rare atypical presentations.

A review in 1997 reported 35 cases of ulcerative sarcoidosis in the literature. Yoo et. al. subsequently reported another 7 cases. Women, African-Americans, and young adults are most often affected by ulcers. The lower extremities are the most common location, and in rare cases ulcers may be generalized. Lesions most often arise within other cutaneous lesions of sarcoidosis, but they may form de novo and may be the presenting sign of sarcoidosis. Patients with ulcerative sarcoidosis often have involvement of other organ systems.

Histopathologic examination reveals the typical noncaseating granulomas. Other causes of granulomatous disease must be excluded, including fungi, mycobacteria, lymphoma, or foreign bodies.

The cause of ulcerations in sarcoidosis is not known. Hypotheses include trauma, necrosis of the epidermis overlying extensive epitheloid cell proliferation, immune complex deposition within endothelial cell gaps, and hyaline degeneration with infiltration of blood vessel walls in the deep dermis.

Ulcerative sarcoidosis may be challenging to treat. Albertini et. al. recommend systemic steroids as first line therapy, and methotrexate for refractory cases. Yoo et. al. suggest prednisone and hydroxychloroquine, with the addition of mycophenolate mofetil or thalidomide. Other immunosuppressive and immunomodulatory agents such as azathioprine and infliximab have been used in sarcoidosis with variable results. These medications may possibly be helpful in the ulcerative variant. Split-thickness skin grafts were temporarily successful in one patient, but ultimately ulceration around the graft developed. Apligraf, a living bilayered skin equivalent, was beneficial in a single case.

REFERENCES

Thomas KW, Hunninghake GW. Sarcoidosis. JAMA. 2003;289:3300-3303.

English JC, Patel PJ, Greer KE. Sarcoidosis. J Am Acad Dermatol. 2001;44:725-743.

Yoo SS, Mimouni D, Nikolskaia OV, Kouba DJ, Sauder DN, Nousari CH. Clinicopathologic features of ulcerative-atrophic sarcoidosis. Int J Dermatol. 2004;43:108-112.

Albertini JG, Tyler W, Miller OF. Ulcerative sarcoidosis: Case report and review of the literature. Arch Dermatol. 1997;133:215-219.

Schwartz RA, Robertson DB, Tierney LM, McNutt NS. Generalized ulcerative sarcoidosis. Arch Dermatol. 1982;118:931-933.

Verdegem TD, Sharma OP. Cutaneous ulcers in sarcoidosis. Arch Dermatol. 1987;123:1531-1534.

Brodkin RH. Leg ulcers. A report of two cases caused by sarcoidosis. Acta Derm Venereol.1969;49:584-587.

Bazex A, Dupre A, Christol B, Cantala P, Bazex J. Sarcoidosis with atrophic lesions and ulcers and the presence in some sarcoid granulomata of orceinophil fibres. Br J Dermatol. 1970;83:255-262.

Baughman RP, Iannuzzi M. Tumour necrosis factor in sarcoidosis and its potential for targeted therapy. BioDrugs. 2003;17:425-431.

Collison DW, Novice F, Banse L, Rodman OG, Kelly AP. Split-thickness skin grafting in extensive ulcerative sarcoidosis. J Dermatol Surg Oncol. 1989;15:679-683.

Streit M, Bohlen LM, Braathen LR. Ulcerative sarcoidosis successfully treated with apligraf. Dermatology. 2001;202;367-370.