Case # 1
Hermansky-Pudlak Syndrome

Resident Physicians
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Attending Physicians
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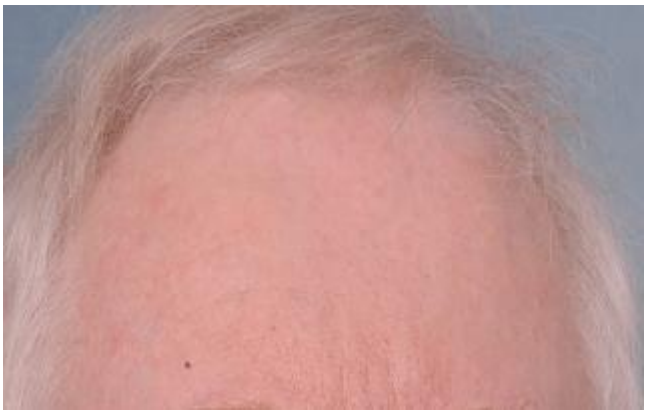

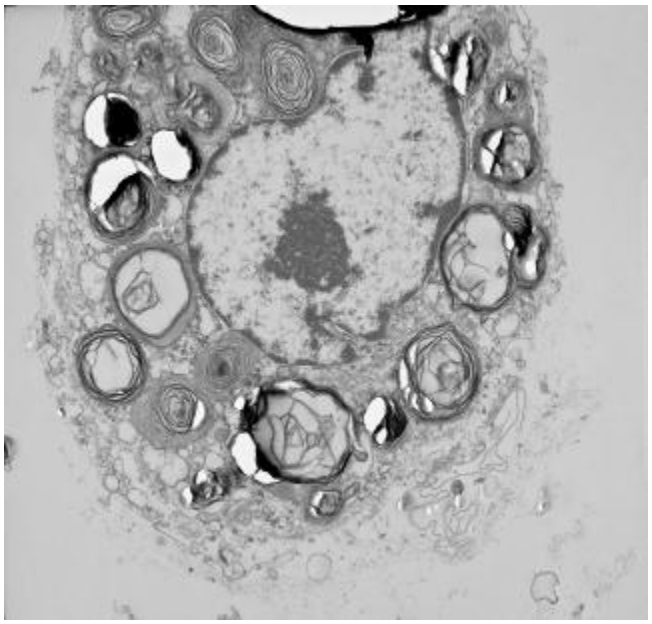

Sites of Interest
Hair, eyes, general pigment dilution.

History
57 year-old man with a childhood history of prolonged bleeding complications from epistaxis and tonsillectomy, pronounced paleness of skin, and vision problems. As an adult, increasing respiratory problems led to a diagnosis of pulmonary fibrosis, and later lung transplantation. His wife's research (Google) eventually led to a platelet study that confirmed Hermansky-Pudlak Syndrome. Albinism and immunosuppression have resulted in multiple non-melanoma skin cancers. He is currently believed to be the oldest living HPS patient in the world.

Clinical Findings
Generalized pigment dilution of skin and hair, trichomegaly, surgical scars are notable on integument examination. Eyes brown, strabismus, and nystagmus present. Lungs previously noted to have fine crackles, but exam has been relatively unremarkable since transplantation.

Laboratory/Studies
Platelet EM (University of Minnesota): absence of dense bodies.

Histopathology
Native lung pathology showed chronic fibrosing interstitial pneumonia. Toluidine blue staining demonstrated heavy alveolar macrophage deposition with metachromatic

cytoplasmic inclusions. Electron microscopy of representative area revealed the depositions within alveolar macrophages are composed of lamellar membrane-like material arranged mostly in concentric whorls, resembling myelin bodies (*see EM photo*).

Clinical Course

Bilateral lung transplantation was performed in 2005 for progressive restrictive disease related to interstitial fibrosis. Lung function significantly improved and graft complications have included rejection and likely bronchiolitis obliterans; however, no recurrent ceroid deposition has been noted on subsequent lung biopsies. Profound immunosuppression (related to standard transplant regimen as well as anti-rejection Campath) and underlying albinism have led to several squamous cell carcinomas. Operative reports from transplant, lung biopsies, and Mohs Micrographic Surgery have not indicated significant bleeding complications. Ophthalmology details were unavailable and followed outside of Duke, but the patient has reported decreased visual acuity and photosensitivity.

Discussion

Hermansky-Pudlak Syndrome (HPS) is a rare autosomal recessive type of tyrosinase-positive oculocutaneous albinism with bleeding diathesis. Platelet counts are normal and bleeding time is prolonged. The standard diagnostic test is platelet electron microscopy showing virtual absence of dense bodies. The seven recognized subtypes of HPS are clinically and genetically distinctive, but are unified by the abnormal formation and trafficking of intracellular vesicles (melanosomes, platelet dense bodies, and lysosomes). Phenotypic differences among subtypes include pulmonary fibrosis and granulomatous colitis (HSP 1, 4); and neutropenia with hemophagocytic risk (HSP 2). Pathophysiology of lung disease is related to lysosomal degradation impairment, accumulation of intracellular ceroid material, and the resultant inflammatory cascade. The histiocytic inflammation induces proliferation of type II pneumocytes and excessive production of surfactant, eventually causing a fibroblastic reaction. Successful lung transplants have been reported in the literature.

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Case # 2
Cutaneous Mastocytosis

Resident Physician
Sean F. Thomas, M.D.

Attending Physician
Amber Atwater, M.D.

Sites of Interest
Back, upper and lower extremities.

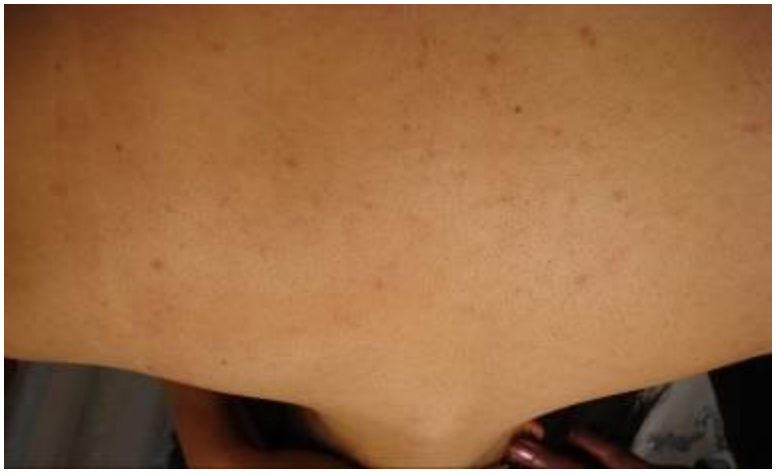
History
31 y/o African American female with a history of "freckles" that have been pruritic and urticate after hot baths since adolescence. She also has a history of chronic abdominal pain with intermittent diarrhea as well as headaches and dizziness.

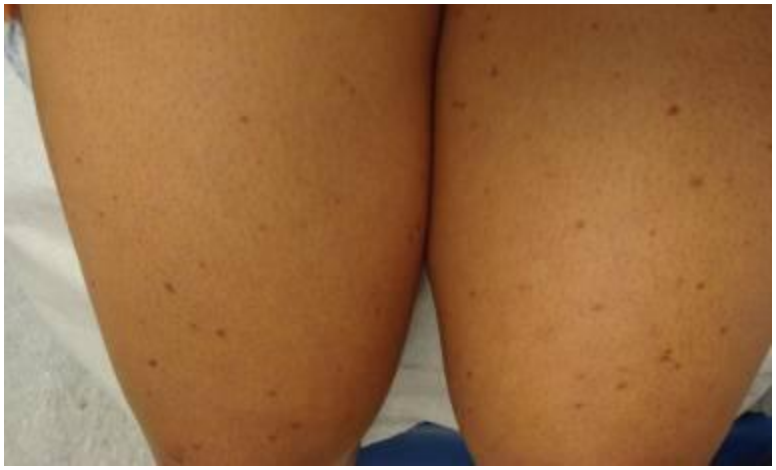
Clinical Findings
Diffuse red-tan macules, 2-3mm round, located on upper back, upper chest, upper and lower extremities. Darier's sign is positive.

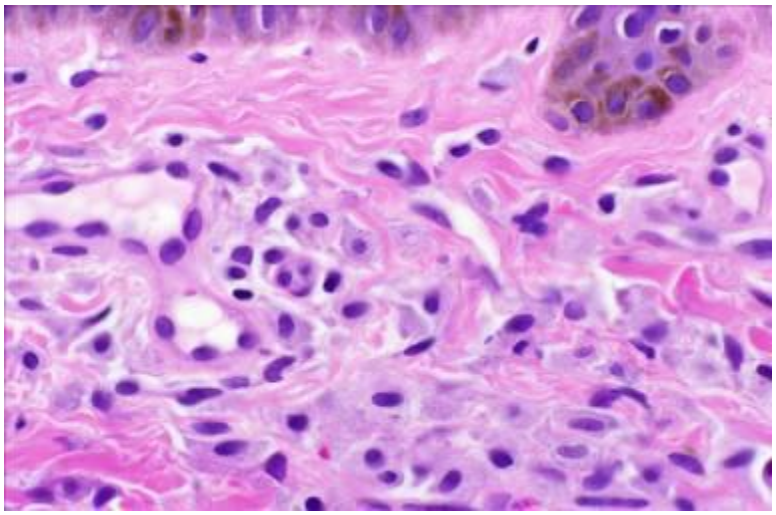
Laboratory/Studies
Normal CBC, CMP, serum total and mature tryptase, LDH, histamine, 24 hour urine histamine metabolites and bone marrow biopsy.

Histopathology
Hyperpigmentation with collections of perivascular mast cells and eosinophils.

Clinical Course
Cutaneous symptoms are controlled with avoidance of triggers and antihistamines. She continues to have abdominal symptoms and eats foods low in histamine. She has extremity and back pain. This will be evaluated by hematology. Recent repeat total and serum tryptase levels are within normal limits.







Discussion

Clinical exam in cutaneous mastocytosis (CM) shows small, fixed, red, yellow to tan or light brown papules that urticate or flush when rubbed (Darier's sign). Labs (CBC, LFTs, serum tryptase) are typically normal but can assist in evaluating for systemic mastocytosis (SM). Urine may reveal metabolites of mast cell activation (24hour urine for N-methyl histamine and 11 beta-prostaglandin F2). The diagnosis of CM is confirmed via biopsy. Stains and markers that can be used to identify mast cells include Geimsa stain, Mast Cell Tryptase and CD117 (KIT).

The diagnostic criteria for systemic mastocytosis require the presence of 1 major and 1 minor or 3 minor criterion. The major criterion is the presence of multifocal, dense aggregates of >15 mast cells as detected with tryptase or other special stains. The minor criteria are: 1) atypical morphology or spindle shapes in >25% of mast cells, 2) mutational analysis of c-Kit showing codon 816 mutation, 3) extracutaneous (CD117+) mast cells expressing CD2, CD25, and 4) persistent serum tryptase >20ng/ml.

Indications for a bone marrow biopsy to evaluate for SM include serum tryptase >20ng/ml, atypical cutaneous mast cells (CD117+ staining cells) that also stain with CD2 or CD25, or systemic symptoms suggestive of mast cell activation such as flushing, pruritus, nausea, vomiting, abdominal pain, diarrhea, vascular instability, and headache.

If the serum tryptase level is >200ng/ml a diagnosis of mast cell leukemia is almost certain. In a recent study 17% of patients with SM required bilateral bone marrow biopsies to confirm the diagnosis. These patients often had minimally elevated serum tryptase levels or normal urine levels of histamine metabolites.

The specific c-Kit mutation in mastocytosis is c-Kit D816V and it is present in 90% of patients with SM. It is also found in 38% of adults with CM and is very rare in children with CM. This gene encodes for KIT, which is a receptor tyrosine kinase for Stem Cell Factor. The mutation leads to unregulated mast cell growth and differentiation. Referral to a mast cell disease research center for processing of the bone marrow specimen with a highly sensitive PCR-based assay and mast cell enriched samples may be needed to confirm the presence of a c-Kit mutation.

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Case # 4
Amicrobial Pustulosis of the Folds

Resident Physician
Tania Peters, M.D.

Attending Physician
Neil Prose, M.D.

Sites of Interest
Bilateral axilla, scalp.

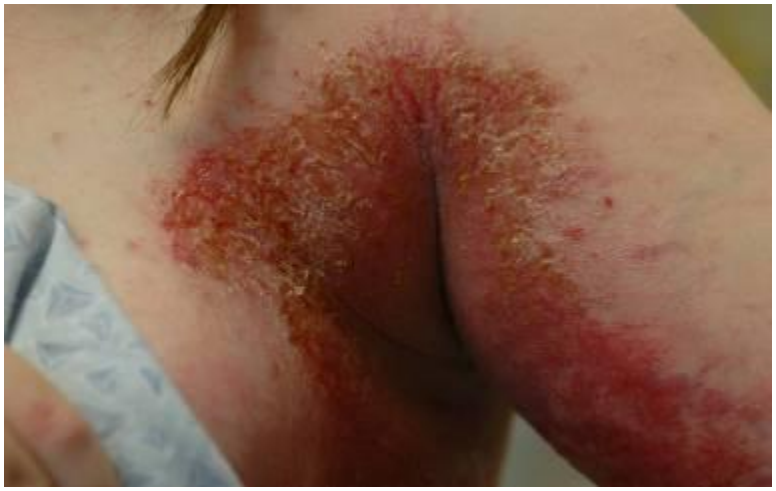
History
15y/o CF well until age of 12, when she developed red scaly areas behind her ears, around her umbilicus and her armpits. These progressively enlarged, became much thicker, scalier with some crusted areas. She developed similar lesions on her buttocks, groin, and pubic area. At its worst, these were severely painful and tender, with purulent discharge. The rash was not associated with any other systemic symptoms.

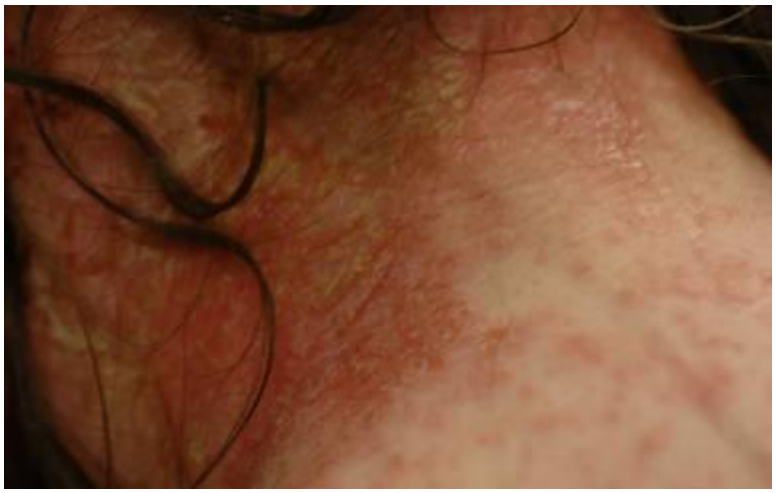
Family Hx
Her grandfather had psoriasis. There is a history of eczema, autoimmune hepatitis, and thyroid disease in her family.

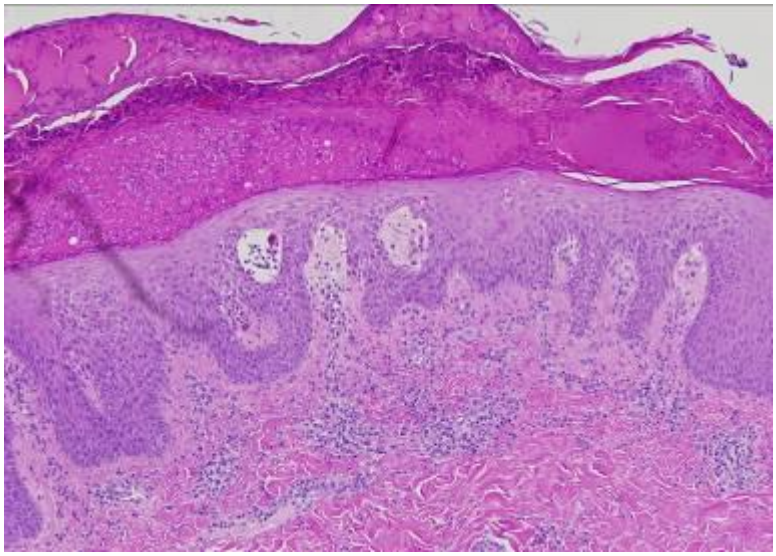
Clinical Findings
Erythema and scale of posterior scalp, posterior neck, and bilateral axilla.

Pathology
Early lesions w/ subcorneal pustules w/ mild epidermal spongiosis, advanced lesions w/ marked psoriasiform hyperplasia of epidermis w/ massive dermal edema. PAS-F and B&B neg for fungal or bacterial forms.

Laboratory Values
ANA pos w/ titer: 1:640, Anti-SM,NP,RO, and LA neg, C3 and C4 wnl. Thyroid fxn wnl.







Clinical Course

Prior to coming to Duke, the patient used topical and oral medications including halobetasol, Westcort, Locoid Lipocream, mupirocin ointment, Dovonex, fluocinonide cream, nystatin, and triamcinolone ointment and cream. She also had several courses of oral antibiotics, such as Septra and Keflex, and short steroid courses. Since she has been seen at Duke, Methotrexate was initially used alone, up to 20mg qweek, and then in combination with Humira then Prednisone. Dapsone was also tried, however, she developed anemia and methemoglobin, followed by Vitamin C and Cimetidine, then Cyclosporine to 150mg BID alone and with the addition of Kineret injections daily for two months, then Prednisone. She was then put on Remicaide with initial improvement, but generalized eruption occurred after her second infusion. She is currently on prednisone and mycophenolate mofetil. She has used intermittent courses of Bactrim throughout.

Discussion

Amicrobial pustulosis of the folds (APF) is a rare condition characterized by acute onset of relapsing, primarily aseptic, pustular lesions predominately affecting the cutaneous folds, scalp, and periorificial regions, such as the mouth, external ear canal, and nostrils. The small follicular and non-follicular pustules tend to coalesce into erosive erythematous plaques. APF is typically included within the spectrum of neutrophilic dermatoses. Histologically, the skin lesions show spongiform pustulation of the upper epidermis and a polymorphonuclear infiltrate of the dermis, requiring differentiation from other noninfectious pustular conditions, including subcorneal pustulosis and pustular psoriasis. Microbiologic examination of fresh pustules is negative, however, cultures from areas of ruptured pustular lesions often shows secondary colonization with Staph aureus.

APF is primarily reported in women in their 20's-30's, and is often associated with autoimmune abnormalities or the presence of serum autoantibodies. LE is the most commonly observed autoimmune disorder, particularly SLE, other associated conditions have included celiac disease, SCLE, discoid LE, Sjogren syndrome, RA, ITP, myasthenia gravis, and erythroblastic anemia. Laboratory abnormalities, especially presence of antinuclear antibodies, have been reported in individuals without associated autoimmune disease. APF usually runs a relapsing course, independent of any underlying autoimmune disease. Similar to other noninfectious neutrophilic dermatoses, APF is typically responsive to medium-dose systemic steroids. Systemic antibacterials are reported to improve secondary impetiginization. Other reportedly effective treatments have included cimetidine w/ and w/o ascorbic acid, dapsone, and cyclosporine. Systemic retinoids have been ineffective.

Table 4. Diagnostic criteria for APF

Obligate criteria	Minor criteria
Pustulosis involving 1 or more major folds, 1 or more minor folds and the anogenital area	Association with 1 or more autoimmune disorders
Histological pattern consisting of intraepidermal spongiform pustules and a mainly neutrophilic dermal infiltrate	Positive ANA at a titer of 1/160 or higher
Negative culture from unopened pustule	Presence of 1 or more serum autoantibodies (notably anti-ENA, anti-dsDNA, anti-smooth-muscle, antimitochondrial, anti-gastric-parietal-cell, antiendomysial,

The diagnosis of APF can be ascertained if obligate criteria and 1 minor criterion are present. ANA = Antinuclear antibodies; ENA = extractable nuclear antigens.

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Case # 5
Phacomatosis Pigmentovascularis

Resident Physician
Tania Peters, M.D.

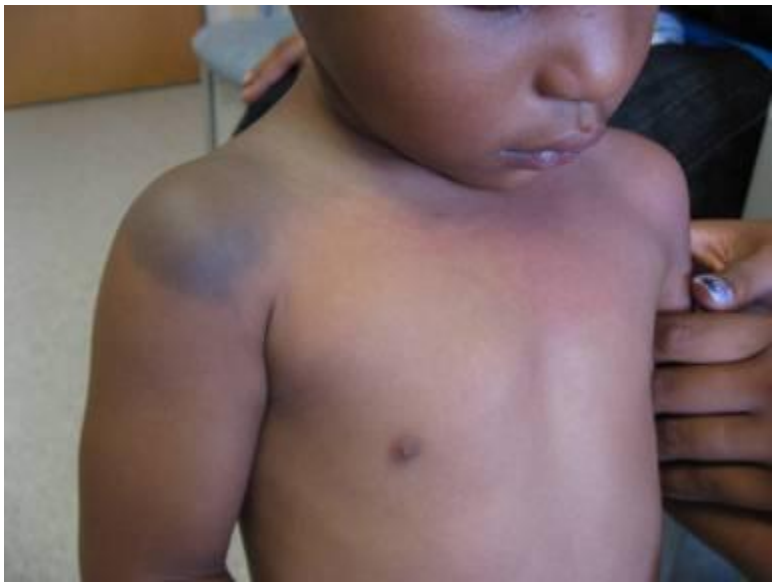
Attending Physician
Neil Prose, M.D.

Sites of Interest
Occipital scalp, right postauricular area/helix, right shoulder, chest, left arm and leg.

History
3y/o AAM who initially presented to dermatology clinic at the age of 15 months for evaluation of multiple blue and red birthmarks. Asymptomatic large blue macules on the head, trunk, buttock, and lower extremities and erythematous large macules on the left side of the chest, left arm and hand, and back were initially appreciated at birth. He was born at 32 weeks secondary to urethral stenosis and inability to make urine and he is now s/p cystoscopy w/ ablation of posterior urethral valves at age of 1 1/12 weeks. He is otherwise a healthy, active child.

Clinical Findings
Large blue macules present on the occipital scalp, right helix, right posterior auricular area, right shoulder, buttocks, left lower leg, and bilateral feet. Erythematous large blanching macules present on the back, and left chest extending from the medial aspect of the left upper extremity to involve the thumb and thenar eminence. Left thumb is slightly larger than the right thumb.

Clinical Course
Laser treatment has been discussed with the patient's family. At this time, no intervention is planned and patient is being monitored for any development of size discrepancy of his left hand/arm.



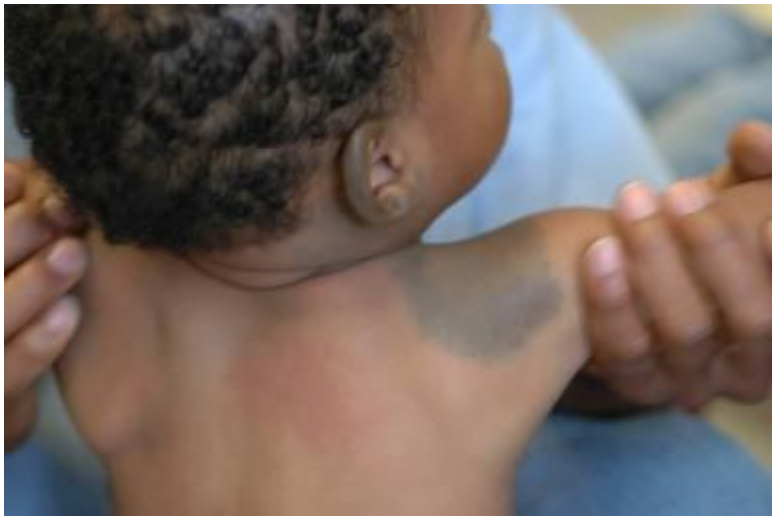


Table. Proposed New Classification of Phacomatosis Pigmentovascularis

Proposed New Name	Type of Coexistent Nevi	Traditional Name	Reported Additional Skin Lesions
Phacomatosis cesioflammea	Nevus cesius (blue spot) and nevus flammeus	PPV type IIa/b	Nevus anemicus, areas of hairlessness, hypoplastic nails
Phacomatosis spilorosea	Nevus spilus (speckled lentiginous nevus) of the macular type and telangiectatic nevus of a pale-pink type	PPV type IIIa/b	Areas of hairlessness, granular cell tumors, lymphedema
Phacomatosis cesiomarmorata	Nevus cesius (blue spot) and cutis marmorata telangiectatica congenita	PPV type Va/b	None
Phacomatosis pigmentovascularis, unclassifiable type	Various types of vascular and pigmentary nevi, sometimes with overlapping phacomatosis cesioflammea and phacomatosis spilovascularis	PPV type IVa/b and no name	Café au lait macules, hypomelanotic macules, nevus anemicus, nevus sebaceus

Abbreviation: PPV, phacomatosis pigmentovascularis.

Discussion

Phacomatosis pigmentovascularis (PPV) is an association of an extensive vascular nevus w/ a widespread pigmentary nevus. PPV is thought to be caused by twin spotting. Loss of genetic heterozygosity is thought to result in the adjacent twin spots.

In the March 2005, *Archives of Dermatology*, Happle reclassified the various types of PPV. He proposed the terms phacomatosis cesioflammea, phacomatosis spilorosea, and phacomatosis cesiomarmorata to replace the traditional number and letter classifications.

Phacomatosis cesioflammea is characterized by coexisting aberrant blue spots (Mongolian spots, dermal melanocytosis) and port-wine stain (nevus flammeus). This is the most frequently occurring type of PPV. The skin lesions may occur alone or with neurologic, ocular, or cutaneous abnormalities, as well as, renal and skeletal anomalies, including limb length discrepancy, scoliosis, and limb hypertrophy or atrophy. The most common cutaneous association is with nevus anemicus, which is reported in up to 50% of patients.

Phacomatosis spilorosea is characterized by coexisting macular nevus spilus and telangiectatic nevus (pale-pink salmon patch) and phacomatosis cesiomarmorata is characterized by coexisting aberrant blue spots and cutis marmorata telangiectatica congenita.

Approximately 50% of patients w/ PPV have systemic involvement. The most frequent associations reported are Sturge-Weber, Klippel-Trénaunay syndrome and melanosis oculi. Neurologic aberrancies, if present, develop in the first few months of life. Eye exam, electrocephalogram, CT, MRI, gait, limb circumference measurements, and X-ray can all be considered in PPV work-up.

PPV without systemic involvement is a benign condition, requiring no intervention, however, cosmetic modifications can be made by treating vascular nevi with pulsed dye laser and pigmentary nevi with Q-switched laser.

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Case # 6
Benign Familial Pemphigus successfully treated with OnabotulinumtoxinA (Botox®)

Resident Physician
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Attending Physicians
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Russell P. Hall, M.D.
John Soderberg, M.D.

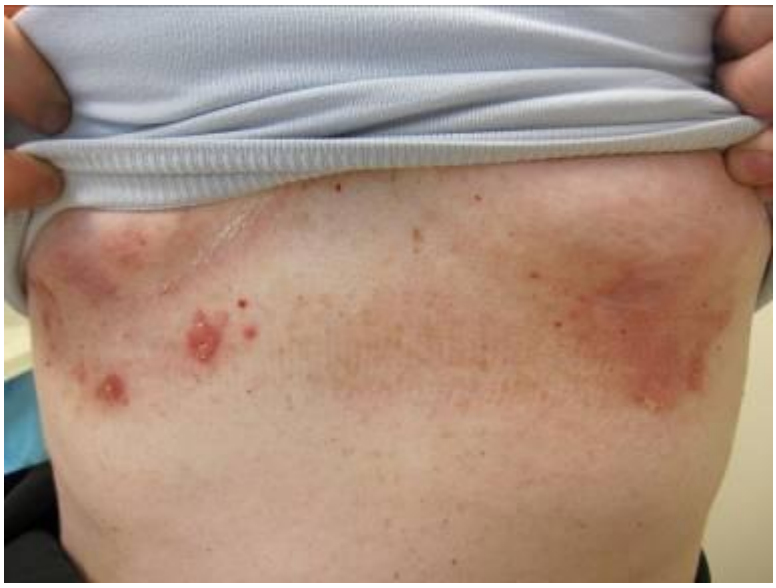
Sites of Interest
Axillae, inframammary, groin.

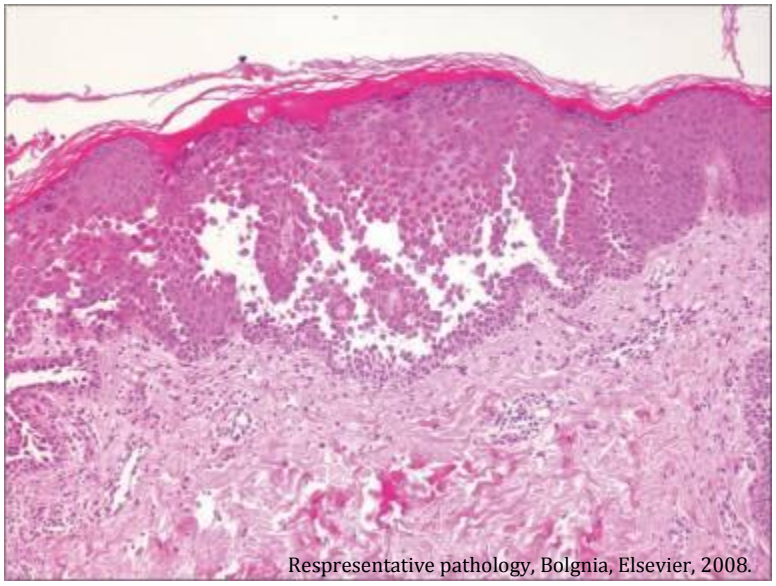
History
34 y/o WF with onset of tender, eroded lesions underneath her breasts and axillae in her mid 20s. Over time, these have spread to her inguinal area and occasionally the back in areas of trauma. The lesions worsened markedly with two pregnancies, and are much worse in the summer with increased sweating or tight clothing. She denies mucosal lesions, and is otherwise asymptomatic and healthy. Prior treatments have included potent topical steroids, pimecrolimus, and systemic antibiotics, with short-term resolution of lesions.

Her grandfather, mother, and brother have a history of similar lesions, all with onset in their 20s. She has one sister who is not affected, and her two children have yet to show evidence of disease.

Clinical Findings
Crusted, coalesced papules with few scattered erosions at the bilateral infra-axillary trunk, inframammary folds, and inguinal folds.

Clinical Course
Because flares of disease are associated with hyperhidrosis, treatment with onabotulinumtoxinA (Botox®) was felt to be beneficial. The patient received one treatment each at the axillae, inframammary folds, and inguinal areas. For each treatment, a dilution of 4 mL of normal saline per 100 units of Botox (4:1)





Respresentative pathology, Bolgnia, Elsevier, 2008.

was used, which is equivalent to 2.5 U per 0.1 mL. Injections were made 1cm apart in the affected areas, for a total of 50 U in each axilla, 150 U across the inframammary area, and 75 U in each inguinal fold. Topical anesthesia was applied prior to each treatment, and a Zimmer Chiller fan was used throughout, which significantly limited discomfort. She experienced resolution of lesions within several weeks, and only has occasional minor flares, which respond very quickly to several days of potent topical steroids.

Discussion

Benign familial pemphigus, or Hailey-Hailey disease, is a chronic blistering disease affecting the intertriginous skin, resulting in erythematous, crusted and eroded papules and plaques that usually begin in the third or fourth decade. It is often aggravated by heat, friction, and sweating, and a history of multiple relapses and remissions is characteristic. Inheritance is autosomal dominant with incomplete penetrance, and approximately two thirds of patients have a family history of the disorder. An overall defect in keratinocyte adhesion is secondary to a primary defect in a calcium pump protein, ATP2C1. Histopathology demonstrates full-thickness acantholysis or the so-called "dilapidated brick wall."

Therapeutic options are limited, and typically consist of topical corticosteroids, or topical or systemic antibiotics. Four case reports have been published in which botulinum toxin type A has been used successfully. The mechanism behind the efficacy of botulinum toxin is the control of hyperhidrosis by inhibiting cholinergic transmission in postganglionic sympathetic fibers of sweat glands. In one study, onabotulinumtoxinA was found to be as effective as laser ablation and dermabrasion therapies. A recent study by Koeyers, et al reported on six patients with extensive Hailey–Hailey disease resistant to multiple therapeutic regimens who received 3-5 treatments of abobotulinumtoxinA (Dysport®). Four patients experienced complete remission at 20 month follow-up, and two patients had partial remission, which then responded very well to topical corticosteroids. The patients experienced mild discomfort during and after the injections, but none had any further side effects.

Although botulinum toxin treatment alone may not be a permanent treatment for severe Hailey–Hailey disease, it has shown promise as a wonderful adjuvant therapy that is easy, long-lasting, well-tolerated, and very effectively reduces the long-term dose of topical or systemic steroids.

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Case # 7
Keratosis Follicularis associated with Cutis Verticis Gyrata

Resident Physicians
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Porcia Bradford, M.D.

Attending Physician
Navjeet Sidhu-Malik, M.D.

Sites of Interest
Scalp, trunk, dorsal hands, fingernails.

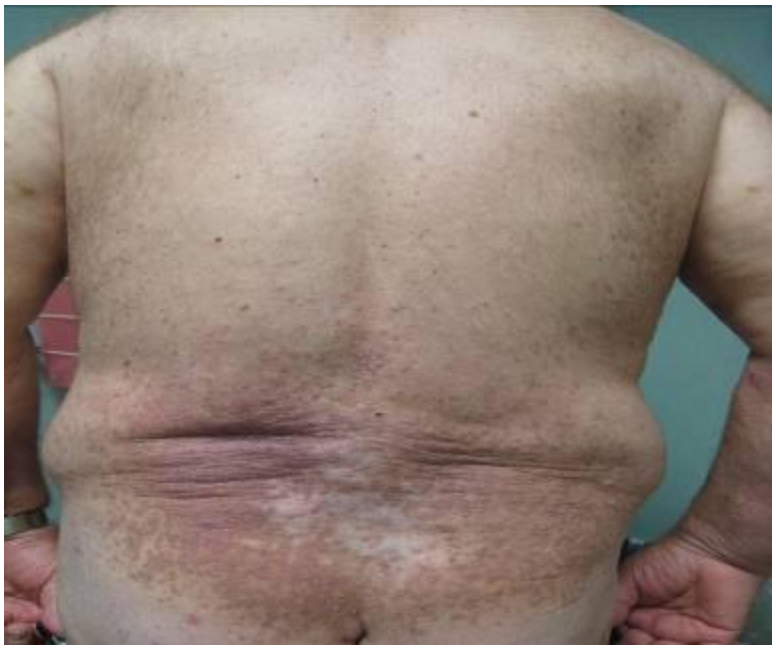
History
67y/o male with longstanding history (since age 14)of hyperkeratotic papules in a seborrheic distribution associated at times with discomfort and secondary infections. He has multiple first-degree family members affected, including his mother, sister, and son.

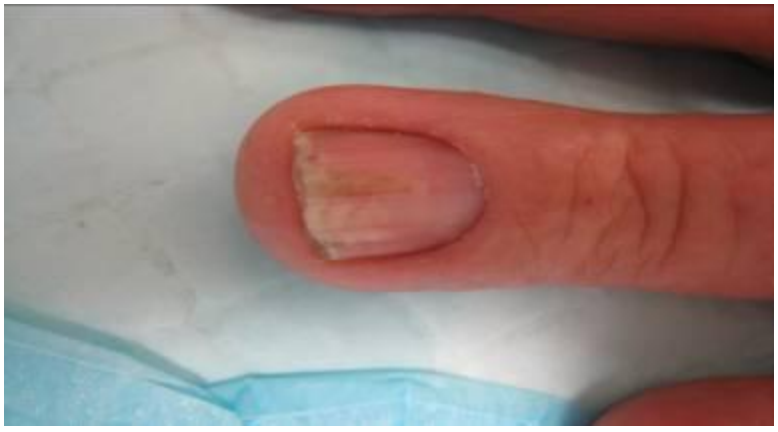
Clinical Findings
Hyperkeratotic brown/ red papules with crust on trunk. Flat-topped skin colored papules on dorsal hands and fingers. Fingernails with red and white longitudinal bands and distal v-shaped nicks. Exaggerated scalp and postauricular skin folds.

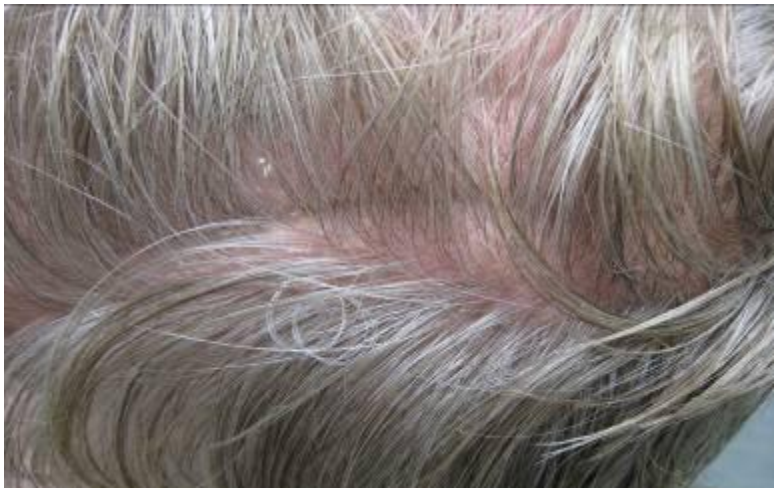
Laboratory
MRSA positive folliculitis.

Histopathology
Acantholysis with suprabasal clefts and dyskeratosis.

Clinical Course
Relatively asymptomatic until recent years when superinfections have complicated disease. Darier's well controlled on daily doxycycline, triamcinolone 0.1% cream, chlorhexidine washes, and PRN hydroxyzine. Superinfections controlled with 14 day course of septra.







Discussion

Keratosis follicularis or Darier's disease is an autosomal dominant genodermatosis caused by mutations in the *ATP2A2* gene, which encodes the sarcoplasmic/endoplasmic reticulum calcium ATP pump that transports calcium out of the cytoplasm and into the endoplasmic reticulum. Family members with confirmed identical *ATP2A2* mutations can exhibit differences in the clinical severity of disease, suggesting that other genes or environmental factors may affect the expression of Darier's disease.[1,2] Our patient has classic disease manifested as hyperkeratotic papules with crust on trunk. His clinical history was also classical, with his lesions occurring first during his teenage years having flares with warm weather.

Approximately half of patients with Darier's disease have hand involvement. Our patient had flat-topped skin colored papules on the dorsal hands and fingers. Interestingly, several patients with acrokeratosis verruciformis of Hopf, a disorder of keratinization characterized by multiple flat-topped, skin-colored keratotic lesions resembling plane warts typically observed on the dorsum of the hands and feet, have been found to harbor mutations in *ATP2A2,* suggesting this condition may actually be a localized form of Darier's disease.[3] Nail changes in Darier's disease include white and red longitudinal bands, longitudinal nail ridges, longitudinal splitting, and subungual hyperkeratosis, all of which our patient had. A sandwich of red and white longitudinal bands, often with a V-shaped nick at the free margin of the nail, is the most pathognomonic nail finding in patients with Darier's disease.

Incidentally, our patient was noted to have exaggerated scalp folds, consistent with cutis vertices gyrata (CVG). Several authors have noticed a high prevalence of mental disorders in patients with Darier's disease and CVG. There have been two case reports of patients with Darier's disease and associated CVG. One case of CVG was thought to be secondary to polyendocrinopathy.[4] The other case was thought to be secondary to chronic skin inflammation associated with Darier's disease.[5] Treatment with acitretin resulted in some involution of scalp furrows in the latter patient's CVG. Our patient's CVG has remained constant.

In conclusion, we present a man with classical Darier's manifested by hyperkeratotic papules on the trunk, hand, and nail findings. Additionally, he exhibits rare cutis vertices gyrata associated with his Darier's disease.

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Case # 8
Unspecified Connective Tissue Disease and Ravnaud's Disease

Resident Physician
Tania Peters, M.D.

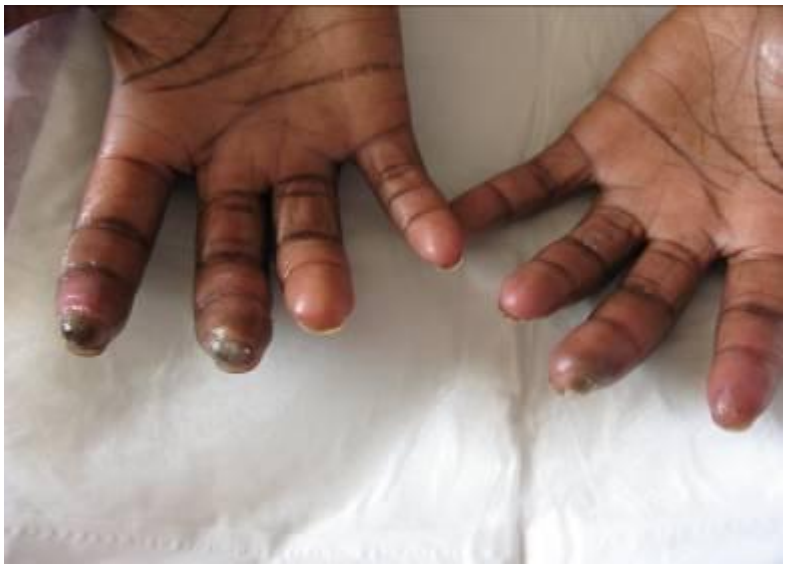
Attending Physician
Navjeet Sidhu-Malik, M.D.

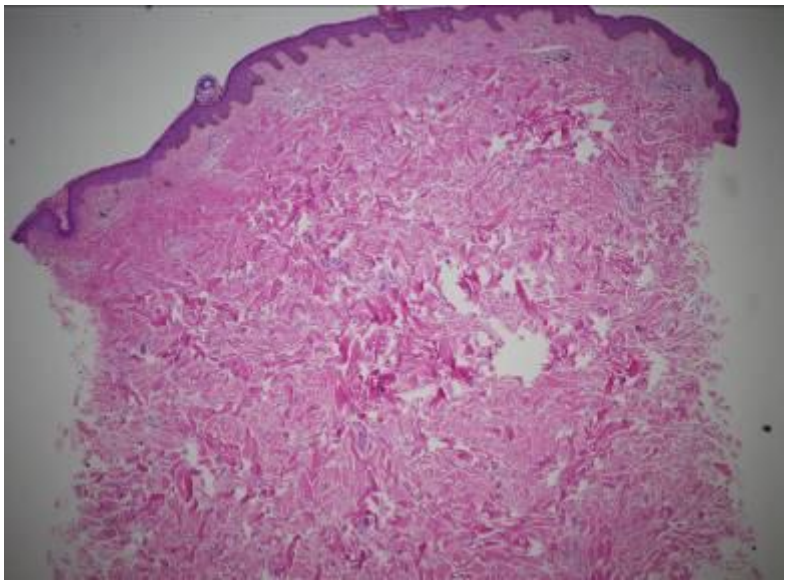
Sites of Interest
Face, posterior neck, hands and fingers.

History
28y/o AAF, well until July 2009, when she developed recurrent pain and white discoloration of the fingertips. This persisted with development of episodic purple to black discoloration of all fingertips, associated with severe pain. Episodes are more frequent when exposed to cold temperatures, with improvement with running hands under warm water. She developed blistering of the fingertips, which evolved into ulceration, beginning September 2009. In addition, in July 2009, she began developing hyper and hypopigmentation of the lower lip, chest, ears, cheeks, and forearms. These areas have subsequently been stable, but persistent.

Clinical Findings
Hyper and hypopigmented macules of the ears, periorbital area, forehead, and cheeks. Depigmented macules on the PIPs, DIPs, and MCPs. Mild swelling and induration of the fingers. Mottled hyper and hypopigmented macules of the posterior neck, forearms, hands, and buttocks.

Laboratory/Pathology
ANA positive at 1:320 and Anti-RNP positive.
Trace protein in the urine.
Dense dermal collagen with decreased adnexal structures.





Clinical Course
She has been treated by dermatology, rheumatology, and orthopedic surgery under a working diagnosis of connective tissue disease, possibly SLE or scleroderma. She has taken Methotrexate 20mg PO wkly, Cialis 10mg every other day, Plaquenil 200mg PO BID, ASA 81mg daily, Nifedipine 120mg daily, Pentoxyfylline 400mg PO TID and used HC 2.5% cream BID and Protopic 0.1% ointment daily to hypopigmented areas of skin. She underwent left hand sympathectomy January 15, 2009, followed by right hand sympathectomy and carpal tunnel release April 16, 2010, with significant improvement in hand pain and ulcers. She continues to have persistent mottled hyper and hypopigmentation, which is a source of frustration to the patient. She has persistent joint pain and does not have complete flexion in the fingers.

Discussion
Raynaud's phenomenon is an episodic vasospasm of the peripheral arteries, resulting in pallor, and subsequent cyanosis and/or erythema. It can cause pain, sometimes paraesthesia, and rarely ulceration of the fingers and toes. Secondary Raynaud's (Raynaud's syndrome) occurs in association with an underlying, usually connective tissue, disorder such as scleroderma, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, and polymyositis. In Raynaud's syndrome, vascular structure and function abnormalities may play a major role in the pathogenesis of the disease and medical treatment remains unsatisfactory in many cases, due to the limited understanding of pathophysiological mechanisms. Lifestyle modifications are first in the treatment algorithm, with proper body insulation, avoidance of cold exposure, stopping possible vasoconstrictive medication and smoking cessation playing important roles. Treatment of underlying disease is fundamental as well.

Medical treatment focuses on regulation of vasomotion by direct vasodilators (nitrates, calcium-channel blockers, prostaglandins, and PDE-V inhibitors) and inhibition of vasoconstriction (endothelin receptor antagonists, angiotensin-receptor blockers, and alpha receptor blockers). Symptoms may also be improved by substances that improve endothelial function, such as rho-kinase inhibitors (Fasudil) and statins, as well as, those that alter interaction with neural vasoregulation, like serotonin reuptake inhibitors. Newer treatments include phosphodiesterase-5 inhibitors (selectively inhibit cGMP-specific phosphodiesterase type 5 which increases cGMP, resulting in enhanced cGMP-dependent microvascular and macrovascular dilation), antioxidants (N-Acetylcysteine has demonstrated activity in patients with RP secondary to systemic sclerosis), and botulinum toxin injections (which may inhibit vasospasm by blocking cold-induced vasoconstriction and may also prevent recruitment of alpha2 receptors to vascular smooth muscle in cold conditions). Surgical interventions, including microsurgical revascularization of the hand, digital arterial reconstruction, and peripheral or digital sympathectomy, are reported to improve digital vascular perfusion and heal digital ulcers and relieve or eliminate pain in cases of severe distal and proximal arterial occlusion and digital vasospasm. Digital ulcer healing usually occurs within four to six weeks of surgery.

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Case # 9
Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) Syndrome

Resident Physician
Sarah Rodgers, M.D.

Attending Physician
Adela Cardones, M.D.

Sites of Interest
Hands.

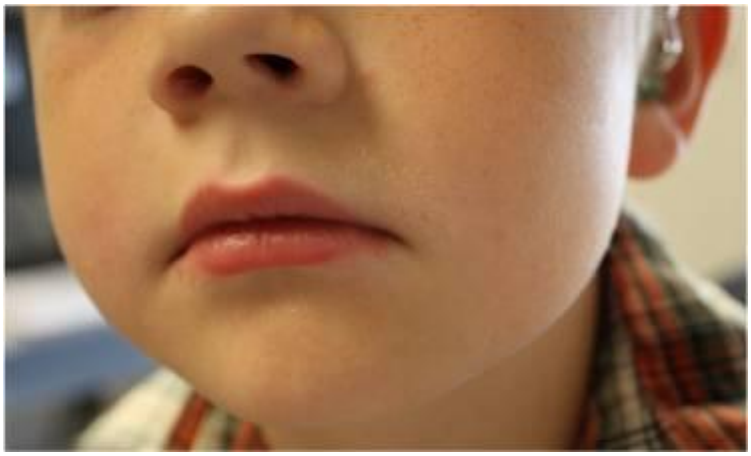
History
Two siblings, a 3 year-old girl and an 8 year-old boy have a history of various cutaneous infections. The older brother has a history of cyclic neutropenia, oral ulcers, bilateral sensory neural hearing loss, astigmatism, partial vocal cord paralysis and recurrent viral and bacterial infections. He had verrucae of the hands and face for 3 years refractory to topical 5-Fluorouracil. The young girl presented with history of neutropenia, >10 ear infections, and upper respiratory and yeast infections. They were diagnosed at the NIH with WHIM syndrome. Their maternal grandmother was diagnosed with neutropenia in her 50's.

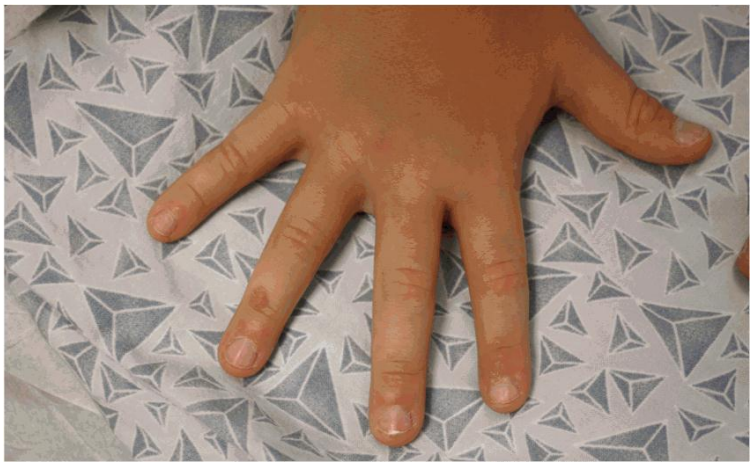
Clinical Findings
3 year-old girl: perianal and genital faintly erythematous plaques with satellite papules/pustules.
8 year-old boy: Multiple 4-5mm verrucous papules on the hands and a single papule on the left cheek near the oral commisure.

Laboratory/Studies
Boy: Bone marrow bx at age 3 showed a normal male karyotype and no clonal abnormalities.
Abs. neutrophil count range: 395-600.
Neg. Connexin 26 gene test

Both: IgG, IgA, IgM & IgE- normal-
12/2009- CXCR4 mutation found.

Clinical Course
Topical 5-fluorouracil cream was ineffective for treatment of verrucae in the young boy. Cryotherapy has resulted in improvement.
Both children take trimethoprim-sulfamethoxazole for bacterial prophylaxis.





Discussion

WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) syndrome is a type of severe congenital neutropenia caused by a mutation in a hyperfunctional chemokine receptor called CXCR4 that has autosomal dominant inheritance. Myelokathexis refers to defective neutrophil egress from the bone marrow, and this occurs in WHIM syndrome because increased CXCR4 causes retention of neutrophils. There is then resulting apoptosis of mature retained neutrophils within the bone marrow and neutropenia serologically.

Aside from neutropenia, clinical characteristics of WHIM syndrome include susceptibility to HPV infections that induce common warts and condyloma acuminata with possible transformation to carcinomas. The warts are characteristically numerous and located on the hands, feet, and trunk. Interestingly, susceptibility to HPV is greatly out of proportion to the general susceptibility to other viral infections in WHIM. Patients also suffer from recurrent infections, especially bacterial, related to B-cell lymphopenias and hypogammaglobulinemia. Cutaneous infections can include cellulitis, thrombophlebitis and abscesses.

Treatment options for WHIM include using G-CSF and periodic IVIG administration and are particularly helpful for resolution of infections with influenza, parainfluenza, herpes simplex, herpes zoster and common respiratory viruses. In a report of similar siblings with recurrent infections by a different mutation, G-CSF daily treatment resulted in normalization of CXCR4 expression and the siblings suffered from nearly no further infections on 2 year follow-up.

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Case # 10
Piebaldism

Resident Physician
Holly Bartell, M.D.

Attending Physician
Neil Prose, M.D.

Sites of Interest
Abdomen, legs, forelock.

History
This is a 4 y/o Caucasian male born with a white forelock and amelanotic patches on his legs and midline abdomen. The size and appearance of the amelanotic patches have been stable since birth, but over the past few years the white forelock has become less apparent. He is growing well and has reached all expected developmental milestones. There is no family history of similar skin findings or genetic abnormalities.

Clinical Findings
Healthy appearing boy in no acute distress. Interacts in an age appropriate manner. He has a white forelock and well circumscribed irregularly shaped depigmented patches on his midline abdomen and legs. There are islands of normally pigmented macules within and at the border of the depigmented patches. There is no facial dysmorphism, or iris heterochromia.

Laboratory/Studies
Genetic testing was negative for Waardenberg syndrome and he has had a normal hearing exam.

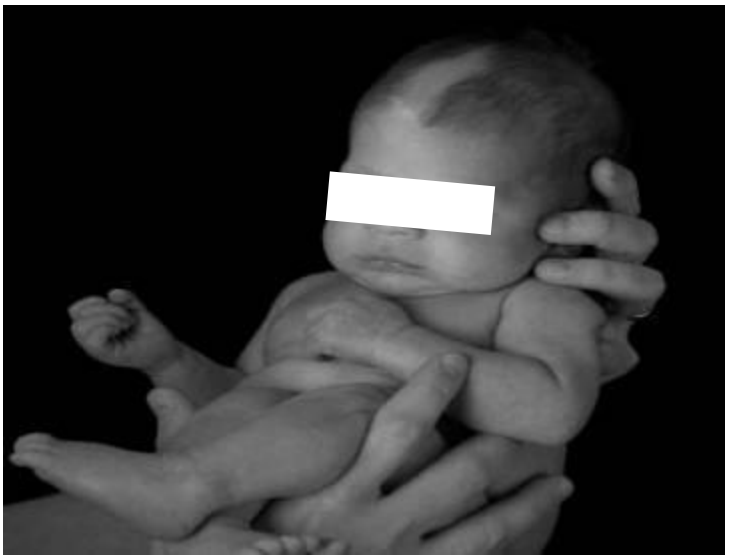
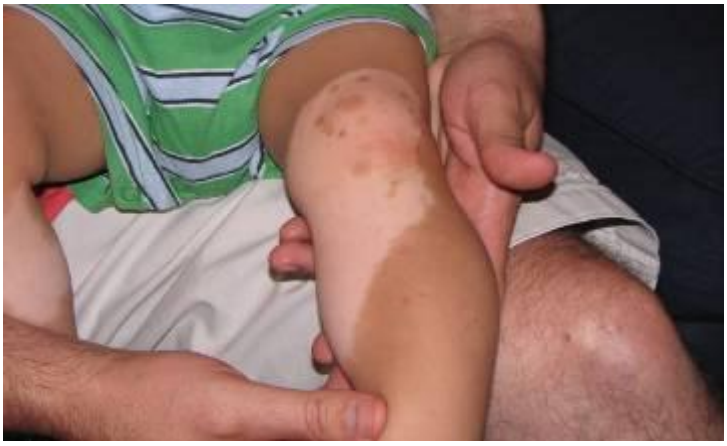
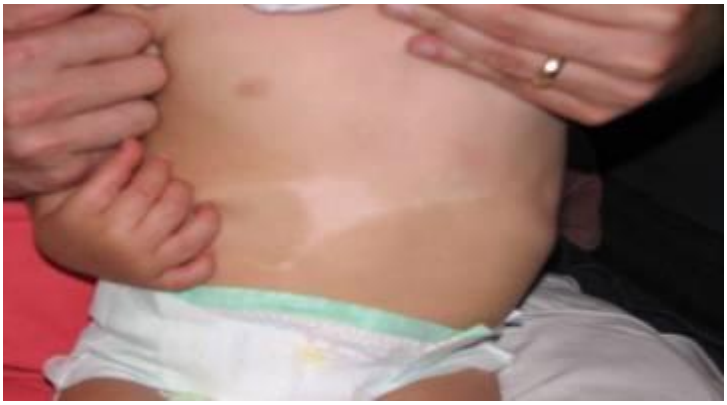


Photo during infancy





Discussion

Piebaldism is a rare autosomal dominant congenital disorder, resulting from mutations in KIT proto-oncogene which encodes a member of the tyrosine kinase family of transmembrane receptors found on the surface of melanocytes. A functioning KIT receptor is required for normal development of melanocytes.[1] Recently, deletions in the SLUG gene, a zinc-finger neural crest transcription factor, have been reported in patients with piebaldism that lacked mutations in KIT.[2] Affected individuals present at birth with characteristic triangular shaped leucoderma with leucotrichia on the forehead, known as a white forelock, and symmetrically distributed irregularly shaped amelanotic patches on the face, trunk, and extremities. Classically, islands of pigmented macules are present within and at the border of the depigmented areas. Interestingly, a number of patients may undergo spontaneous repigmentation, either partially or completely.

A white forelock of hair, often triangular in shape, may be the only manifestation in 80-90% of cases, or both the hair and the underlying forehead may be involved.

Except for cutaneous findings, most patients with piebaldism are otherwise healthy.[3] However, there are rare reports of piebaldism associated with Hirschsprung disease, mental retardation, NF1, Grover disease, congenital dyserythropoietic anemia type II, Diamond-Blackfan anemia, deafness, and cerebellar ataxia.[4]

There are a number of other syndromes associated with piebald-like hypopigmentation of the skin and hair with other anomalies, but are not associated with anomalies of the kit gene. (Table 1)[5]

TABLE I. Genetic Pigmentary Disorders

1. Disorders of melanoblast migration from the neural crest into the skin
Piebaldism
Waardenburg syndrome (WS)
Dyschromatosis symmetrica hereditaria
2. Disorders of melanosome formation in the melanocyte
Hermansky–Pudlak syndrome
Chédiak–Higashi syndrome
3. Disorders of melanin synthesis in the melanosome
Oculocutaneous albinism (OCA)
4. Disorders of mature melansome transfer to the tips of dendrites
Griscelli syndrome

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Case # 11
Congenital Hypertrichosis Lanuginosa

Resident Physician
Sarah Rodgers, M.D.

Attending Physician
Elise Olsen, M.D.

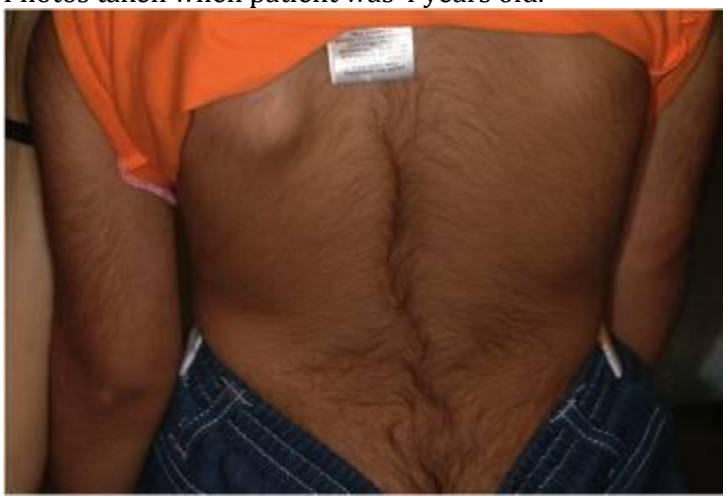
Sites of Interest
Face, extremities and back.

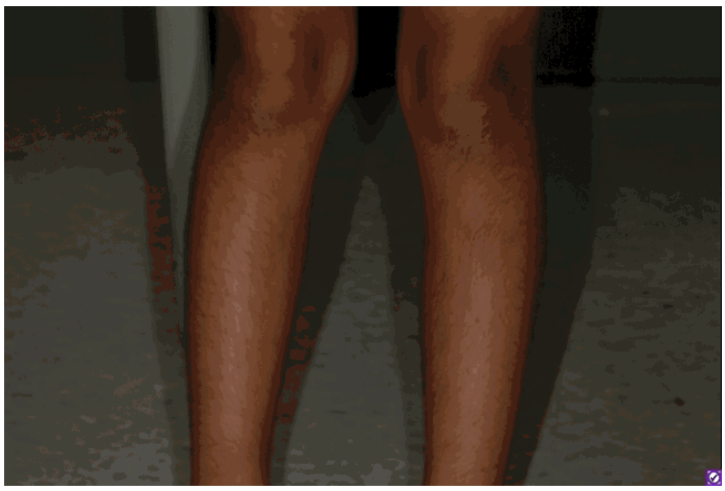
History
This patient is an 8 year-old Indian girl who presented to Dr. Olsen in 2007 with a history of excessive hair growth on her trunk and extremities since birth. The hair growth had worsened as she grew older. Her mother denied any problems with the pregnancy. The patient did not have any visual, dental, gingival, nail or developmental abnormalities. No family members have had hair abnormalities. Previous lab work-up by endocrinology was normal for testosterone, 17-hydroxy- progesterone, DHEA, DHEAS, androstenedione and cortisol.

Clinical Findings
She is a well-developed female. Hypertrichosis of the glabella, bilateral temples, back, upper extremities and lower extremities is noted. No facial structure or nail abnormalities present.

Clinical Course
Her family is considering laser hair removal at a future date.

Photos taken when patient was 4 years old.





Discussion

Congenital hypertrichosis lanuginosa (CHL) is an autosomal dominant disorder in which excessive hair growth presents at birth or within the first year of life. The hair is typically silvery gray to blond and may involve the entire body surface except the palms, soles, lips, and distal phalanges. Variants of CHL exist such as Ambras syndrome in which individuals have dysmorphic facial features under darker confluent facial hair that may measure up to 10 inches in length. Most individuals with CHL are otherwise normal, but associations with glaucoma, photophobia, infantile genitalia and mental retardation have been reported. Hereditary gingival fibromatosis associated with generalized hypertrichosis has been mistakenly reported as CHL in the literature.

Management options include shaving, bleaching, chemical removal, electric epilation and laser hair removal. Successful hair removal in a child with CHL has occurred with Q-switched neodymium:YAG laser used in conjunction with a topical carbon-containing solution in order to damage the hair follicles.

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Case # 12
Alopecia Areata successfully treated with Methotrexate

Resident Physician
Bishr Al Dabagh, M.D.

Attending Physician
Elise Olsen, M.D.

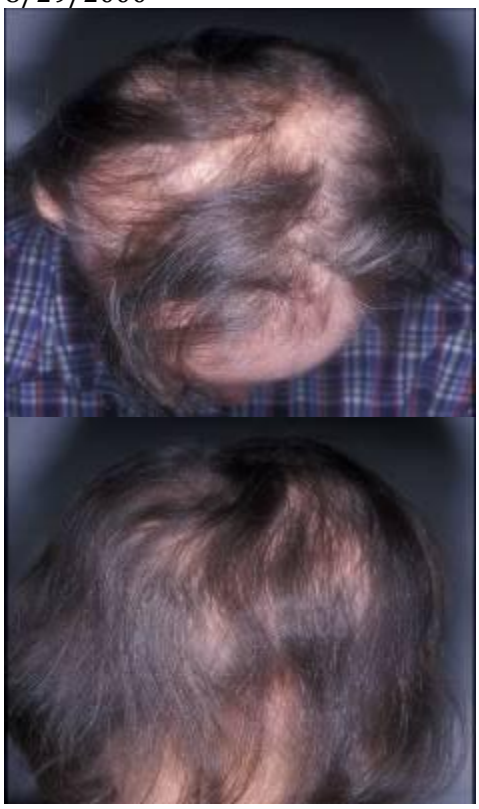
Sites of Interest
Scalp, eyebrows, eyelashes.

History and Clinical Course
The patient is a 47 year old woman who experienced her first episode of alopecia areata (AA) at 16 years of age. Her hair regrew over a period of a few months without any treatment. She had continuous episodes of patchy hair loss and one episode of alopecia universalis (AU) in 1983 which responded to topical minoxidil and topical steroids. In 1989 she experienced alopecia totalis (AT) which responded to systemic steroids. Hair loss began again in 1999.
She first presented to Dr. Olsen in the Duke Hair Disorders Research and Treatment Center in August 2000 with ~50% scalp hair loss and diffuse loss of eyelashes, brows, and body hair. She continued on the topical clobetasol and topical minoxidil with stable, patchy hair loss, but then developed more extensive hair loss in 2002. At the time, she was placed on a prednisone taper which she did not tolerate due to irritability. Methotrexate (MTX) was initiated in 2003.

PMH
Chronic diarrhea diagnosed with lymphocytic colitis in 2003. She was also seen by rheumatology for sacroiliac pain and diagnosed with an undifferentiated connective tissue disease in 2003.

Present Clinical Findings
Scalp: Several, discrete, annular areas of hair loss on the vertex of the scalp as well as the biparietal scalp and occipital scalp. Each of these areas has fine terminal hair regrowth within them. There is no scale, pustules, or erythema. Eyebrows, eyelashes, and body with some hair loss. Nails: Minimal pits on the right third fingernail. Other fingernails are normal in appearance.

8/29/2000



5/24/2010

Laboratory/Studies (2003)
Thyroid function tests normal. Liver function tests normal**.** Positive ANA 1:160, speckled and nucleolar; 1:40 homogeneous. Negative RF. Negative anti-SM, RNP, RO, LA, dsDNA, endomysial antibody. Normal ESR. MRI of the hips normal.

Clinical Course
Initial dose of MTX in January of 2003 was 10 mg weekly and the patient's alopecia and chronic diarrhea both responded. In November 2004, the patient began to experience dizziness and MTX dose was temporarily decreased to 2.5 mg/week because the patient did not want to discontinue it. However, in June 2005 she began to have areas of significant hair loss and her MTX was increased again to 10 mg weekly. Her alopecia and colitis responded again. In 2006, the patient had a hysterectomy and was taken off the methotrexate. Given that the dizziness continued off MTX, it was felt unrelated but no etiology was determined on neurologic work-up. 10 mg of MTX/wk was reinstituted post-op and in October of 2006, she had only 1% scalp hair loss and had re-grown her eyebrows and eyelashes. Attempts to get her dose down to 5 mg/week were unsuccessful. MTX was stopped again in December of 2007 at a cumulative dose of 1.85 grams but the hair loss progressed off therapy and MTX was restarted again in October of 2008. She has been on continuous MTX therapy since that time. On last clinic follow-up in May 2010, she was on 7.5 mg /wk, with only ~ 5% scalp hair loss. The patient reports that while on the MTX, if she does experience hair loss, it is not as extensive and it takes a much shorter time to re-grow.

Discussion
The goal of alopecia areata (AA) therapy is to suppress disease activity; however, its management remains difficult. The lack of randomized, double-blind, placebo-controlled studies as well as the high rates of spontaneous remission makes evidence-based assessment of various therapeutics a challenge. Joly treated 16 patients with AT or AU with 15-25 mg of weekly MTX and 10-20 mg of oral prednisone (which was given initially and then tapered off, and stopped if possible, at the beginning of terminal hair growth) and 6 patients with 15-25 mg of weekly MTX alone. Of the 6 treated with MTX alone, 3 had a complete response, 2 had an incomplete response, and one did not respond. Of the 16 treated with both MTX and prednisone, 11 had a complete response and 4 had a partial response. Relapse was common if the MTX was decreased or stopped. However, restarting MTX resulted in hair re-growth. When using MTX or any agent for AA, a 3 month trial should be given to insure enough time to see results.

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Case # 13
Central Centrifugal Cicatricial Alopecia

Resident Physician
Kristen Thomas, M.D.

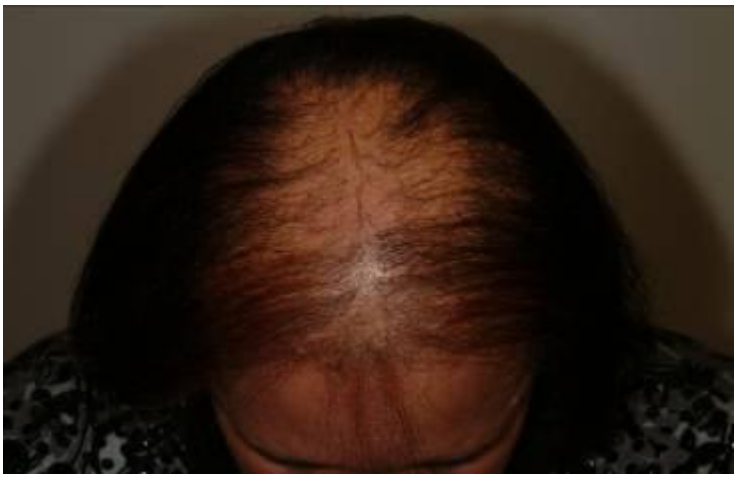
Attending Physician
Elise A. Olsen, M.D.

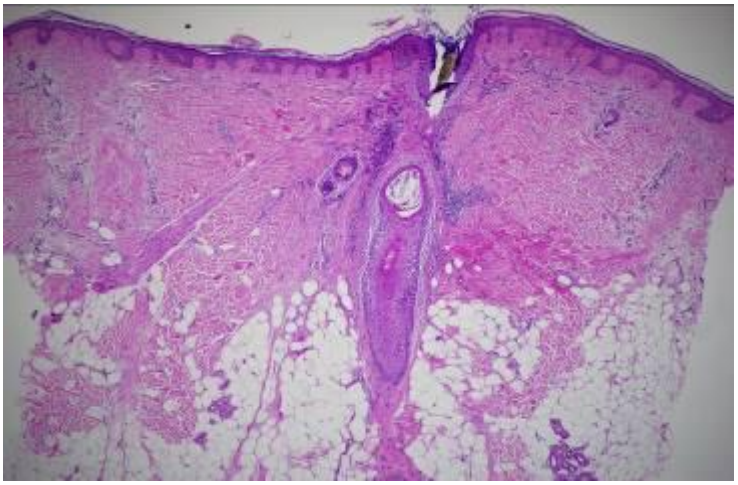
Sites of Interest
Scalp.

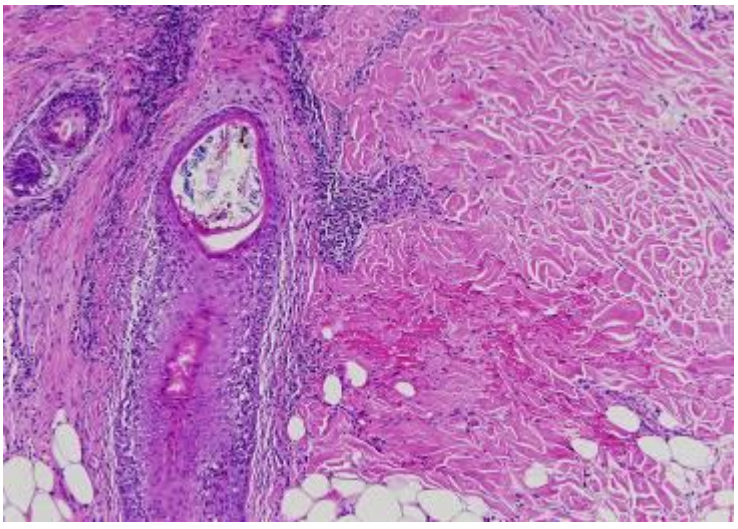
History
52 y/o AAF, who was seen by Dr. Olsen in the Duke Hair Disorders Research and Treatment Center clinic, presented with a 12 year history of hair loss that began with thinning on the vertex of her scalp, and has since spread to the frontal, mid, and temporal areas. There is no associated pain or pruritus. She has tried several home remedies for treatment such as vitamins and topical lotions and oils, which did not seem to help very much. Previous hair care practices have included use of relaxers for the last 30 years and hair color for the last 17 years. She goes every six to ten weeks to salon to have these done, and also has deep conditioner applied in addition to heat. She used to wear braids before she started to lose hair.

The patient had a hysterectomy 12 years ago but she was never placed on any hormone replacement therapy. She did take oral contraceptive pills starting when she was approximately 18 years old up until when she had her hysterectomy. Her great aunts have a history of thinning on the top of their scalps, but her mother does not have any hair loss.

Clinical Findings
Examination of the scalp reveals marked thinning on the frontal, middle, and vertex of the scalp, with less pronounced thinning of the temporal regions. There is evidence of scarring and loss of follicular ostia, but no scale or follicular plugging. The occiput appears normal with no evidence of scarring or decreased density.







Laboratory/Studies
CBC, CMP, iron studies, thyroid studies, ANA, and hepatitis studies are all within normal limits or negative.

Histopathology
Scarring inflammatory alopecia with a diminished number of hair follicles. A superficial perifollicular predominantly lymphoid infiltrate is noted at the infundibulum. Vacuolar change and dyskeratotic cells are seen. Neutrophils are present, mainly around vessels. Perifollicular mucinous fibrosis is also noted. A PAS stain is negative for fungal hyphae.

Clinical Course
The patient began using a light oil on her hair only instead of her scalp. She began pressing her hair instead of using a relaxer, and avoided braids and weaves that put pressure on the scalp. She took doxycycline 100mg po daily and used fluocinolone solution for 5 months. At her follow up visit, she had noticed mild improvement in her hair density. She declined to use topical minoxidil.

Discussion
Central centrifugal cicatricial alopecia (CCCA) refers to the central scarring hair loss seen mostly in African American females and is the most common cause of permanent hair loss in this population. The process begins on the vertex or mid scalp and symmetrically spreads centrifugally: a photographic scale has recently been developed by the NAHRS to capture gradations of severity. Histologically, but not clinically, CCCA may resemble pseudopelade or lichen planopilaris, highlighting the need for clinical-pathologic correlation for diagnosis. At this point, the etiology remains idiopathic, but Olsen has suggested this represents female pattern hair loss with an inflammatory component from physical, chemical, or infectious causes triggering an inflammatory/scarring process. Recommendations for limiting inflammation include avoiding tight braids, heavy extensions, and excessive heat. Chemical processing should be limited and assiduously neutralized. Scalp scale should be evaluated for fungal infection and if no infection noted, treated with non-occlusive emollients and non-drying shampoo and conditioners with avoidance of occlusive greases. Pustules should be cultured for bacteria and fungus and treated as necessary. Oral antibiotics, especially tetracyclines, and low to mid strength topical steroids may be utilized to control inflammation. Once inflammation is controlled, topical minoxidil may be helpful to stimulate recovering hair. Hair transplants may be considered in cases which have shown no progression or overt inflammation for several years. It is also recommended that these women undergo screening for hyperandrogenism, and that women with less defined central hair loss have a scalp biopsy to help distinguish between female pattern hair loss, in which treatment may induce hair re-growth, and CCCA, in which the focus is on prevention of further loss.

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Case # 14
Frontal Fibrosing Alopecia

Resident Physician
Stavonnie Patterson, M.D.

Attending Physician
Elise Olsen, M.D.

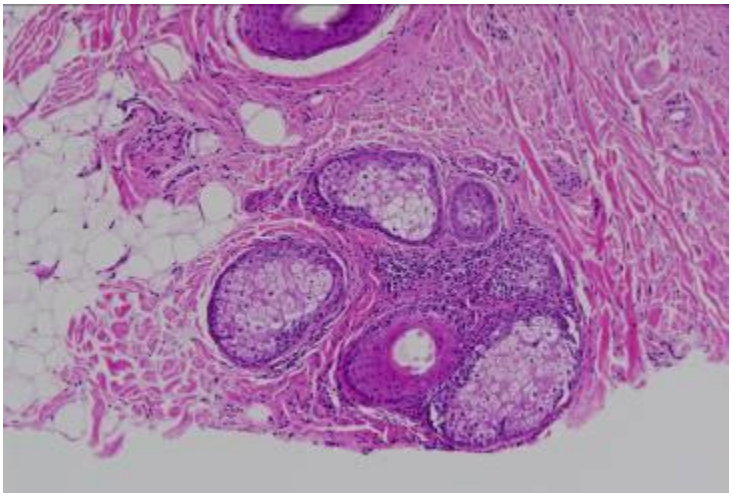
Sites of Interest
Fronto-temporal scalp, eyebrows.

History
62 y/o female was referred to Dr. Olsen by Dr. Catherine Hren and first seen in the Duke Hair Disorders Research and Treatment Center in 2008 with a 6 month history of progressive hair loss. This was most prominent at the frontal hair line and lateral eyebrows. Her overall health was good. No laboratory abnormalities were noted. PMH was significant only for a total hysterectomy in 2000 and history of oral hormone replacement therapy. At presentation and currently she is using the Vivelle Estrogen patch.

Clinical Findings
Recession of frontal and temporal hair line with loss of follicular ostia, but no atrophy. Perifollicular erythema in frontal hair line. Bilateral lateral eyebrow hair loss. No oral or cutaneous evidence of lichen planus.

Laboratory/Studies
Testosterone: Total 11 (8-60 ng/dL), Free 0.2 (0.3-1.9 ng/dL), both normal for menopausal status
TSH 3.27 (0.34-5.66 uIU/ml)
T4 1.11 (0.52-1.21 ng/dL)
Ferritin 118 (11-204 ng/ml)
Iron saturation 33 (15-55%)
HGB 15 (12.0-15.5 g/dl)
HCT 43 (0.35-0.45L/L)
ESR 38 (0-15 mm@1hr)

Histopathology
Lymphocytic infiltrate around the isthmus and infundibular region of the hair follicles, dermal fibrosis, 14 hairs per 4 mm punch.



Clinical Course
On presentation to Duke in June 2008, the patient was being treated with clobetasol solution. At her initial appointment she was started on dutasteride, 0.5 mg daily for two weeks then 0.5 mg weekly. At six month follow up, she was noted to have regrowth at the frontal hairline, measured as a 0.7 cm decreased distance from the nasal tip to the frontal hairline. In addition, there was no progression of hair loss at the temporal hairline. In August 2009, minoxidil 0.5% solution twice daily was added.

Discussion
Frontal fibrosing alopecia (FFA) is a scarring alopecia characterized by progressive recession of the fronto-temporal hairline in a band-like distribution, with or without loss of the eyebrows.[2,4,5] It was first described by Kisser in 1994. A minority of patients also report hair loss in other areas, including the extremities, axillae and pubic areas. Perifollicular erythema is frequently seen. FFA occurs almost exclusively in postmenopausal women, although it has been reported in both premenopausal women and men. This condition is currently considered a variant of lichen planopilaris; histological there is a similar lymphocytic infiltrate and many patients have a concurrent or prior history of cutaneous or mucosal lichen planus lesions. The course is variable and often results in spontaneous stabilization, but not reversal of the process.

Histologically, FFA is characterized by a lymphocytic infiltrate around the infundibulum and isthmus of affected hair follicles and follicular drop-out.[2] A concentric, lamellar fibrosis is characteristic. Vellus and intermediate follicles are most commonly affected.

The etiology of FFA is unknown. However, an androgen related component is hypothesized due to the high frequency in postmenopausal women and clinical response in some to antiandrogens. Finasteride, a type I 5α-reductase inhibitor was shown to halt progression of FFA in four of eight postmenopausal women treated with this medication.[6] More recently dutasteride, a type I & II 5α-reductase inhibitor, has been used as therapy in 13 patients with FFA.[1] Six patients showed complete arrest of the disease and two had clinical improvement. Compared to finasteride, this agent reduces DHT about 95% compared to about 67% with finasteride in men with MPHL and has led to greater regrowth in MPHL.[3] Other therapies that have been tried in FFA include topical and systemic steroids, minoxidil, hydroxychloroquine and calcineurin inhibitors.[1,5] When minoxidil was used in combination with finasteride, progression of alopecia was halted in half of patients. One patient treated with dutasteride and pimecrolimus showed moderate improvement of her scalp alopecia and significant regrowth of the eyebrows and axillae.[1] A recent study showed that hydroxychloroquine is effective in reducing signs and symptoms of FFA and has maximal benefit within the first 6 months of treatment.[4]

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Case #15
Lichen Planopilaris

Resident Physician
Elizabeth Naylor, M.D.

Attending Physician
Elise Olsen, M.D.

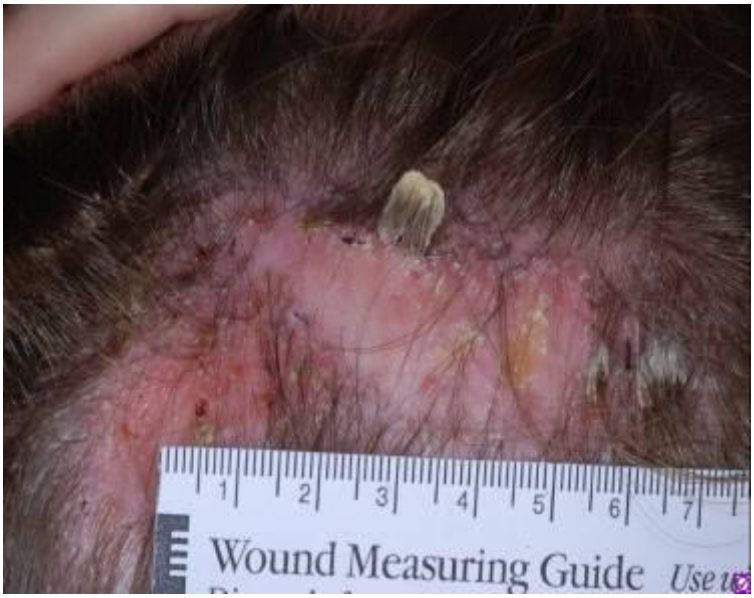
Sites of Interest
Scalp.

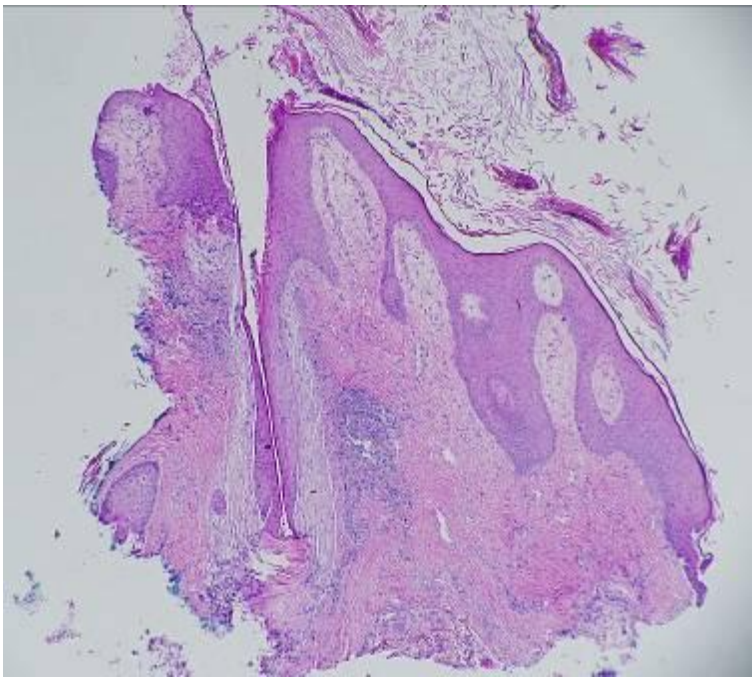
History
A 40 y/o female with 5 year history of hair loss associated with pruritus, scale, and inflammation is presented. The patient's medical history is significant for psoriasis.

Clinical Findings
There is an irregularly shaped area of atrichia on her left frontoparietal scalp. The skin is bound down and depigmented. There are small islands where the hair follicles are intact within this area of hair loss. There is pronounced perifollicular erythema involving the hair follicles within the alopecic patch as well as surrounding it. There is also thick scaling around the area involved. Her eyelashes, eyebrows, and body hair are intact. No nail abnormalities are noted.

Histopathology
Biopsy reveals neutrophilic crust, epidermal acanthosis with hypergranulosis, and focal perifollicular neutrophils. Bacteria and neutrophils are visualized within the stratum corneum and superficial follicles. The follicles in the dermis demonstrate perifollicular scarring with thinning of the follicular wall.

Clinical Course
The patient has been treated in the past with topical and intralesional steroids as well as methotrexate 25 mg PO weekly for 14 months without significant improvement. She was enrolled in a clinical trial using Raptiva (efalizumab) but discontinued after 15 weeks due to worsening of her psoriasis. The patient is currently being treated with daily application of clobetasol scalp solution and dermasmoothe scalp oil.





Discussion

Lichen planopilaris(LPP) is an inflammatory, cicatricial alopecia more commonly seen in women. Diagnosis requires histopathologic evaluation. Patients may have associated clinical findings such as skin, mucous membrane and nail findings consistent with lichen planus. Treatment is a challenge. High dose topical steroids and intralesional steroid injections are often tried initially. Small retrospective reviews of tetracycline antibiotics used to treat small numbers of patients have not shown dramatic results. Brief use of oral steroids commonly results in relapse after discontinuation.

Recent publications have drawn attention to the potential for improvement with hydroxychloroquine[3] and mycophenolate mofetil[4]. The new Lichen Planopilaris Activity Index(LPPAI), used in both of the above studies, may help to standardize future studies evaluating treatment results in LPP. On retrospective review of 12 patients treated with mycophenolate mofetil, 5 had 85% or more decrease in LPPAI; another 5 patients had a 25-85% decrease in LPPAI[4]. Retrospective review of 40 patients with LPP and frontal fibrosing alopecia treated with hydroxychloroquine revealed a decrease in LPPAI in 83% of patients at one year. A recent case report[5] highlights the promise of pioglitazone hydrochloride, a PPAR-γ agonist, with sustained resolution of inflammation in a patient who had previously not responded to prednisone, hydroxychloroquine, or mycophenolate mofetil. Use of PPAR-γ agonists is logical given that PPAR-γ is known to regulate inflammation and to be downregulated in LPP.

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Case # 16
Uncombable Hair Syndrome

Resident Physician
Holly Bartell, M.D.

Attending Physician
Neil Prose, M.D.

Sites of Interest
Scalp hair.

History
Two sisters, age 2 and 3 years old, presented with a hair abnormality that became evident around 3 months of age. From 3 months of age on, their hair was difficult to manage, but grew at a relatively normal rate. There were no reported teeth or nail abnormalities and they were developing normally, reaching all expected developmental milestones. There was no known family member with similar hair abnormalities. Previous evaluation included a cardiovascular exam and both patients had normal echocardiograms.

Clinical Findings
The girls behaved in an age appropriate manner and appeared well developed and had normal facial features. The youngest had brownish straw colored hair and older sister had lighter blondish colored hair. Both patients had a lusterless appearance to the scalp hair and it appeared frizzy. The body hair, eyelashes, eyebrows were normal. General physical examinations were unremarkable, and there were no associated abnormalities of the skin, nails, or teeth.

Laboratory/Studies
Electron microscopy pending. In example shown nearly all hairs showed longitudinal, canal-like depressions of the shaft, and many were triangular in cross section. (Figures 2 and 3)

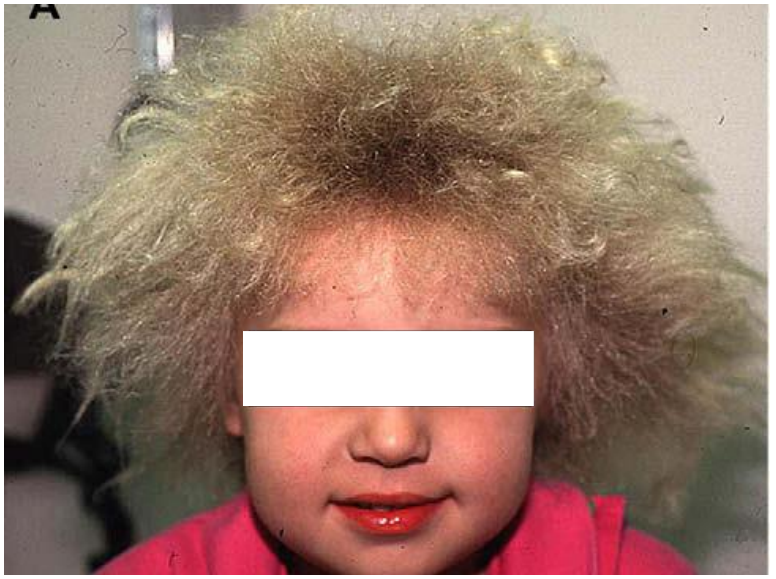

Fig 1. Representative Photo of Uncombable Hair (1)

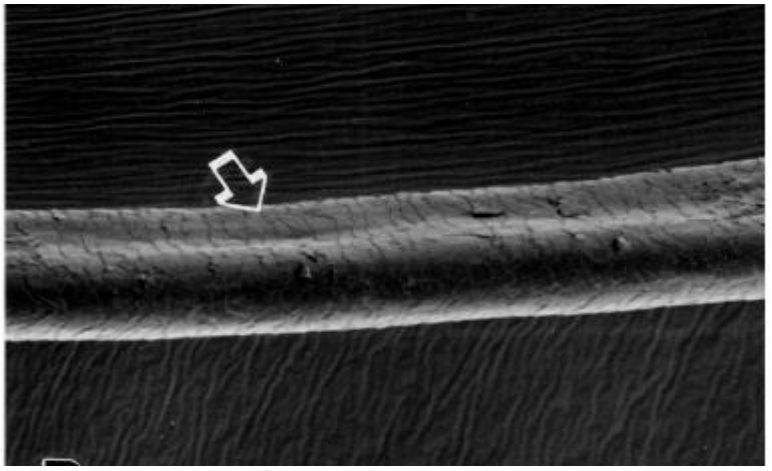
Fig 2. Scanning EM – Cannicular Grove (5)

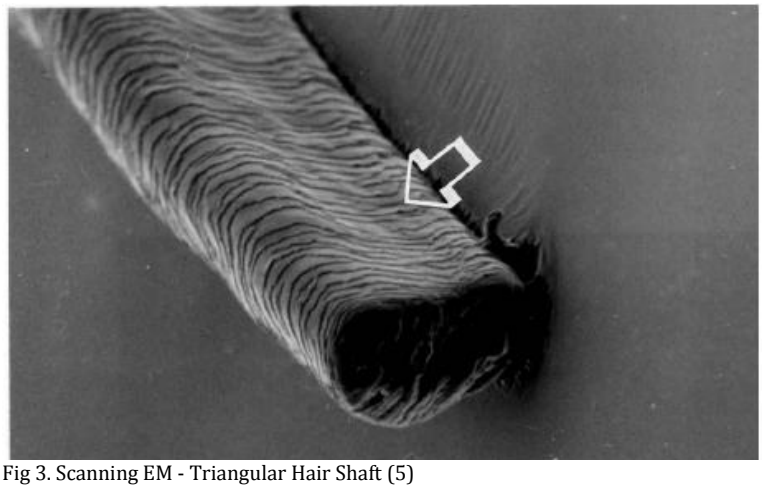
Fig 3. Scanning EM - Triangular Hair Shaft (5)

Discussion

The initial description of uncombable hair syndrome in the early 1970's described it as cheveux incoiffables and spun-glass hair. Since then, uncombable hair syndrome, UHS, or *pili trianguli et canaliculi* has become a readily identifiable condition with classic clinical features.

The hair is spangled or glistening in appearance and is characterized as being frizzy, standing away from the scalp and unable to be combed flat. Interestingly, only scalp hair is affected, while eyelash, eyebrow, facial, and body hairs are normal. Alterations in the combability of the hair usually present during the first year of life with the first terminal hair growth or following a period of normal hair growth. The affected child's hair also becomes drier, lighter in color (silvery-blond to light brown), curlier, and progressively uncombable. There is no decrease in the quantity of hair, and the hair is not fragile or brittle. Hair growth rates can be decreased or normal. Typically, the entire scalp hair is involved; however, certain individuals have a localized form. There is no gender predilection, with both males and females equally affected. Autosomal dominant and recessive forms, as well as sporadic cases, have been described in the literature and abnormal hair can been shown in unaffected relatives of individuals with UHS. Spontaneous improvement in combability, to a certain degree, may occur over time. Routine light microscopic examination demonstrates lightly pigmented hairs with occasional twists at irregular intervals. Polarized light microscopic evaluation may be helpful by showing a dark longitudinal band along the center of the hair shaft. Scanning electron microscopy provides the optimal evaluation of uncombable hairs for triangular cross-sectional shapes with indentation and longitudinal grooving and flattening of the hair surfaces.

The finding of uncombable hair is usually an isolated finding and not associated with physical, neurologic, or mental abnormalities. However, other conditions and syndromes have been associated with *pili trianguli et canaliculi*. Longitudinal grooving of the hair shafts has been seen with ectodermal dysplasia, retinal dysplasia, pigmentary dystrophy, juvenile cataract, digit abnormalities, dental anomalies, phalangoepiphyseal dysplasia, woolly hair nevus, ichthyosis vulgaris, Marie Unna hypotrichosis, acquired progressive hair kinking, drug-induced kinking, uremia, *pili torti*, eczema, progressive alopecia areata, hamartomas, nail abnormalities, lichen sclerosus and monilethrix. Specifically, thorough examination of the skin, nails, eccrine glands, and teeth in addition to the hair should be performed. Physical signs that may be evident depending on the disorder include: dysmorphic facial features; dry, hypopigmented skin; reduced sweating, tearing, and/or salivation; dystrophic nails; and dental anomalies, such as malformed or absent teeth.

No proven therapy exists for pili trianguli et canaliculi. Typically, improvement occurs over time. A limited number of children have been treated with biotin which has shown mixed results.

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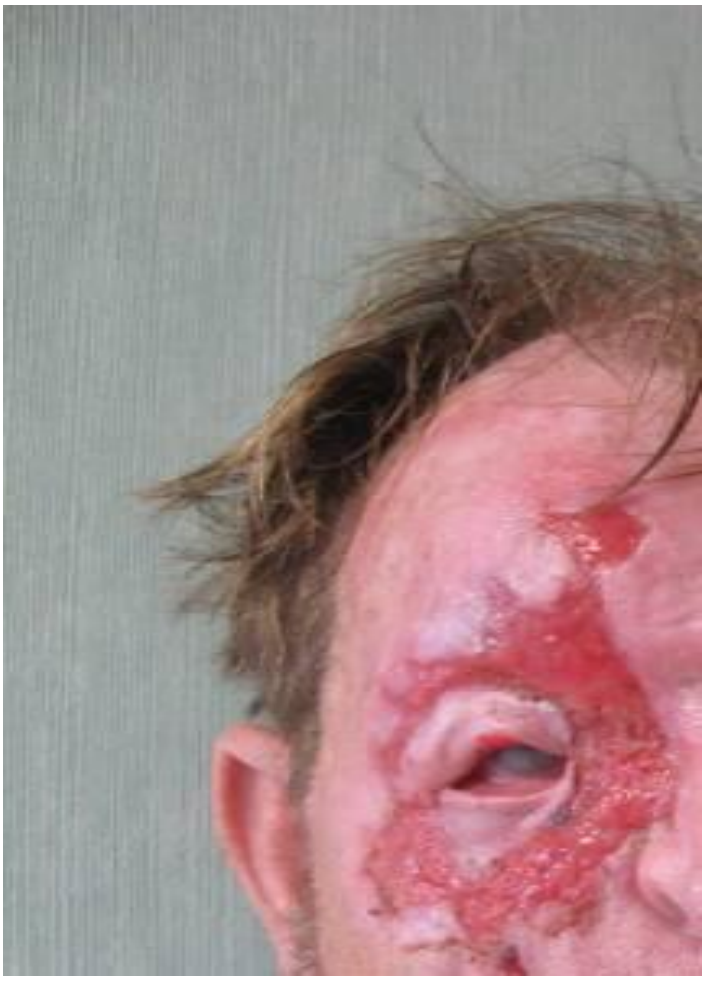
Case # 17
Trigeminal Trophic Syndrome

Resident Physician
Sarah Rodgers, M.D.

Attending Physician
Caroline Rao, M.D.

Sites of Interest
Face.

History
This patient is a 61 year-old male with a history of right-sided trigeminal neuralgia since the early 1980's who was diagnosed with trigeminal trophic syndrome. The patient has an extensive surgical history including six craniotomies.
Following an episode of right pre-septal periorbital cellulitis in 2005, he developed poorly healing ulcers on the right cheek extending to the scalp. This progressed with subsequent scarring and contraction. He denies manipulation of the skin. He has Type 2 diabetes mellitus and hepatitis C.



Clinical Findings
Broad irregular well-demarcated ulcer with granulation tissue encompassing the right malar cheek, periorbital and right lower forehead skin. Face is asymmetric with elevation of R nasal ala, mouth, and cheek, and depression of the right forehead. Contraction of R upper and lower eyelids, and corneal scar.

Histopathology
Right cheek biopsy in 2005 showed ulcer and superficial bacterial infection.

Clinical Course
The wounds have been complicated by MRSA and HSV superinfections. The ulcers and pain have never fully resolved despite antimicrobials, neuroleptics and extensive pain management. He has been followed closely by plastic surgery and dermatology with progression of this disease. He was recently provided with a prosthetic device to wear as a covering over the affected right face.

Discussion

Trigeminal trophic syndrome is a rare complication that occurs after peripheral damage to the trigeminal nerve such as ablation for trigeminal neuralgia or stroke. It consists of the triad of loss of sensation, paresthesias, and ulcerations in the trigeminal nerve distribution. It is believed that patients, often unknowingly, self-manipulate the skin, exacerbating ulceration. The nasal ala is the most frequently affected site at the junction of the first and second divisions of the trigeminal nerve, though other facial and scalp sites may be involved. There is often characteristic scarring with contracture elevating the lip and nasal ala. Treatment is difficult and education about manipulation is key. Carbamazepine is considered the first line treatment and may help by reducing both paresthesias and behavioral factors influencing manipulation. Other reported successful pharmacological treatments include pimozide, amitryptyline, and diazepam. Swan et al reported a case refractory to pharmacological treatment and several surgical flaps that was successfully treated with a custom-made facemask. With full compliance that patient had complete healing within 3 months. Our patient has noted improvement with his new facemask custom-made by anaplastology at our hospital.

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Case #18
Progressive Macular Hypomelanosis

Resident Physician
Elizabeth Naylor, M.D.

Attending Physician
Neil Prose, M.D.

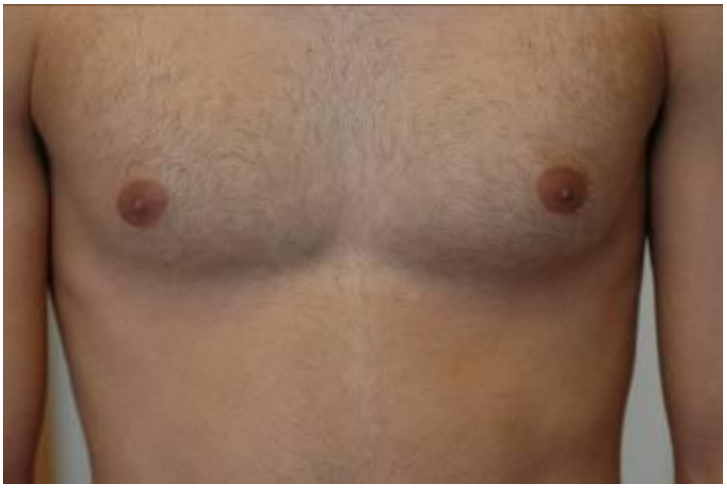
Sites of Interest
Trunk.

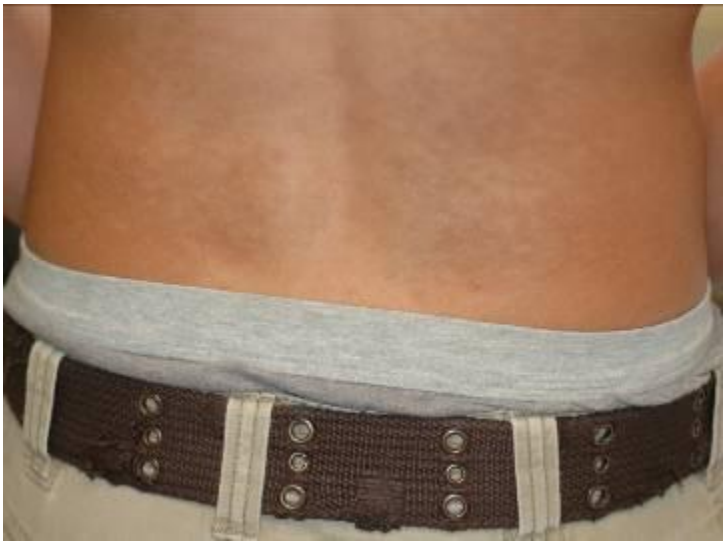
History
The patient is an 18 year old with 2 year history of asymptomatic scaly white areas on the trunk and upper extremities. The rash is most apparent during the summer months.

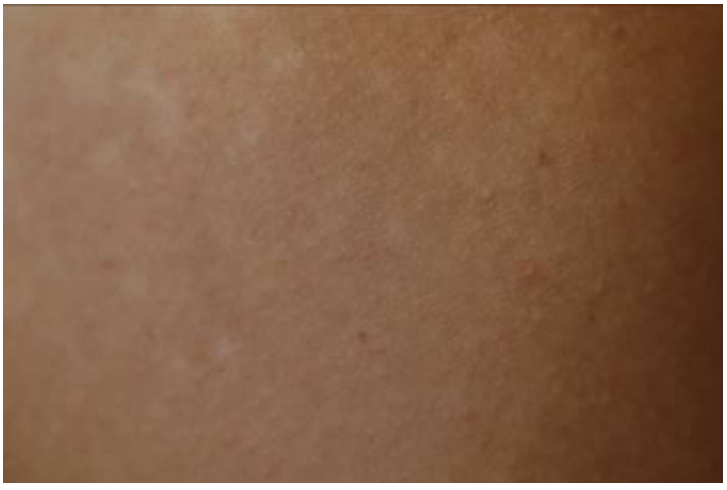
Clinical Findings
Poorly demarcated discrete and confluent hypopigmented macules are present on the trunk and, to a lesser extent, the upper extremities.

Histopathology
There is mild perivascular lymphocytic infiltrate with exocytosis in a background of epidermal spongiosis. Papillary dermal edema and vascular ectasia are noted. No significant lymphocytic atypia is seen. Very focal melanin incontinence is identified. The PAS exhibits isolated yeasts in the stratum corneum.

Clinical Course
The patient's rash resolved completely with daily use of Benzaclin, clindamycin 1% lotion, and benzoyl peroxide 10% wash. After recurrence of the rash, the patient was switched to erythromycin and obtained a near complete response.







Discussion

Progressive Macular Hypomelanosis (PMH) was first described by Guillet in the 1980s.[6] Over the years, this entity has also been referred to as cutis trunci variata, creole dyschromia, idiopathic multiple large-macule hypomelanosis, and nummular and confluent hypomelanosis of the trunk.

The disease is primarily limited to the trunk and presents in adolescents and young adults of all races with no preceding pruritus, pain, or inflammation. The differential includes tinea versicolor, pityriasis alba, and post inflammatory hypopigmentation. Proprionibacterium bacteria have been thought to play a role in this disease, possible by secreting an unknown hypopigmenting factor.[1] Red follicular fluorescence has been noted on Wood's lamp examination of lesional skin in patients with PMH.[5] Characteristic pathology reveals decreased pigment, a normal appearing dermis, and gram positive bacteria in the pilosebaceous ducts of affected skin. Electron microscopy shows that lesional skin has fewer mature (stage III/IV) melanosomes.[2]

Treatment options include benzoyl peroxide, topical clindamycin, doxycycline, PUVA, and UVB. The largest treatment study to date involved a left-right comparison of 45 patients who were treated for 14 weeks with benzoyl peroxide 5% gel and clindamycin 1% lotion (one side) and fluticasone 0.05% cream (remaining side). Both areas were also treated with UVA.[4] The authors found the antimicrobial regimen led to better repigmentation than treatment with fluticasone.

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Case # 19

Generalized Hypopigmentation and durable response of Metastatic Melanoma after Interleukin-2 Therapy

Resident Physician
Bishr Al Dabagh, M.D.

Medical Student
Amanda Raymond

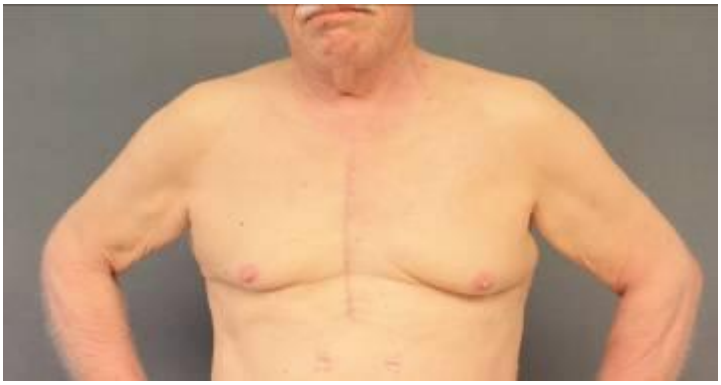
Attending Physician
Kelly Nelson, M.D.

Sites of Interest
Generalized.

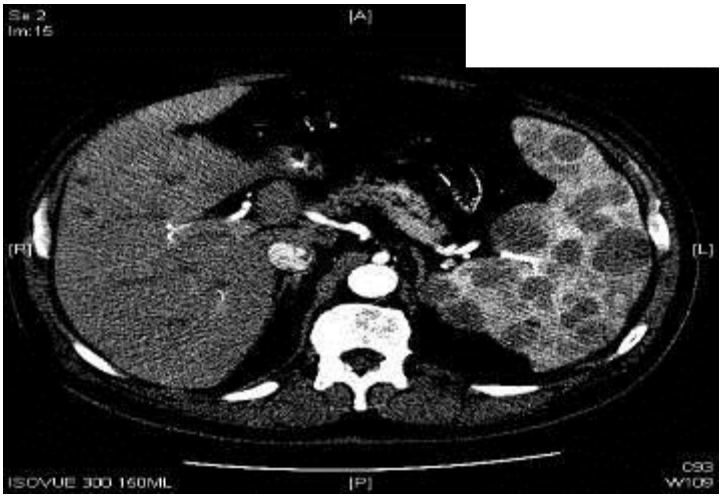
History
WH is a 74 year old Caucasian gentleman with a history of invasive melanoma (Breslow depth unknown) to the left upper back, diagnosed in 2003. Three months following wide local excision, the patient developed symptomatic lymphadenopathy of the left axilla; axillary dissection revealed 9/10 nodes positive for metastatic disease. Staging scans performed thereafter demonstrated multiple hepatic and splenic low-attenuation lesions consistent with metastases.

Following two one-week courses of interleukin-2, complicated by acute renal failure and hypotension necessitating pressor support, the patient demonstrated gradual but complete resolution of all previously documented hepatic and splenic lesions over the following three years. Along the same time course, he noted gradual decreased pigmentation of his skin and hair. No coinciding visual changes were noted.

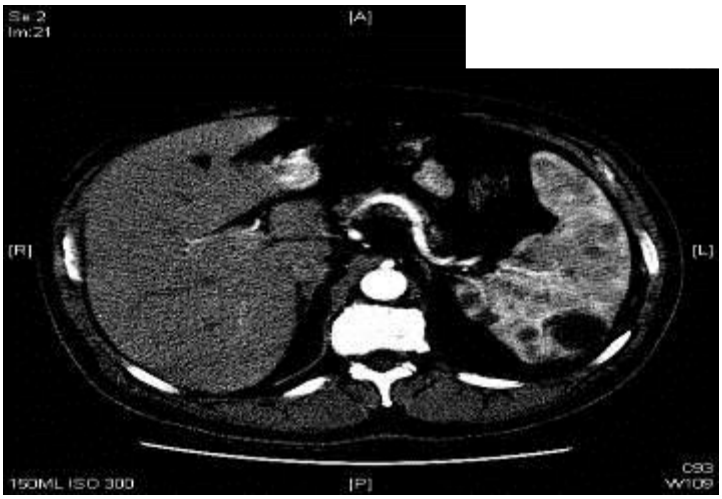
Clinical Findings
Significant hypopigmentation of the hair and skin when compared to pictures from 2004 (pre- interleukin therapy).



Pre-treatment



Post-treatment



Laboratory/Studies
2/20/04: a CT scan revealed lymphadenopathy in the left axilla, as well as multiple hypodense areas in the spleen and liver.
2/25/04: left axillary dissection was performed, pathology showed 9 of 10 positive lymph nodes with metastatic melanoma and extracapsular extension.
2/26/04: restaging studies were obtained. Again, multiple hypodense masses were noted in the liver as well as the spleen.
6/21/2004: brain MRI- negative for metastatic disease. Multiple studies at regular intervals have been negative for metastatic disease.
5/24/2005: CT scan showed significant decrease in size of multiple hepatic and splenic metastatic lesions, compatible with a response to therapy.
8/22/2007: CT scan without any evidence of metastatic disease. Multiple interval scans have been stable to date.

Clinical Course
WH has had a durable response to chemotherapy with two courses of interleukin-2; following the chemotherapy he has had hypopigmentation of his skin and hair. He has been in remission since 2004. In 2007 he had abdominal aortic aneurysm repair. In April, 2010 he had an MI and underwent triple bypass surgery.

Discussion
Hypopigmention following chemotherapy for melanoma may be the result of an immune response against antigens shared by melanoma cells and regular melanocytes. Antigens found in both tumor cells (melanoma)and their normal cellular counterpart (melanocytes) are known as melanocyte differentiation antigens. The depigmentation is the result of melanocyte destruction. Biopsies of skin examined with silver nitrate staining to detect melanin and by transmission electron microscopy confirm the absence of melanocytes. However because melanocytes transfer melanin to keratinocytes (which may take days to weeks to slough), there may be a delay between depigmentation and melanocyte destruction. Diffuse erythema during IL-2 administration may mask the local inflammatory response during melanocyte destruction. Patients who respond to IL-2 with a durable response are more likely to experience depigmentation than patients who do not respond.

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Case # 20
Generalized Severe Morphea

Resident Physician
Kristen Thomas, M.D.

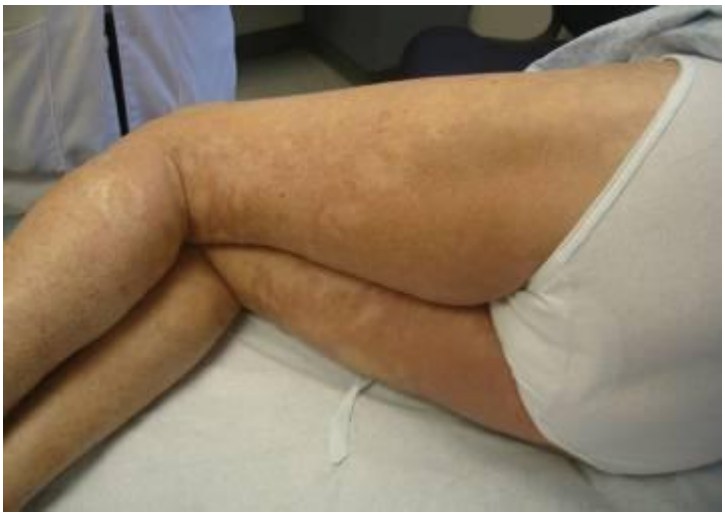
Attending Physician
Clare Pipkin, M.D.

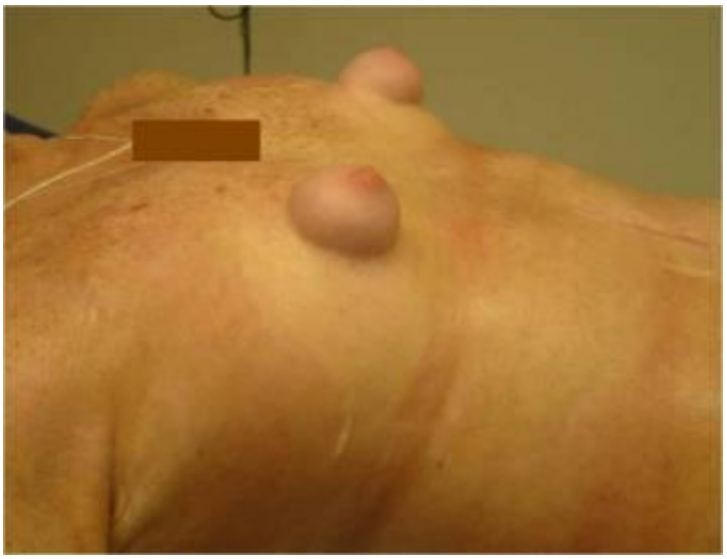
Sites of Interest
Trunk and extremities.

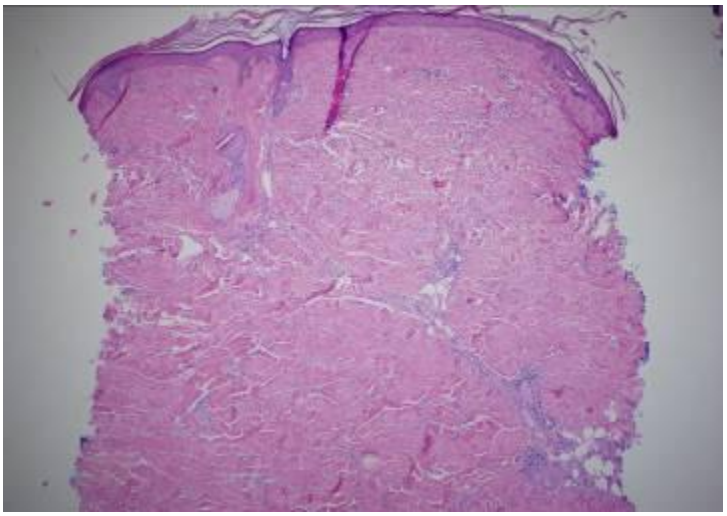
History
66 y/o WF with onset of skin thickening and pruritus on her abdomen and back in July 2009 that has since continued to spread to her chest, extremities, and buttocks. The affected areas have become thicker and tighter with time, and the skin is extremely sensitive to touch. She denies recent dietary supplements, including L-tryptophan, and denies recent MRIs with contrast. She has undergone multiple abdominal surgeries in the past and developed a chronic abdominal wound post-operatively in July 2009. She has used triamcinolone as well as over-the-counter lotions for pruritus.

Systemically, she denies heartburn or dysphagia, but occasionally feels like food gets stuck in her throat. She has not had problems with diarrhea or loose stools. She denies alopecia, ulcerations in her nose and mouth, dry eyes or dry mouth. She denies Raynaud's symptoms but reports sensitivity to cold. She has chronic dyspnea and has a smoking history. She reports no changes in her chronic joint symptoms associated with her history of osteoarthritis.

Clinical Findings
Diffuse indurated plaques primarily involving the upper chest and upper back but extending onto the abdomen; proximal arms and legs are more severely affected that distal. There are no periungual telangiectasias; the face is relatively spared.







Laboratory/Studies
ANA positive 1:160, speckled pattern; negative/normal rheumatoid factor, ENA panel, SCL70 and centromere antibody, SPEP. PFTs and CT Chest revealed emphysema and no evidence of pulmonary fibrosis. ECHO was WNL, and she is up to date on cancer screening (colonoscopy, mammogram).

Histopathology
Full thickness sclerosis of the dermis, consistent with morphea. There is an infiltrate of lymphocytes admixed with plasma cells in the fibrous trabeculae of the subcutaneous fat.

Clinical Course
She initially was given plaquenil 200 mg twice a day but could not tolerate it due to side effects. She was then initiated on Methotrexate 15 mg weekly in March 2010. She did undergo one series of three infusions of methylprednisolone 1000 mg, but due to enlargement of the abdominal wound after treatment, she discontinued this therapy. She continues to have persistent disease on her breasts and extremities, though she has had some skin softening of her back and abdomen. For the skin burning, she is taking gabapentin 800 mg three times a day with some relief. Her insurance has denied coverage of imatinib, and due to logistics, she is unable to pursue phototherapy.

Discussion
Morphea, or localized scleroderma, is a disease of fibroblast proliferation and excessive accumulation of extracellular matrix proteins, mainly collagen, in the dermis, subcutaneous tissue, or both. It is classified into plaque, generalized, linear, or deep subtypes. It lacks sclerodactyly, Raynaud phenomenon, nailfold capillary changes, telangiectasias, or internal organ involvement, which are features of systemic sclerosis. Morphea can present with fever, lymphadenopathy, arthralgias, CNS involvement, dysphagia, or dyspnea. Abnormal lab findings may include eosinophilia, polyclonal gammopathy, or a positive ANA. The pathogenesis is unknown, but an autoimmune etiology is supported by the presence of auto-antibodies.

Patients with generalized or deep morphea typically require more aggressive therapy. Mixed results have been found with calcitriol, oral retinoids, IFN gamma, hydroxychloroquine, mycophenolate mofetil, and cyclosporine. Successful treatment of severe and/or rapidly progressive morphea with systemic corticosteroids (eg, high-dose intravenous methylprednisolone in monthly pulses or oral prednisone at various intervals) in combination with weekly low-dose methotrexate has been reported in several case series. UVA1 has produced marked clinical improvement of morphea lesions due to its anti-inflammatory effects on fibroblast functioning. Because UVA1 wavelengths penetrate deeper into the dermis, this modality is particularly effective in the treatment of morphea. Few cases have shown benefit using extracorporeal photopheresis, particularly for generalized deep morphea. There may also be a role for imatinib, with its ability to inhibit the activation of fibroblasts by TGF-β and the platelet-derived growth factor receptor (PDGFR). In addition, a recent case report demonstrated a significant reduction in clinical sclerosis and dyschromia on the trunk and extremities of a woman with recalcitrant generalized morphea after four infusions of infliximab.

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Case # 21
Dominant Dystrophic Epidermolysis Bullosa

Resident Physician
Tania Peters, M.D.

Attending Physician
Russell Hall, M.D.

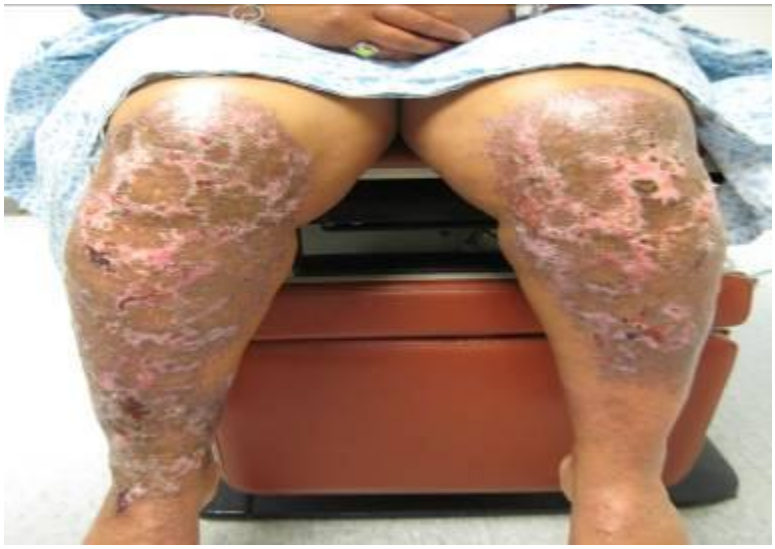
Sites of Interest
Bilateral elbows, knees, hands and feet.

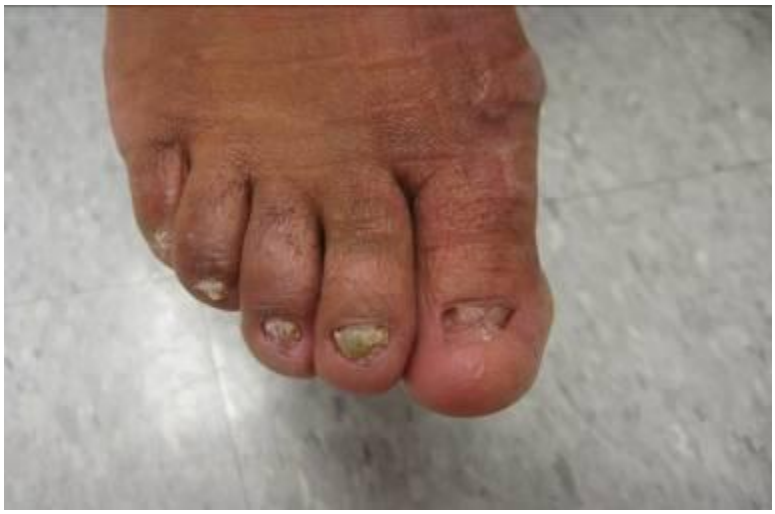
History
29y/o AAF with history of dominant dystrophic epidermolysis bullosa (DDEB) who moved to the Durham area in August 2006. KMG was diagnosed with DDEB soon after birth, when the tape on her umbilical cord and attempts at feeding caused erosions.

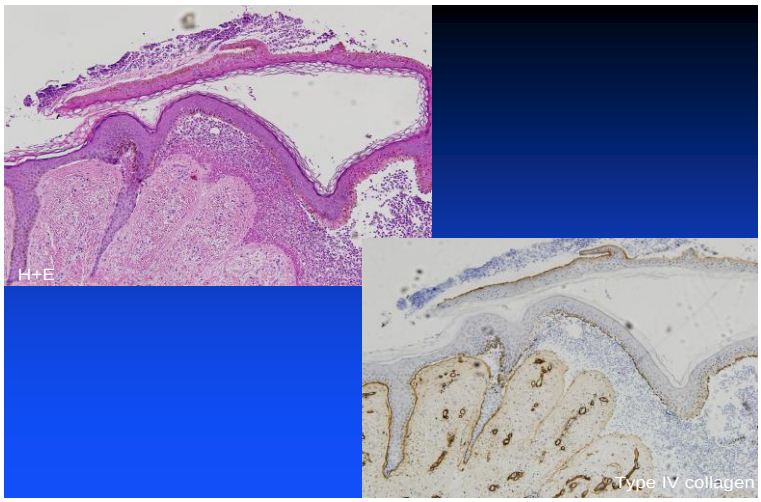
Family Hx
Grandfather, father, aunt, and cousin with DDEB.

Clinical Findings
Scarring on the upper forehead, upper back, upper chest, and bilateral hands particularly at the fingertips. On the bilateral anterior lower extremities, she has plaques extending from the knees to the ankles with overlying erosions. There is trace edema of the bilateral lower extremities and toenail dystrophy.

Pathology
Subepidermal bulla, with detachment and partial necrosis of overlying epidermis. Bulla cavity contained numerous neutrophils, fibrin deposition on the base and cell debris. Immunohistochemical staining for Collagen IV found basement membrane present on the roof of the blister with the floor of the blister showing naked dermis with overlying fibrin deposition.







Clinical Course
Her skin disease has been treated with TAC 0.1% and Zyrtec 10mg PO qHS for pruritus, Mupirocin and Bactroban ointment for open areas, and a standing prescription for Keflex 250mg PO QID x 10days should infection occur. She was also treated with Unna boots for lower extremity swelling, however, she was unable to tolerate this treatment secondary to burning and irritation of the posterior calves. Her skin disease is currently stable and she carefully watches for signs of infection and new skin lesions. Despite new erosions that occur and past scarring, she has been able to live a relatively uninhibited life teaching and having her first child in 2006 by C-section.

Discussion
Dominant dystrophic epidermolysis bullosa (DDEB) is a subtype of one of the three types of epidermolysis bullosa, which include epidermolytic (EB simplex), lucidolytic (junctional EB), and dermolytic (dystrophic EB (DEB)). According to the National EB Registry in 2007, the incidence of all types of DEB was 6.5 per million live births in the US population. Mild forms of DDEB were estimated at 2.9 per million, however, this was likely an underrepresentation.

Clinically, the blistering in DDEB is often mild and limited to hands, feet, knees, and elbows, but nonetheless heals with scarring. A common finding is dystrophic nails, especially toenails. This may be the only manifestation of DDEB. Improvement in the blistering in DDEB is often seen as patients age, possibly as a result of decreased physical activity.

DDEB is caused by mutations in the type VII collagen gene (COL7A1). The mutations commonly involve glycine substitutions within the triple helix of COL7A1. The level of expression of COL7A1 has an inverse correlation with clinical severity. Not all glycine substitution mutations are dominant and at this time, it is unclear why some glycine substitutions are dominant while others have no clinical phenotype in the heterozygous state. The position of the mutation within the collagenous domain of COL7A1, and the resulting degree of abnormal folding, may influence the severity of the phenotype.

Establishing a diagnosis of DDEB requires transmission electron microscopy (EM) or immunofluorescent (IF) antibody/antigen studies. Ultrastuctural findings in DDEB, resulting from the mutations in type VII collagen, include normal or decreased numbers of anchoring fibrils in the sub-lamina densa. In IF studies, staining of collagen VII using antibodies is abnormal or absent. In mild cases of DEB, staining for collagen VII may appear normal, but cleavage planes in the form of vesicles or microvesicles can be seen below the lamina densa and below the collagen VII staining.

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Case # 22
Cutaneous Langerhans Cell Histiocytosis (LCH)

Resident Physician
Tania Peters, M.D.

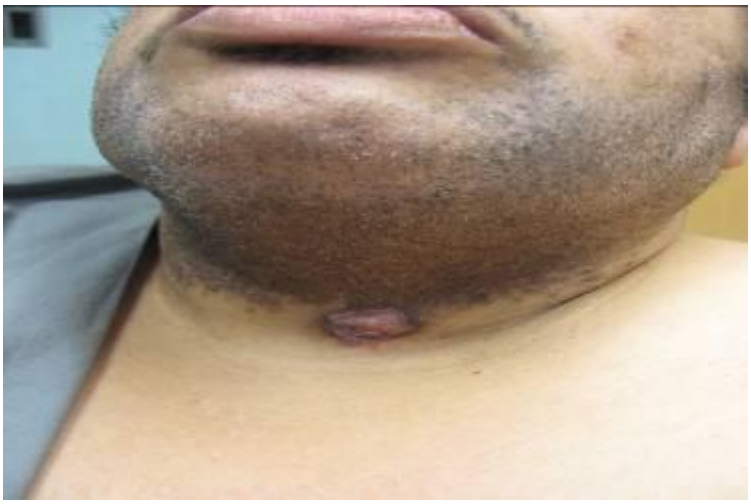
Attending Physician
Navjeet Sidhu-Malik, M.D.

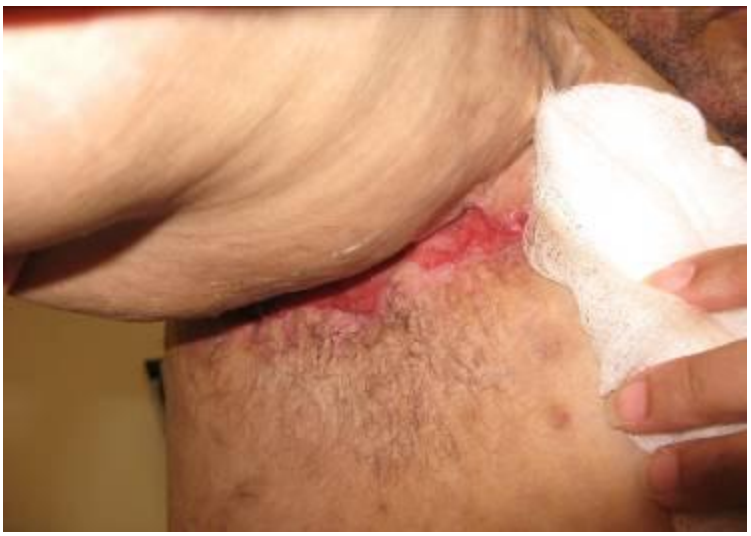
Sites of Interest
Anterior neck, axilla.

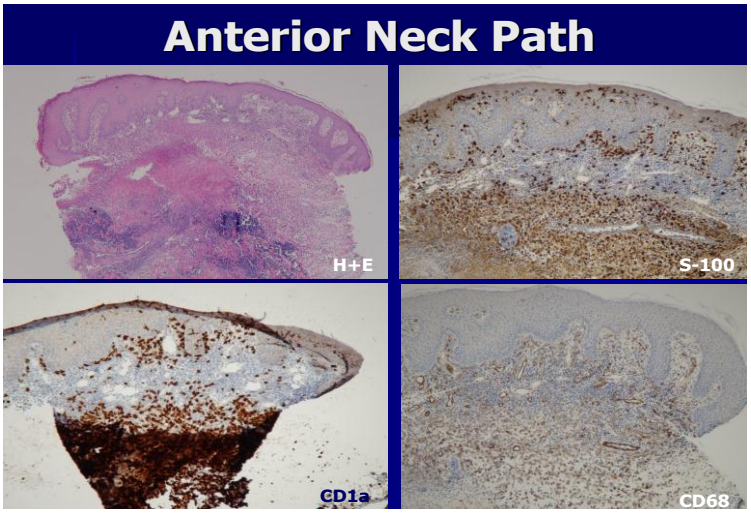
History
41y/o AAM w/ 10yr h/o recurrent, persistent, axillary, inguinal and gluteal fold and perirectal ulcerations carrying a diagnosis of hidradenitis suppurativa for as many years. He presented w/ a new painful ulcerated nodule May 2010, present for 9 months, treated w/o improvement w/ Bacitracin and TAC ointment. Biopsy c/w LCH. Follow-up biopsy of axilla and restaining of prior biopsies c/w LCH. CXR, Chest CT, bone scan, skeletal survey, u/a, and bone marrow biopsy performed. All wnl.

Clinical Findings
Round ulcer on anterior neck w/ undermined borders and fibrinous granulation tissue at base. Large ulcerations bilateral axilla. Fibrous scar tissue gluteal cleft and inguinal areas. Ulceration present at inguinal areas.

Pathology
July 2008 chronic buttock wound - acute ulcer w/ cellulitis, positive for candida. April 2009 panniculus - superficial ulcerations. May 10, 2010 anterior neck ulcer and May 24, 2010 left axilla – LCH w/ immunohistochemical stains positive for CD1a and S100, negative for CD68. June 14, 2010 immunohistochemical stains of prior biopsy specimen performed w/ same staining pattern.







Clinical Course
While carrying the diagnosis of hidradenitis suppurativa, pt was treated w/ courses of prednisone, cyclosporine, accutane, entanercept, adalimumab, infliximab, numerous antibiotic regimens, and surgical resections at bilateral axillary, inguinal, and gluteal folds, and perirectal area and is s/p diverting colostomy. Once diagnosis of LCH was made, his treatment course has included methotrexate.

Discussion
Langerhans cell histiocytosis (LCH) is characterized by a clonal proliferation of pathologic cells in single or multiple organs. It is a rare disease, thought to be of reactive or neoplastic origin. The reported incidence of LCH in adults is 1 to 2 cases per million. 1% of patients w/ LCH have an affected relative. The skin is the most involved organ after bone and up to 50% of pts w/ single or multi-organ LCH initially present w/ cutaneous symptoms. Papulopustular, seborrheic-like, xanthomatous, purpuric, hemorrhagic, ulcerative, and pigmented lesions have been reported. Common sites of involvement include the scalp, seborrheic areas of face, trunk, body folds (esp. inguinal region), and genitals (esp. vulva). Lesions may be disseminated or localized, with the latter most often being periorifical or intertriginous. LCH often goes misdiagnosed in adults given the uncommonness of the disease and the fact that it can mimic many other conditions. Classically, LCH was confirmed by presence of Birbeck granules on EM or CD1a on immunohistochemistry. Birbeck granules can now also be demonstrated in LCs by immunohistochemical staining of Langerin (CD207), a novel C-type lectin, specific to cell surface and cytoplasm of LCs, which induces the formation of Birbeck granules.

According to the guidelines of the Histiocyte Society, LCH has been classified into single-system disease, which is divided into single site (unifocal bone, skin or LN) and multiple site (multifocal), and multisystem disease, which is involvement of two or more organs at diagnosis w/ or w/o organ dysfunction. Multisystem disease is divided into "low risk" and "risk." "Low risk" has a good prognosis and accounts for approximately 20% of patients, and includes patients with no "risk" organs. "Risk" patients have involvement of one or more of the following organs; liver, lungs, spleen, or haematopoetic system, and has a high mortality. Isolated skin LCH has a good prognosis, w/ ~50% of patients having regression w/i months. However, poor response to treatment and recurrence may allow pts to progress to the disseminated form in some cases. As a result, in skin-limited LCH, close observation for prolonged periods is mandatory. Surgical excision is the treatment of choice for isolated skin nodules. Topical steroids are a first line treatment, however, recurrence after treatment is common. In cases of severe skin LCH, topical nitrogen mustard or PUVA has been used. Topical tacrolimus and imiquimod are also anecdotally effective. Response of cutaneous and ano-genital LCH to thalidomide and interferon has been reported in adults and mild systemic chemo (prednisone w/ or w/o vinblastine) is recommended in widespread disease. Successful treatment with prolonged PO etoposide or methotrexate has also been reported in adults.

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Case # 23
Monilethrix

Resident Physician
Tania Peters, M.D.

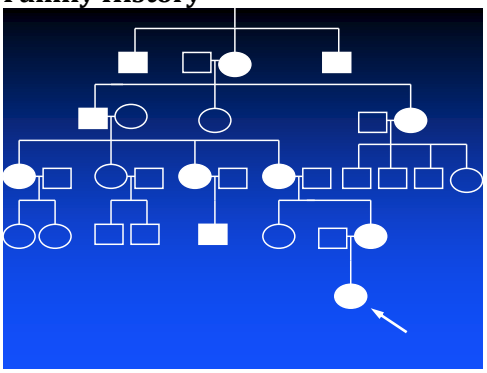
Attending Physician
Neil Prose, M.D.

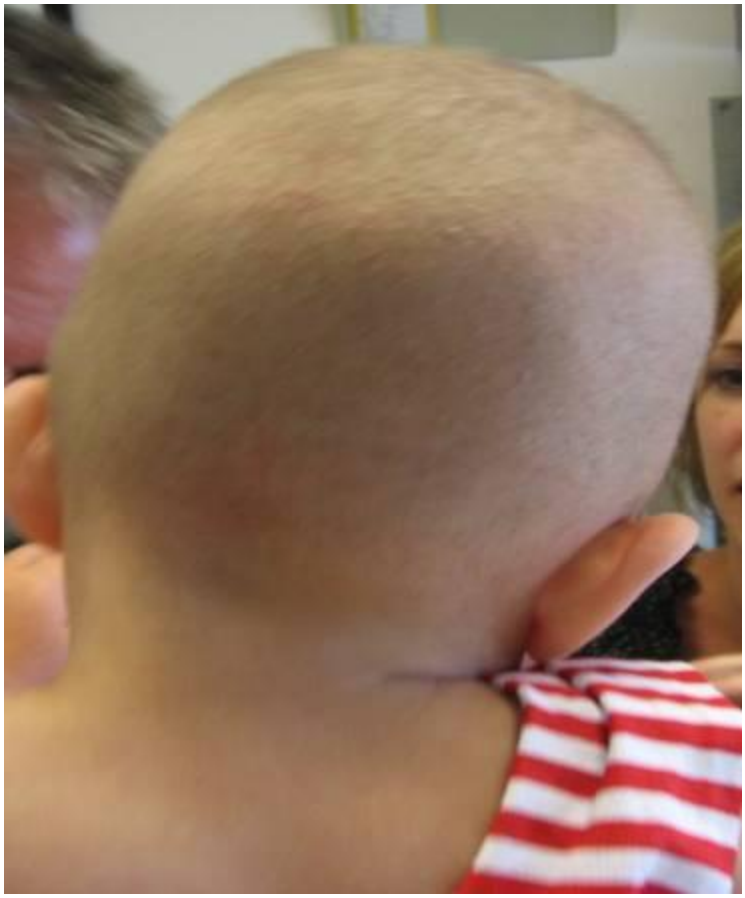
Sites of Interest
Scalp.

History
2y/o developmentally normal CF with no hair abnormalities appreciated at birth, but complete alopecia within the first 3-4months of life. She has had some short, sparse hair re-growth over the scalp.

Clinical Findings
Well-appearing, alert infant. Light brown short hairs, 5-8mm in length, on the scalp. Perifollicular, hyperkeratotic papules in posterior scalp. Normal eyebrows, eyelashes, and nails.

Family History





Microscopic hair examination
Beading of hair at regular intervals.

Clinical Course
She continues to meet developmental milestones and is a pleasant, happy child. No treatment has been attempted.

Discussion

Monilethrix is caused by a rare ectodermal defect. It is predominantly inherited as an autosomal dominant trait, with incomplete penetrance and variable expressivity. Defects causing Monilethrix have been mapped to keratin gene clusters on chromosomes 12q11-q13 and 17q12-q21, where type II hair keratin genes hHb6 or less commonly hHb1, hHb3, and desomglein 4 (autosomal recessive variant), are found. Type II hair keratins hHb1, hHb3, and hHb6 share identical α–helical rod domains and all are expressed in the hair cortex, as is desmoglein 4. Sporadic mutations in the 1A helix initiation motif results in the phenotypes seen in Monilethrix. Non-conservative mutational hot spots in the 2B helix initiation motif, Glu413Lys are most frequently affected in hHb6, while Glu402Lys is altered in hHb1, and Glu407Lys in hHb3. No genotype-phenotype correlation has been observed.

Clinically, Monilethrix presents with dry, beaded, brittle hair. Microscopic examination of the hair reveals thinning of the hair shaft in rhythmic node-internode pattern. There is great variability in clinical severity and associated symptoms. Some associations seen with Monilethrix, include keratosis pilaris, koilonychia and other nail anomalies, dental anomalies, juvenile cataracts, arginosuccinic aciduria, and neuromental disorders. Hormonal and seasonal influences may alter the disease course, with reports of improvement during first menses, pregnancy, and summer.

Newer methods for rapid diagnosis of Monilethrix include dermoscopy and trichoscopy. Under dermoscopy, uniform elliptical nodes and multiple constrictions of the hair shaft is observed. This method avoids diagnosing "iatrogenic pseudomonilethrix" where crossed hairs on a slide may mimic the rhythmic node-internode pattern. On trichoscopy, videodermoscopy of the hair and scalp that allows viewing at X20 to X160 mag, hair shafts bend regularly in multiple places and curve in different directions, leading to the suggested "regularly bended ribbon sign."

There is no known successful treatment for Monilethrix. Limiting hair shaft breakage with protection against excessive brushing and friction is recommended. Improvement has been reported with acitretin, iron for pt w/ iron deficiency anemia, and hormonal therapy.

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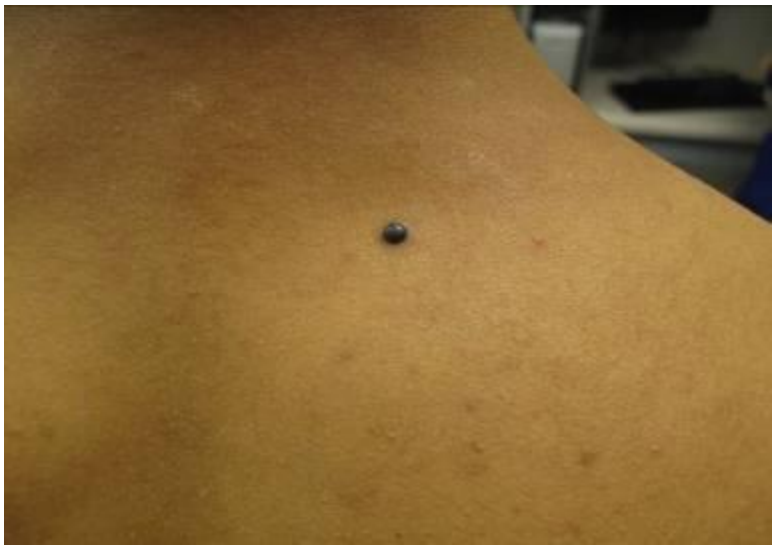
Case # 25
Pigmented Epithelioid Melanocytoma

Resident Physician
Tania Peters, M.D.

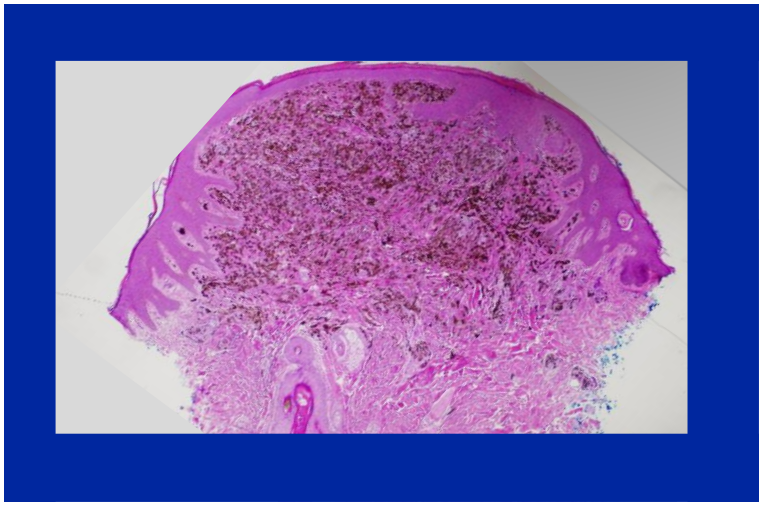
Attending Physician
Kelly Nelson, M.D.

Technology of Interest
Reflectance Confocal Microscopy.

History
16y/o AAM presented to dermatology clinic for evaluation of a slowly growing, asymptomatic black bump on the right upper back present for at least one year. Pt has no personal or family h/o skin cancer and no other dermatologic history.

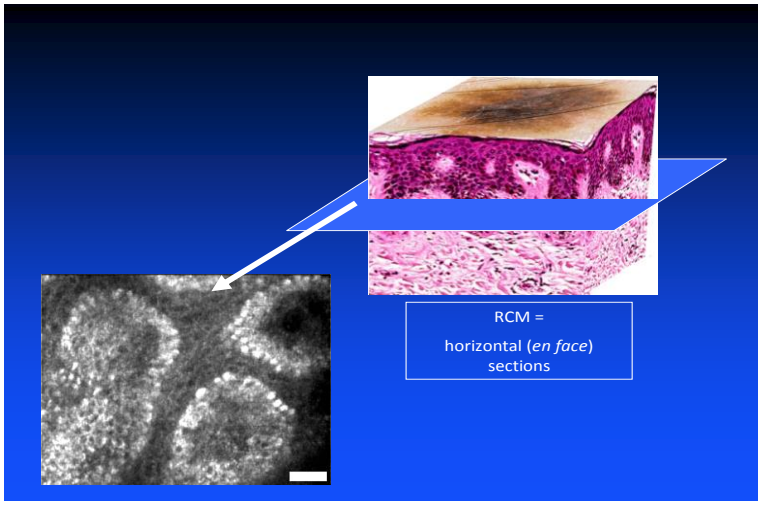


Clinical Findings
Discrete 4mm round, firm black papule present on the right upper posterior shoulder. Demoscopy demonstrated a homogeneous black and blue coloration with an overlying blue-white veil.



Pathology
Heavily pigmented melanocytic lesion composed of spindled and epithelioid cells extending to a depth of 2.5mm. MART1 and HMB45 decorated melanocytes, CD68 highlighted dermal macrophages. Ki67 did not show any increased proliferation.

Clinical Course
Lesion was biopsied December 2009. Subsequently, he has had wide local excision, January 2010, as well as sentinel lymph node biopsy. Right axillary and supraclavicular nodes were negative for malignancy. No residual pigmented epithelioid melanocytoma or malignant melanoma was identified within the excision specimen. Pt is followed clinically every 6 months, currently exhibiting no signs of recurrence.



Discussion

Pigmented epithelioid melanocytoma (PEM) is a newer entity which encompasses both epithelioid blue nevus (of Carney complex) and tumors previously considered "animal-type melanoma." Clinically, PEMs, present as dark brown, black, or blue-black patches, plaques, or nodules measuring from 1-4cm. They can present on any body surface, including genitals and mucosa, demonstrating no predilection for chronically sun-damaged skin. PEMs are roughly equally represented in both males and females and have been reported in individuals ranging from 6 months to 85 years of age.

The majority of PEMs demonstrate loss of expression of a Carney complex gene, cyclic adenosine 3′,5′ monophosphate-dependent protein kinase regulatory subunit 1α. Histologically, PEMs are melanocytic neoplasms with a dense dermal infiltrate of intensely pigmented spindle cells and epitheloid cells, a mean thickness between 2.2-3.3mm, and may demonstrate infiltrative margins. PEMs express MART-1, S-100, and HMB-45.

Although 30-50% of PEM cases demonstrate nodal involvement, they have a more favorable prognosis than Breslow-matched "conventional" melanomas. There have been two cases of hepatic metastases reported, both of whom were alive at last follow up several years post-diagnosis. Only 2% of cases in the literature demonstrate disease-related mortality. At this time, there are no histologic features to separate metastasizing from non-metastasizing lesions, although younger age at diagnosis, smaller tumor diameter, and absence of nodal disease predict a more indolent course.

Currently, the literature suggests that PEMs should be considered a low-grade melanoma or borderline melanocytic tumor with the capacity for nodal spread and rare mortality. The prognostic and staging metrics for Breslow-matched "conventional" melanoma cases cannot be held to PEM cases; the current recommendation for sentinel lymph node biopsy for PEM lesions greater than 1mm Breslow depth or 0.75-1mm with high-risk features is utilized with the goal of reducing the risk of bulky nodal disease. Completion nodal dissection may be considered in light of this goal, while adjuvant interferon-α2b for young patients with positive nodal disease should be carefully weighed, in light of the minimal associated mortality and marginal therapeutic benefit.

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Case # 26
Angioma Mucinosis vs. Angioma Serpiginosum with Extensive Involvement

Resident Physicians
Victor J. Marks, M.D.
Porcia Bradford, M.D.

Attending Physicians
Claude Burton, M.D.
Kelly Nelson, M.D.

Sites of Interest
Extremities, torso.

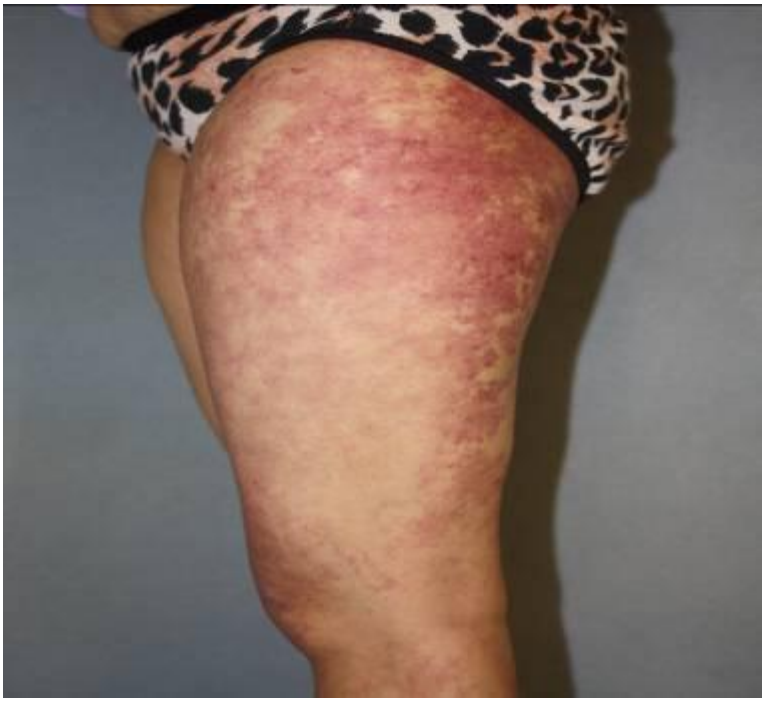
History
Patient 1: 29 y/o Indian woman with an initial red birthmark on her hip and a 7 year history of progressive asymptomatic retiform macular erythema on her extremities and torso. Rash improves with heat and worsens with cold exposure. Dermoscopy revealed numerous red puncta.

Patient 2: 67 y/o woman with a history of a red birthmark on her leg and widespread asymptomatic progression over the last 30 years. Similarly, she experiences improvement in summer months and worsening with cold exposures. Dermoscopy was identical.

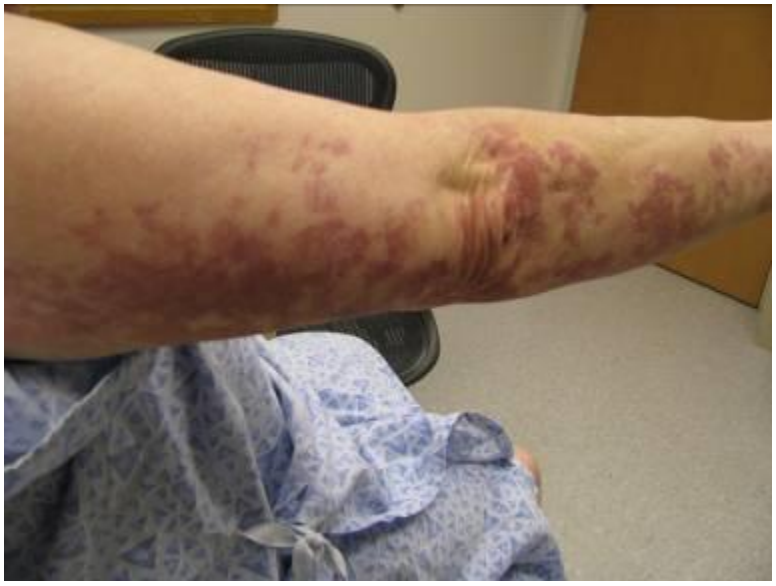
Clinical Findings
Both with broad patches of retiform blanchable macular erythema on the extremities and torso.

Laboratory/Studies
Both with weakly positive ANA.

Reflectance Confocal Microscopy was identical for both patients, demonstrating vascular dilation with erythrocytes flowing more slowly in the papillary dermis compared to the superficial dermis. Leukocyte adhesion with endothelial walls was also observed.



Patient 1



Patient 2

Histopathology
Dilated thin-walled capillaries in the papillary dermis and ectatic vessels in superficial dermis. Colloidal iron stain demonstrated mucin deposition in both cases.

Clinical Course
Both have continued to demonstrate progression of their rashes, but have not shown other extracutaneous complications. Pulsed-dye laser has shown modest improvement for one, but not the other. Hydroxychloroquine has not been effective.

Discussion
Our patients' clinical and dermoscopic findings are remarkably similar to previously reported cases of angioma serpiginosum with extensive involvement. However, the increased dermal mucin in our two cases is a microscopic feature not described in classic angioma serpiginosum, although special stains for mucin were not mentioned in previous reports. Furthermore, the clinical history in our cases does not resemble classic angioma serpiginosum, which begins focally and migrates from its origination point. Our patients describe multifocal origination of their process, supported by noncontiguous lesions in a widespread distribution. It appears more likely to be a unique – albeit perhaps related – dermatologic condition.

In addition, these cases represent the first documentation of the reflectance confocal microscopic features of this condition. The adhesion of leukocytes to the vascular endothelium in the absence of perivascular inflammation is quite striking. Similar findings have been reported in basal cell carcinoma, particularly in areas underlying superficial ulceration**.** Visualization of marginalized leukocytes has not been reported in other benign conditions demonstrating increased vascularity, such as cherry angiomas and psoriasis**.** Appreciation of a deeper vascular plexus arranged parallel to the epidermal surface, with vertical feeder vessels, could explain the counterintuitive clinical improvement with exposure to warm temperatures. Dilatation of the deeper plexus could effectively drain the superficial vessels, resulting in diminished prominence of the retiform patches.

We report two unique cases of women – unacquainted but living six miles apart – with evolving and widespread retiform erythematous patches and red punctate vessels. The clinical presentations resemble that of previously described cases of angioma serpiginosum with extensive involvement, but bear distinctive clinical and histological findings. The diffuse dermal mucin deposition was suggestive of a collagen vascular disorder or reticular erythematous mucinosis; however, the underwhelming inflammation and more prominent vascular ectasia in the absence of other systemic findings make these diagnoses unlikely. We believe these two cases to represent an entity not previously described, at least in full, and suggest the name angioma mucinosis.

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Case # 28
Voriconazole Phototoxicity

Resident Physicians
Diana McShane, M.D.
Bishr Al Dabagh, M.D.

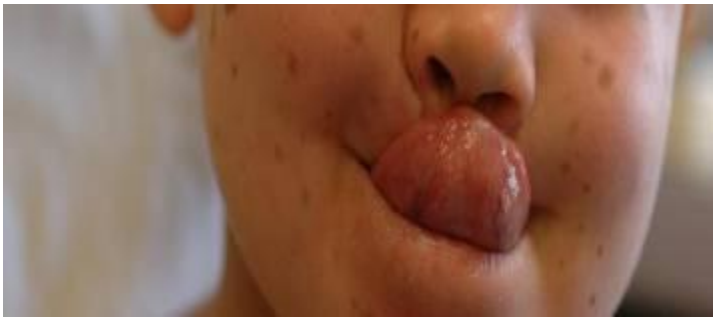
Attending Physician
Neil Prose, M.D.

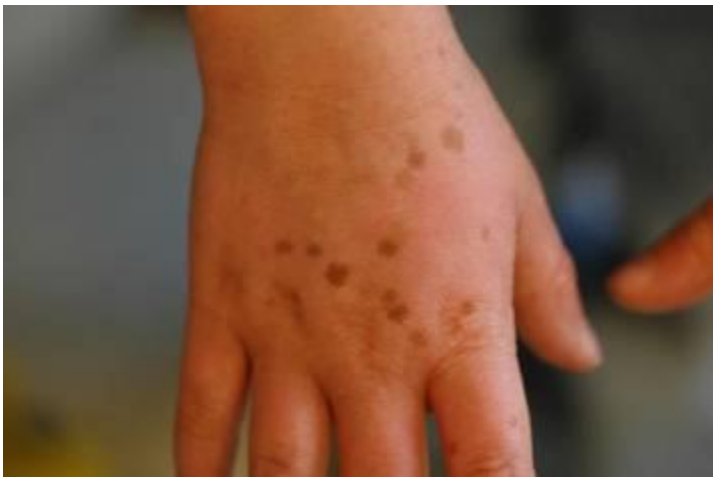
Sites of Interest
Face, Forearms, Neck.

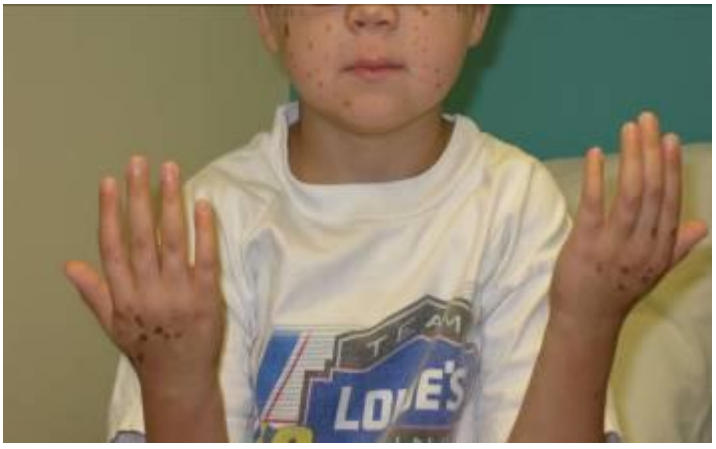
History
RM is a 6 year old patient who presented in November 2008 for redness and dark spots on his face, neck, and arms. He has a history of stage IV neuroblastoma treated with chemotherapy (vincristine, cisplatin, doxorubicin, cyclophosphamide, etoposide) prior to autologous bone marrow transplant in February 2007. He was started on Voriconazole in June 2007 for a severe fungal sinusitis and continued on it until our clinic visit. The family had notice some sun-sensitivity as well.

Clinical Findings
Photodistributed multiple evenly colored brown macules with feathered borders over the face, hands, and forearms consistent with lentigines. Erythema of sun-exposed areas.

Clinical Course
In agreement with his oncology team, he was changed to posaconazole with subsequent resolution of his erythema but he continues to have persistent lentigines. First two pictures taken on initial clinic visit in November 2008. Last picture from June 2009.







Discussion

Photosensitivity due to voriconazole most commonly presents as a sunburn, however, it may manifest in other ways, including cheilitis, exfoliative dermatitis, pseudoporphyria cutanea tarda, or discoid lupus erythematosus-like lesions. These reactions are usually reversible upon stopping the drug. However, as in this case, pigment changes limited to the photoexposed surfaces of the skin in voriconazole-treated pediatric patients have been described. This suggests accelerated photoaging and chronic photodamage. The mechanism of damage is unknown but thought to be due to a metabolite of the drug.

In addition, there are several reports of skin cancer in association with long term use of voriconazole in association with photosensitivity in both adults and children. The majority of the skin cancers reported have been squamous cell carcinoma, but a recent case series of melanoma in situ in the setting of severe voriconazole photosensitivity has also been published. Immunocompromised patients treated with voriconazole should be carefully monitored for the development of photosensitivity, pre-cancerous lesions and skin cancer. Should these changes develop, alternative antifungal medications should be strongly considered.

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Case # 30
Neurofibromatosis Type 1

Resident Physician
Porcia Bradford, M.D.

Attending Physician
Vikas Patel, M.D.

Sites of Interest
Scalp, face, trunk, arms, legs.

History
58 y/o Asian F with a h/o multiple brown well circumscribed macules since birth and soft, skin-colored papules over her trunk and arms since age 30. These have progressed in size and number. Since age 23, she has had a nodule on her scalp with new onset of tenderness, bleeding, and hair loss over the area. No significant family history. No ocular abnormalities, bone abnormalities, endocrine involvement, or learning disabilities.

Clinical Findings
Scattered brown, well circumscribed macules, consistent with café au lait macules. Brown macules in bilateral axillae. Scattered soft, flesh-colored papules with positive buttonhole sign on face, arms, trunk, and legs **(Figure 1)**. Thick, irregular shaped tumors with underlying discoloration on right abdomen and left lower back **(Figure 2)**. 3.5 x 4cm flesh colored, soft nodule on right posterior occipital scalp with underlying patch of alopecia **(Figure 3)**.

Histopathology
Punch biopsy of rt pos occipital scalp nodule shows haphazardly arrayed neural tissue in the dermis, consistent with neurofibroma. Epidermis with spongiosis and a perivascular infiltrate of lymphocytes in the papillary dermis.

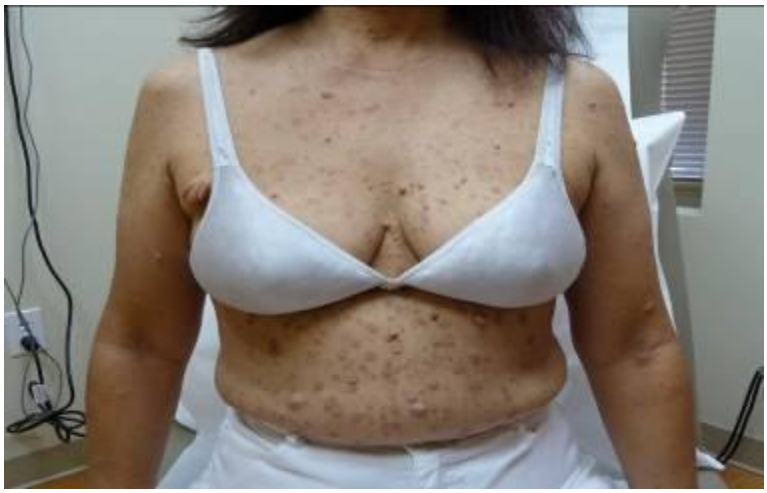

Figure 1. Neurofibromas

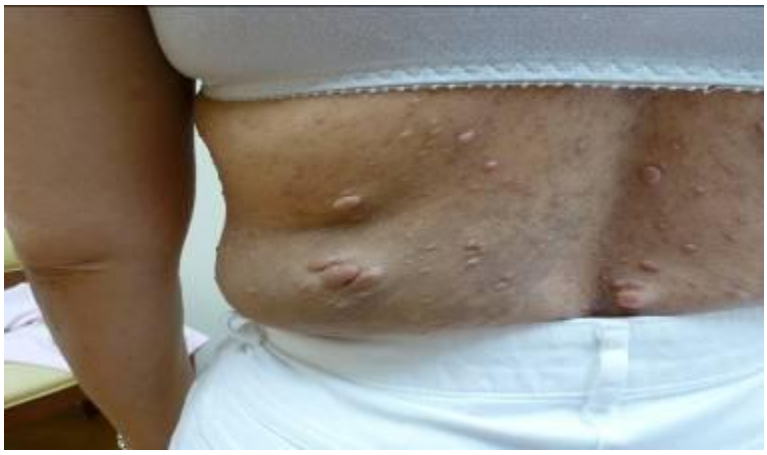

Figure 2. Plexiform neurofibroma

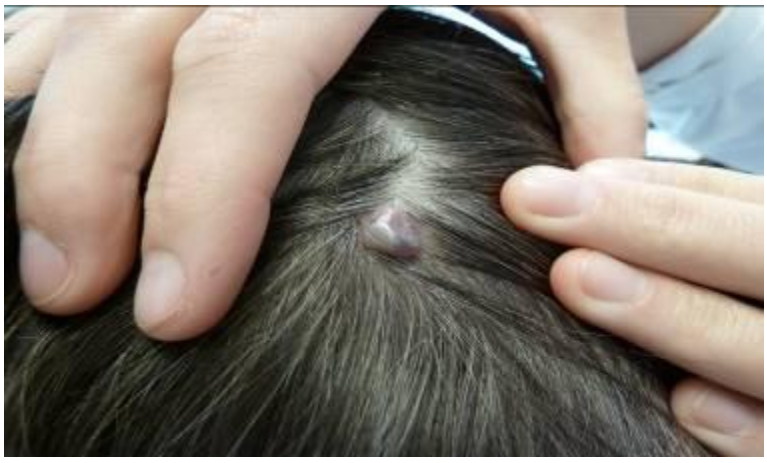

Figure 3. Plexiform neurofibroma

Clinical Course
After biopsy of neurofibroma of posterior scalp, pt continued to have irritation and bleeding in the area. She has been using clobetasol 0.05% solution PRN to posterior scalp with good results.

Discussion
Neurofibromatosis is an autosomal dominant neurogenetic disorder that affects the bone, the nervous system, soft tissue, and the skin. Increased concentrations of nerve growth stimulating activity have been linked with the development of NF. Type 1 NF, also known as von Recklinghausen neurofibromatosis, is the most common subtype. Type 1 NF is linked to a gene on band 17q11.2 (1) that encodes neurofibromin, a protein that has been shown to be essential for the negative regulation of Ras; this finding suggests that neurofibromin acts as a tumor suppressor.

Cafe au lait macules are often present at birth, but they increase in number during the first few years of life (2). Cutaneous neurofibromas form in late adolescence. Neurofibromas are the most common benign tumor of type 1 NF. Plexiform neurofibromas are non-circumscribed, thick, and irregular, and they can cause disfigurement by entwining important supportive structures. The plexiform subtype is specific for type 1 neurofibromatosis. Eighty percent of type 1 neurofibromatosis patients have axillary freckling, also known as the Crowe sign.

Bone involvement can include pseudoarthrosis of the tibia, bowing of the long bones, orbital defects, and mild scoliosis. Type 1 NF may be associated with vasculopathy, including aortic stenosis, occlusion, aneurysm, pseudoaneurysm, rupture, or arteriovenous fistula formation (3). Endocrinologic problems associated with NF include short stature, growth hormone deficiency, sexual precocity, and, pheochromocytoma. 25-40% of Type 1 NF patients may have learning disabilities, such as neuromotor dysfunction, attention deficit hyperactivity disorder, and visuospatial processing.

Diagnostic criteria for Type 1 NF (criteria met if 2 or more features listed are present)

6 or more CALMs >5mm in prepubertal individuals or >15mm postpubertal individuals	2 or more Lisch nodules
2 or more neurofibromas of any type or 1 plexiform neurofibroma	Distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex
Freckling in the axillary or inguinal regions	A first-degree relative with type 1 NF according to the above criteria
**Our pt satisfied criteria 1, 2, and 3	

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Case # 31
Atypical Mixed Lobular Panniculitis

Resident Physician
Kristen Rice, M.D.

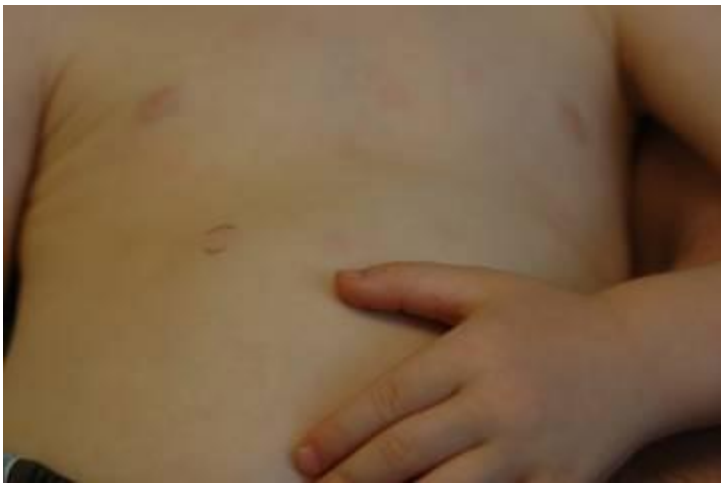
Attending Physician
Neil Prose, M.D.

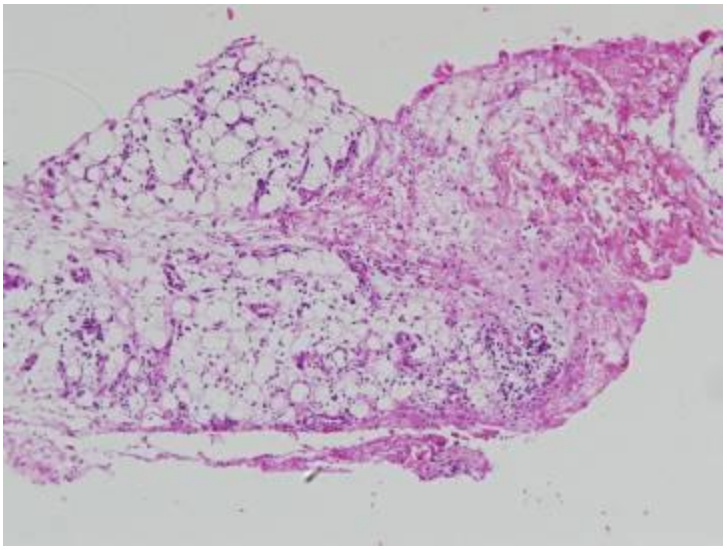
Sites of Interest
Abdomen, back and chest.

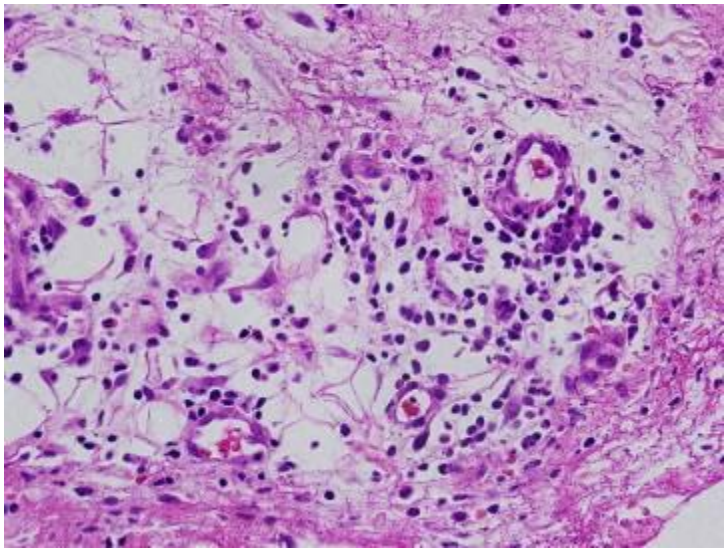
History
The patient is a 2 year old Caucasian male who presented with recurrent erythematous nodular lesions that began at the age of 1 year old. They last from 4 to 14 days at a time and spontaneously resolve. The nodules develop on his abdomen, chest, back, axillae and buttocks and he is rarely without a lesion. He also started to experience occasional arthralgias behind bilateral knees, usually at night which can wake him up from sleep. Otherwise, he has been a healthy child without other medical problems.

Clinical Findings
Scattered mildly erythematous, non-tender, mobile, firm, dermal nodules that change in location at each presentation; nodules have been noted on the abdomen, chest and back.

Laboratory/Studies
T cell gamma chain PCR result could not be determined secondary to either low number of T cells in the sample or insufficient quality of DNA recovered from the tissue. ESR was high at 13. CRP was normal. Epstein-Barr virus antibody was negative. Alpha-1-antitrypsin level was normal. ANA was negative. CBC and CMP were within normal limits. LDH was normal. Chest x-ray was negative. Blood smear was normal.







Histopathology
There is a mild superficial and deep perivascular and periadenexal mononuclear cell infiltrate composed of slightly irregular lymphocytes and histiocytes with rare eosinophils and neutrophils. Cell apoptosis is noted. Immunohistochemical stains were performed which failed to demonstrate the atypical cells. The infiltrate is composed of primarily T cells (CD3 positive) with a few scattered B cells (CD20 positive). CD34 is negative.

Clinical Course
The patient has not developed any associated illnesses and has remained well, other than the occasional arthralgias of bilateral knees. Because the nodules are not bothersome to him, and he has no other findings of systemic disease or illness, we have elected to not treat him at this point. The patient's family will continue to keep us informed on the patient's clinical status.

Discussion
The meaning of this form of panniculitis is unclear. In some patients, it seems to resolve spontaneously over time; in others, it may lead to the development of a collagen vascular disease or very rarely lymphoma.

Several cases of atypical lymphocytic lobular panniculitis (ALLP) have been documented, initially described in the literature in 2004. The histologic findings appear similar to subcutaneous panniculitis-like T-cell lymphoma (SPTCL), but these patients do not demonstrate the typical clinical course of SPTCL. The lesions are described as ecchymotic-like lesions of variable induration on the trunk and extremities with a waxing and waning course. This condition is considered a form of cutaneous lymphoid dyscrasia, but may not necessarily eventuate into malignant lymphoma. It is recommended only to treat aggressively for patients manifesting clinical progression. Many patients have a favorable response to Prednisone, although lesions tend to recur with treatment withdrawal. Isotretinoin has been documented to be an effective treatment. Other treatment options may include T-cell immunomodulatory therapy, including interferon and cyclosporin.

Another type of panniculitis in childhood is known as Idiopathic Lipoatrophic Panniculitis in Childhood. It has been proposed that this is a form of autoimmune disease of the fat. Patients are usually children who show inflamed, tender, subcutaneous, violaceous nodules that are mainly located on the trunk and extremities. Lesions present as flares, and older lesions resolve spontaneously leaving behind a lipoatrophy. Other forms of childhood panniculitis must be ruled out before diagnosis can be made.

Rest and NSAIDs are usually effective treatment, but for more severe disease, oral corticosteroids, methotrexate and cyclosporine should be considered.

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Case # 32
Cutaneous B-cell Chronic Lymphocytic Leukemia

Resident Physician
Sarah Rodgers, M.D.

Attending Physician
Adela Cardones, M.D.

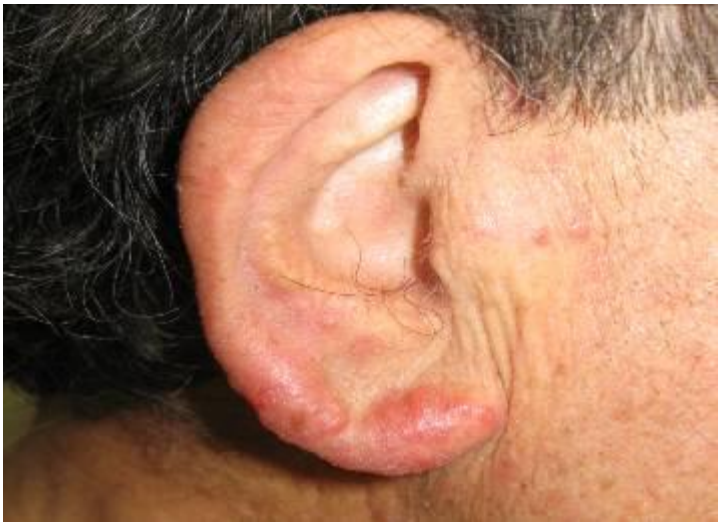
Sites of Interest
Face, earlobes.

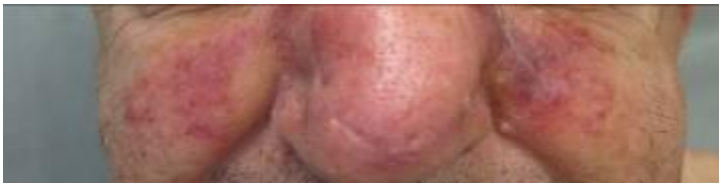
History
This patient is a 76 year-old male with a 17 year history of B-cell chronic lymphocytic leukemia (CLL) who presented 2 years ago with central face violaceous erythema on the cheeks and erythematous earlobe nodules. Earlobe and forehead biopsies revealed cutaneous B-cell lymphocytic leukemia. Past treatments for systemic CLL and relapses have included rituximab, fludarabine, and trial chemotherapeutics. Cutaneous involvement has improved with rituximab and subsequently with irradiation for recurrent earlobe involvement. He also has a history of several squamous cell carcinomas.

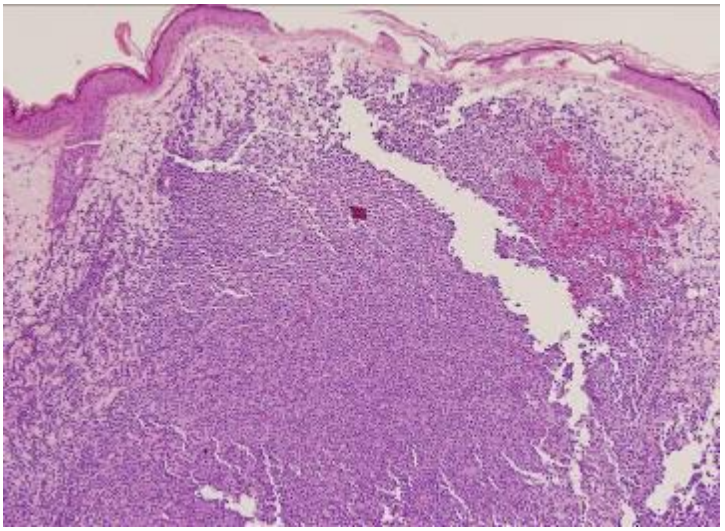
Clinical Findings
-Ill-defined non-blanching violaceous and erythematous patches on the glabella, upper eyelids, nose and malar cheeks with accentuation along scars.
-Bilateral earlobes have soft non-scaly erythematous papules and nodules particularly along the rim.

Histopathology
Diffuse dermal lymphocytic infiltrate of small to medium-sized lymphocytes that stain positively for CD20, CD5 and focally CD23, and negatively for CD10 and cyclin D-1 (ruling out Mantle cell lymphoma).

Clinical Course
Recent chemotherapy with a trial drug flavopiridol has improved his facial and ear cutaneous involvement.







Discussion

B-cell CLL is the most common form of leukemia in Western countries and consists of a low-grade, B-cell lymphoproliferative monoclonal disorder with progressive accumulation of immunologically incompetent lymphocytes. Cutaneous involvement, which is rare, occurs predominantly on the head and neck as erythematous indurated papules, plaques and nodules. Interestingly, patients with CLL can have an exaggerated responses to insect bites, and CLL infiltration may appear at previous sites of infection such as with herpes zoster or simplex. These reactions are thought to result from incidental CLL infiltration as part of a normal physiologic inflammatory response. CLL is also found incidentally on biopsies of non-melanoma skin cancers and other inflammatory processes, and at the same time patients with B-CLL are more prone to the develop of SCC's, BCC's, melanoma and merkel cell carcinomas.

Our patient exhibited a facial pattern of involvement mimicking a rosacea distribution or lupus pernio pattern on the nose and earlobes. Similar cases have been described and it is not clear as to whether cutaneous B-cell CLL infiltration represents true metastatic disease or a normal inflammatory response in our patient to an antigenic stimulus albeit with atypical lymphocytes.

Histologic supportive immunophenotype expression includes CD 20 lymphocyte positivity and coexpression of CD5 and CD23 with Kappa light chain restriction.

The prognosis in CLL is improved or at the least not altered by the presence of cutaneous disease as compared to other forms of leukemia cutis which have a worsened prognosis. Treatment, then, is dependent upon the extent of systemic disease. With asymptomatic systemic disease local treatment may be with intralesional steroids, radiation or excision. Treatment of extensive or concurrent systemic disease is with chemotherapeutics such as rituximab or fludarbine as managed by an oncologist.

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Case # 34
CD8+ Epidermotropic Cutaneous T-cell Lymphoma

Resident Physician
Porcia Bradford, M.D.

Attending Physician
Elise Olsen, M.D.

Sites of Interest
Arms, back, thighs, feet.

History
72 yo WM who presented with erythematous plaques on the arms, back, thighs, and feet in 2004. The most severe lesions were on the left wrist and right thigh. A biopsy was performed in 2005 showing CD8+ CTCL. He was staged as T3 N0 M0 B0 disease and initially treated with PUVA and IFN α with partial clearance of his disease. Afterwards, he was treated with Targretin and local radiation to his left wrist and right thigh.

He was referred to Dr. Olsen's Cutaneous Lymphoma clinic in May 2009. At that time his stage was T1 N0 M0 B0 disease. Because of the 3 years of PUVA, this was discontinued, and Intron A was increased. In July 2009, he was noted to have an increase in the number of plaques on his left buttock and thigh, so Targretin was increased. In October 2009, he had an increased number of plaques on his trunk and extremities. Intron was increased, and topical nitrogen mustard and clobetasol were added. In January 2010, he had an increase in overall involvement with multiple erythematous plaques on his trunks and extremities. Intron and Targretin were discontinued, and the patient was switched to Methotrexate. In April 2010, his skin was doing much better on methotrexate, nitrogen mustard, and clobetasol with T2N0M0B0 disease.

Clinical findings
Left posterior thigh with erythematous, irregularly shaped, indurated plaques; erythematous macules with minimal scale on right shin and left forearm.

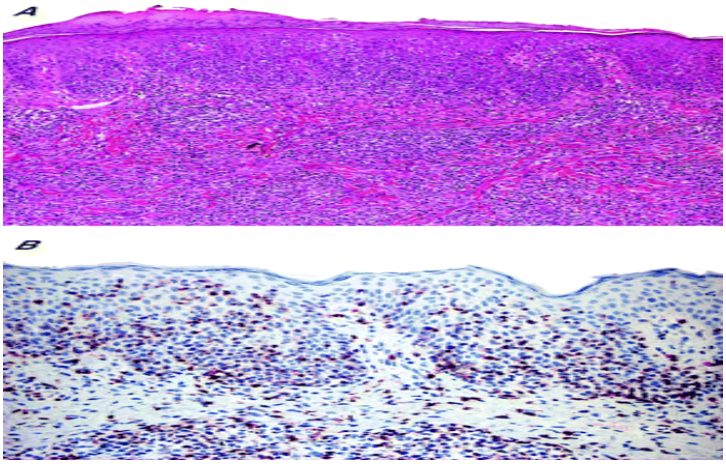

Figure 1. (A) Lymphoid infiltrate with marked epidermotropism; and (B) positivity for CD8. Cerroni L. J Clin Pathol 2006; 59:826.


Figure 2.

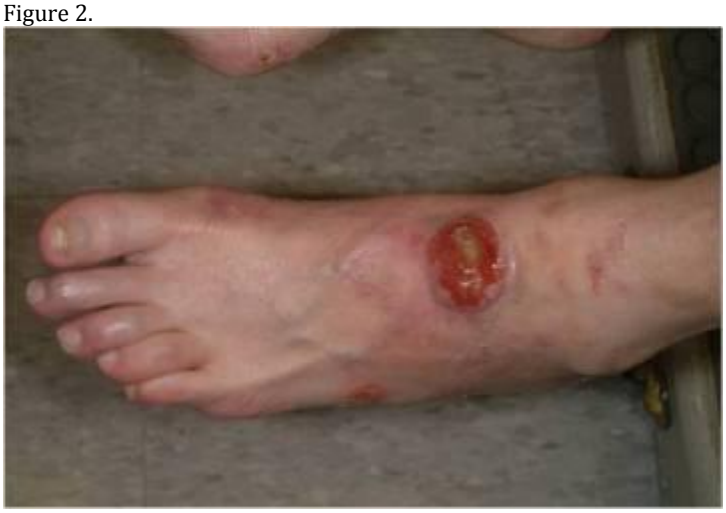
Figure 3.

Histopathology
There is a predominance of CD4 (80%) expression in the dermal small lymphocytes, however, the large epidermotropic lymphocytes, which comprise 20% of the cells, are CD8+. CD7 reveals an approximate 40-50% loss of expression, especially the large epidermotropic lymphocytes. This is consistent with CTCL, mycosis fungoides type, with a CD8+ phenotype. A monoclonal T Cell population was detected by TCR Beta chain PCR in fresh tissue, but negative in the blood. Blood immunophenotyping was wnl.

Laboratory/Studies
Leukopenia (WBC-2,800) and neutropenia (800) on a dose of Interferon of 1.5 million units TIW.

Clinical Course
In August 2010, the patient reported progression of his disease. A tumor with central ulceration was noted on the left wrist (Figure 2), as well as the dorsum of his left foot (Figure 3). Smaller erosions were noted on the plantar surfaces of the feet, bilateral wrists, and the left inferior buttock. Methotrexate and topical nitrogen mustard/clobetasol were continued. Local radiation to the bilateral feet, left wrist, and left buttock will be performed.

Discussion
Here we present a case of CD8 epidermotropic CTCL. CD8+ CTCL is a relatively rare subset of cutaneous non-Hodgkins lymphoma. Similar to its more common CD4+ counterpart, CD8+ CTCL can present in many different clinical patterns. There are three subtypes of CD8+ CTCL. Primary cutaneous epidermotropic CD8+ cytotoxic T cell lymphoma, also known as Berti's lymphoma, is characterized by a proliferation of epidermotropic $CD8^+$ cytotoxic T-cells and an aggressive clinical behavior.[1] Clinically, these lymphomas are characterized by the presence of localized or disseminated eruptive papules, nodules, and tumors showing central ulceration and necrosis or by superficial, hyperkeratotic patches and plaques. It has an aggressive behavior, with occasional metastases to the viscera and CNS, but not the lymph nodes. The median survival is 32 months. Pathologically, there is epidermotropism, spongiosis, and keratinocyte necrosis. The tumor cells have a betaF1$^+$, $CD3^+$, $CD8^+$, granzyme B^+, perforin$^+$, TIA-1$^+$, $CD45RA^+$, $CD45RO^-$, $CD2^-$, $CD4^-$, $CD5^-$, $CD7^{-/+}$ phenotype. T-cell gamma chain PCR positive. It is difficult to obtain clearance or remission. In a review by Berti et al, 0/8 patients achieved complete remission with PUVA, IFN-a, retinoids, TBEB, polychemo-therapy, or allogenic BMT.[2] All died with disseminated disease.

The second group of CD8+ CTCL is CD30+ lymphoproliferative disorders.[3] These have a clinical behavior and prognosis similar to the more common CD4+ cases. It responds better to standard therapies, including retinoids, interferons, and UVA/UVB. The third subtype is subcutaneous panniculitis-like TCL,[4] a cytotoxic T-cell lymphoma predominantly affecting the legs. Cases with an α/β^+ T-cell phenotype are usually $CD8^+$, are restricted to the subcutaneous tissue (no dermal and/or epidermal involvement), and often run an indolent clinical course. Patients generally present with solitary or multiple nodules and plaques, which mainly involve the legs, or may be more generalized. Ulceration is uncommon. Dissemination to extracutaneous sites is rare. SPTL may be preceded for years or decades by an seemingly benign panniculitis. The 5-year survival rate is 82%. Doxorubicin based chemotherapy is the treatment.

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Case # 35
Erythrodermic CTCL treated with Interferon and Leukonychia due to Vorinostat Therapy

Resident Physician
Sean F. Thomas, M.D.

Attending Physician
Elise A. Olsen, M.D.

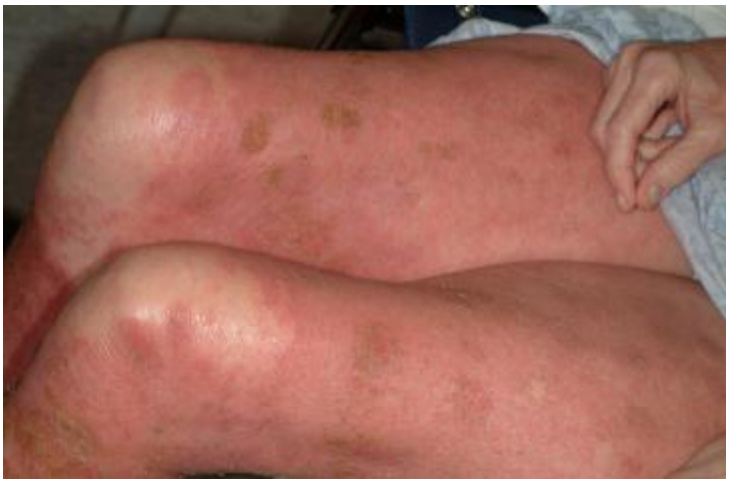
Sites of Interest
General skin exam compared to photos.

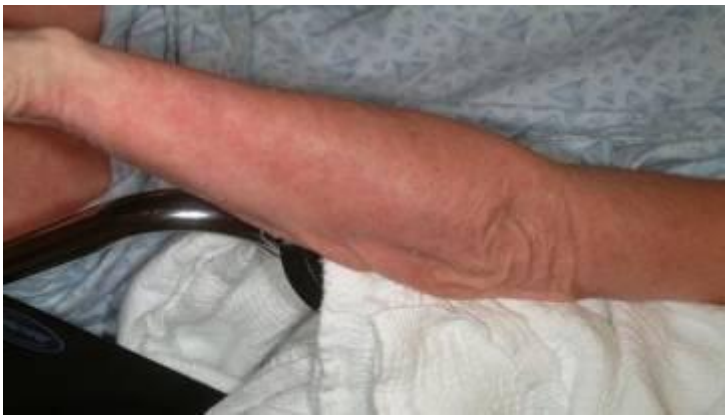
History: 67 y/o WF diagnosed with Stage-1A CTCL in 2003 and initially followed at another facility. She was treated with PUVA from 2003 to 2008 and initially did well but eventually progressed. PUVA was discontinued after she experienced a burn and she started Targretin in April 2009. Olux foam and Derma-smoothe helped reduce her scalp symptoms but Topicort and Desonide did not provide any relief. Efudex was started the month prior to her referral to Duke.

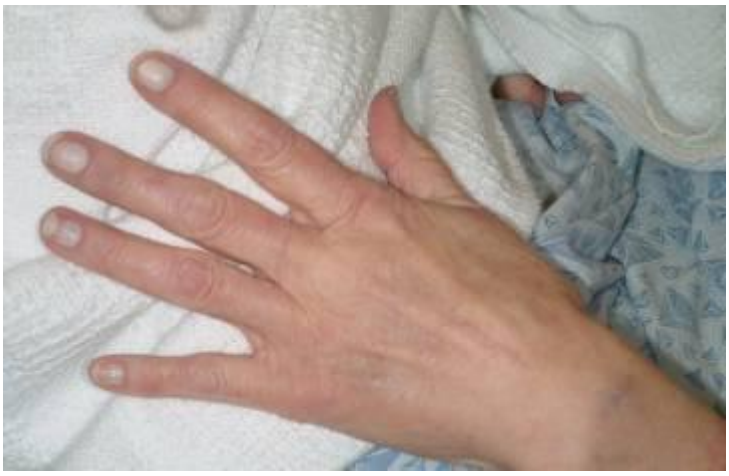
She was first seen by Dr. Olsen in the Duke Cutaneous Lymphoma Research and Treatment Center clinic in September 2009. She presented with a worsening erythematous rash after she was unable to tolerate an increased Targretin dose. (Clinical course follows on next page)

Past Medical History: Breast cancer in 1995 treated with chemotherapy, lumpectomy and tamoxifen; osteoporosis; arthritis; anxiety; depression; mitral valve prolapse; MRSA colonization; allergic rhinitis; diabetes mellitus; mild chronic renal insufficiency; chronic sinusitis.

Clinical Findings: There is diffuse erythema of the scalp with coalescing bright red papules on the forehead and posterior neck. There are several annular erythematous plaques with raised borders on the back, upper and lower extremities. Intact vesicles are located on the dorsum of the left foot. The perianal and perivaginal areas have erythematous vesicles with a raised border and some scaling. Bilateral fingers with leukonychia but no dystrophy. Lentigenous macules were noted on the lower vermillion and have remained stable.







Histopathology
Atypical lymphocytic infiltrate consistent with CTCL – MF. There is epidermotropism of atypical lymphocytes with a non-quantifiable decrease in CD7 staining cells. A lymph node biopsy showed dermatopathic lymphadenopathy and was classified as N1, (Dutch system category 1 with no atypical cells, and NCI class LN2.)

Positive TCR gene rearrangement clone in the blood, however TCR gene rearrangement studies were inconclusive in the lymph node and tissue specimens. Serum immunophenotyping was normal and showed CD4+/CD7- 3%, CD4+/CD26- 3%, CD4+:CD8+ = 1:2 and Sezary count 4%.

Other Laboratory/ Radiographic Studies
WBC 6.8, H/H 11/32 with normal comprehensive metabolic panel, TSH, free thyroxine and iron studies. CT scan of the chest, abdomen and pelvis showed subcentimeter lymphadenopathy and a minimal fullness in the left subareola.

Clinical Course: The patient was staged at T2, N1, M0, B0. Treatment options were discussed with the patient and her referring oncologist treated her with Vorinostat from November 2009 until April 2010. She did not respond to this medication and she also developed bilateral fingernail leukonychia. In May 2010 she started Pegylated interferon alfa-2a (Pegasys) at 180mg subcutaneous per week. Her last visit was three months after initiation and she has experienced a clearance of approximately 80% of her previous lesions. Her leukonychia resolved with subsequent splitting and pitting of the distal 2/3 of her finger nails. Her current stage is T1, N0, M0, B0.

Discussion:
Pegasys is a long acting form of interferon alfa-2a that is administered on a weekly basis. Most studies have used the standard form of interferon in a wide range of doses with objective response rates between 70% and 80% for stages IA-IIA and 63% - 70% with stage III-IV (tumor, erythroderma, and Sezary syndrome)[1]. A study that evaluated the effectiveness of interferon combined with PUVA in patient with stages IB – IVB MF and Sezary Syndrome had an overall objective response rate of 90% and overall complete response rates of 63% with 40% in cases of tumor or nodal disease. The non-responders consisted of 3 of the 6 patients with histologically large cell phenotype[2]. Maintenance therapy should be continued for several months following clinical improvement.

Vorinostat (Zolinza) is a zinc dependent histone deacetylase (HDAC) inhibitor that is FDA approved for CTCL and has been reported to cause an apparent leukonychia[3]. This subtype of leukonychia is due to a pathologic process of either the nail bed or nail plate and not a result of abnormal keratinization as is the case in true leukonychyia. This side effect may be due to a compromise of endothelial cell function in vasorelaxation and angiogenesis that is a result of repression of endothelial nitric oxide synthase by Vorinostat.

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Case # 36
Extranodal NK/T-cell Lymphoma

Resident Physician
Kristen Thomas, M.D.

Attending Physician
Elise A. Olsen, M.D.

Sites of Interest
Right leg.

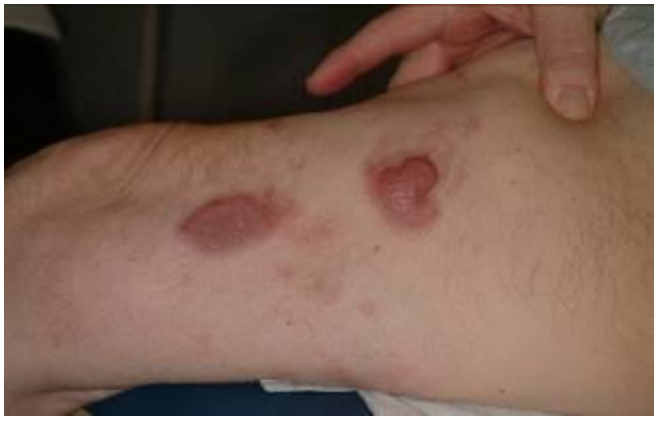
History
75 y/o WM, who was first seen by Dr. Olsen in the Duke Cutaneous Lymphoma Research and Treatment Center clinic in March 2010, presented with a rash on the right inner thigh that began in the summer of 2009. He had used various topical steroids with no change, and the lesions continued to grow and spread.

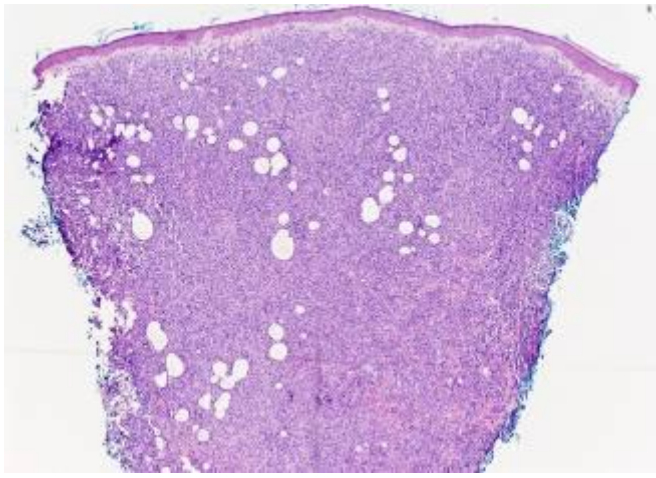
The patient has a PMH of untreated prostate cancer, diabetes mellitus, mild chronic renal insufficiency, chronic sinusitis, Hx of MI in 1988 and 1998 s/p CABG, and a 30 pack year history of tobacco use, quit in 1970. He has never travelled outside of the US, except for a family vacation to Canada in 2001. He has no risk factors for HIV.

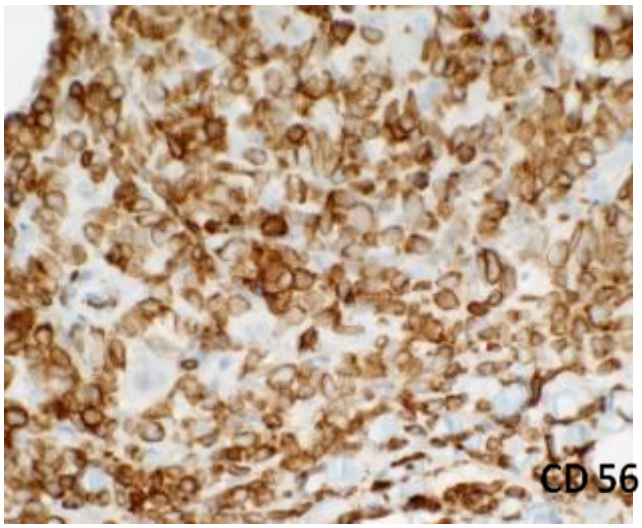
Clinical Findings
Skin exam on 3/22/10 was most notable for an erythematous tumor (2 x 2.5cm) and an erythematous plaque (2.5 x 4cm) on the right medial thigh. There were also erythematous patches on the posteromedial right thigh.

Histopathology
Atypical lymphocytic infiltrate consistent with extranodal NK/T-cell lymphoma. The dermis is replaced by a proliferation of medium to large lymphocytes with abundant cytoplasm and a second population of small reactive lymphocytes. The tumor cells are positive for CD3, Granzyme B, and CD56. CD30 and TIA-1 were negative. The cells are positive for Epstein Barr virus.

Positive tissue TCR gene rearrangement clone matched that in the blood. There are no abnormal T or B cells noted in the peripheral blood.







Laboratory/Studies
PET/CT showed no definite evidence of sinonasal lymphoma, but did show symmetric hypermetabolic activity within the maxillary sinuses which was thought to likely represent sinusitis. It also revealed a hypermetabolic right shoulder subcutaneous mass, aortocaval lymph node mass, and medial right thigh masses concerning for lymphomatous involvement. Attempts were made by a local dermatologist to biopsy the right shoulder mass, but there was little clinically present and biopsy was negative.

Bone marrow biopsy showed trilineage hyperplasia (50%), decreased iron stores, no infiltrative lesions, no abnormal flow or evidence B or T cell lymphoproliferative disease.

Clinical Course
The patient received local electron beam radiation at a local cancer center with 50 Gy in 25 fractions to the right thigh. He completed radiation on 5/12/10 and was begun on Interferon alfa-2b and Targretin 150 mg/m2 on 5/25/10. On follow-up 8/10/10, he had resolution of the initial tumors, but a 2cm erythematous, flat plaque on his right posterior thigh was noted immediately outside of the area that was previously irradiated. Biopsy was consistent with recurrence of NK/T-cell lymphoma. Repeat CT of the abd/pelvis revealed stable portacaval, aortocaval, and porta hepatis lymph nodes with no new lymphadenopathy identified. He is scheduled to begin repeat local radiation to the right leg in the near future.

Discussion
Extranodal NK/T-cell lymphoma, nasal type, is an Epstein-Barr virus (EBV)–positive non-Hodgkin lymphoma of small, medium, or large cells, usually with an NK-cell, or, more rarely, a cytotoxic T-cell phenotype (CD8+, TIA-1, granzyme B, perforin). The skin is the second most common site of involvement, with the nasal cavity/nasopharynx being the most common and the reason why it was once known as a lethal midline granuloma. Cutaneous involvement may be primary or secondary. Because both primary and secondary involvement are clinically aggressive, they require the same type of treatment. Because this is an extremely rare malignancy, a standard treatment protocol has not been outlined. Patients may be treated with local radiation therapy and/or systemic chemotherapy. The disease is aggressive, with a median survival of 5 months for patients with cutaneous and extracutaneous disease. In patients presenting with only skin lesions, however, a median survival of 27 months is reported.

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Case #37
Necrobiotic Xanthogranuloma with Paraproteinemia

Resident Physician
Stavonnie Patterson, M.D.

Attending Physician
Claude Burton, M.D.

Sites of Interest
Face and neck.

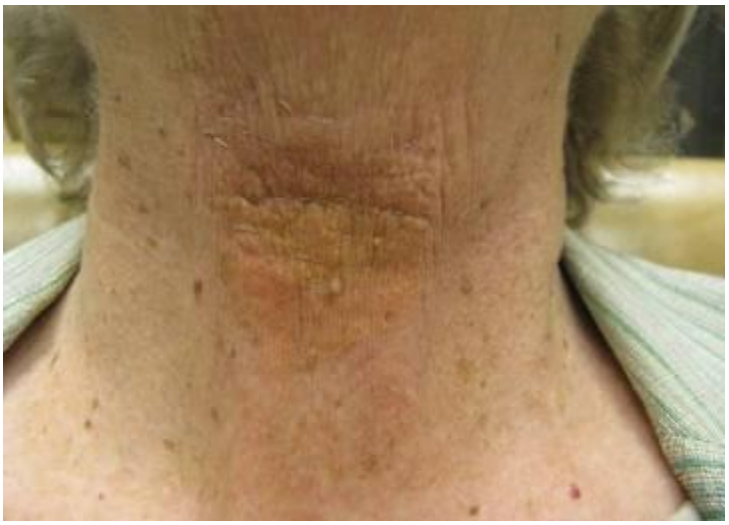
History
85 y/o female presented in 1996 with periorbital and right temporal yellowish plaques present since 1995 and the more recent onset of diplopia secondary to unilateral ophthalmoplegia. A monoclonal gammopathy was demonstrated by SPEP and was characterized as an IgG kappa by IEP. Her cutaneous and ocular lesions resolved with pulsed dexamethasone. In 2009 her cutaneous lesions recurred with a tender plaque on the neck. All biopsies were consistent with Necrobiotic Xanthogranuloma (NXG).

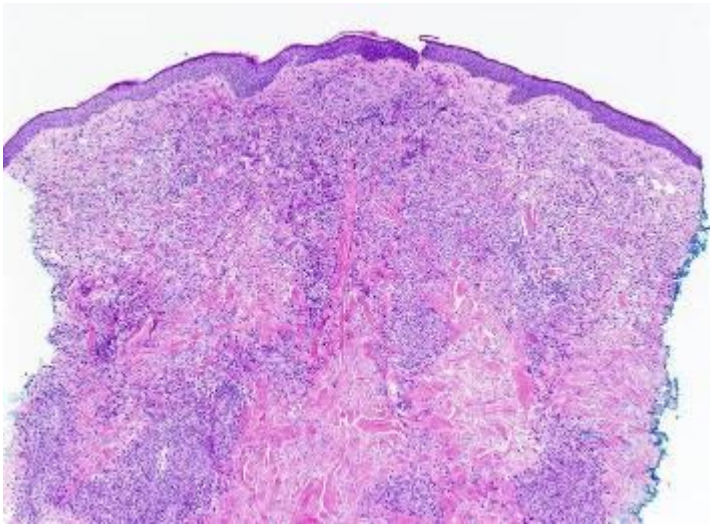
Clinical Findings
Yellow, tender, firm plaque on neck, periocular scarring from previous disease.

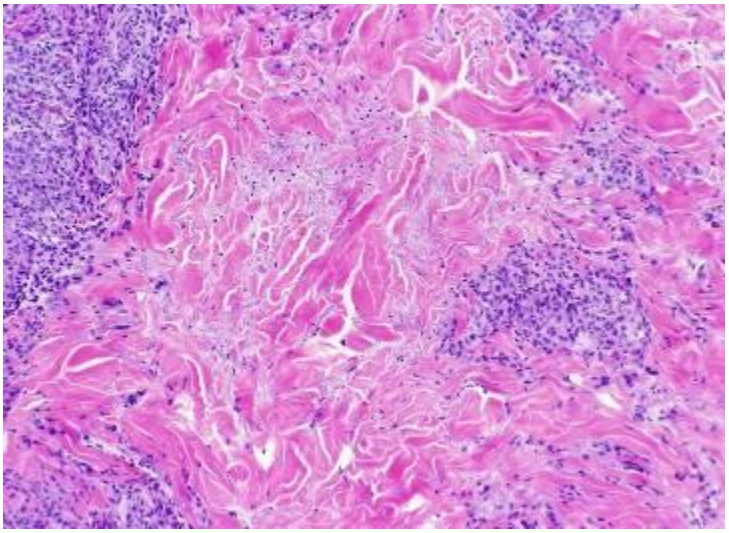
Laboratory/Studies
SPEP: Monoclonal IgG Kappa 0.66 g/dl
Total cholesterol: 233 mg/dL
Triglycerides: 320 mg/dL
ESR: 27 WBC: 15.9

Histopathology
The tissue demonstrates a superficial and deep dermal granulomatous dermatitis with histiocytes and giant cells. Necrobiosis is present. Scattered neutrophils are present.

Clinical Course
HP first experienced lesions in 1989. She was not diagnosed with NXG at that time and was treated with Prednisone for two years. Upon presentation to Duke in







1996, a diagnosis of NXG was established. She was treated with pulsed dexamethasone and had a complete response. On recurrence in 2009, HP did not respond to treatment with topical or intralesional corticosteroids. She was treated with dexamethasone 6 mg, four times daily on the first four of every fourteen days until in remission, and had a complete response. Therapy was discontinued after two months. She has not had a recurrence of her skin lesions since that time. Her monoclonal gammopathy declines, but does not entirely disappear, during pulsed therapy.

Discussion

Necrobiotic xanthogranuloma (NXG) is a rare condition of unknown etiology, characterized by firm, yellow plaques and nodules in a periorbital distribution. Lesions have a distinct histopathology. This consists of a band-like granulomatous infiltrate with touton giant cells and collagen necrobiosis. Cholesterol clefts and lymphoid aggregates are sometimes seen. NXG is often associated with an IgG monoclonal gammopathy and rarely multiple myeloma.

Periorbital and other facial lesions are most characteristic. However, many patients also have lesions on the trunk and proximal extremities. Ulceration, telangiectasias and atrophy are common. Lesions are usually asymptomatic; however, periorbital lesions may be associated with ophthalmic complaints such as burning, itching and painful eyes. Blepharoptosis, restricted ocular motility, scleritis, keratitis and diplopia have also been reported. There is occasionally systemic involvement. The respiratory and cardiac systems are most commonly involved.

Frequent laboratory findings are an elevated ESR, leukopenia, C4 deficiency and monoclonal gammopathy. In approximately 80% of cases the monoclonal gammopathy is of the IgG-Kappa type. However, IgG-lambda monoclonal gammopathies are also seen. In the general population, multiple myeloma is found in 18% of patients with a paraproteinemia; this rate is much lower in NXG patients with a paraproteinemia. A bone marrow biopsy can be performed to evaluate for multiple myeloma. Lipid levels can be normal or elevated.

NXG tends to be a chronic disorder with varied response to therapy. Chlorambucil, Melphalan, and Cyclophosphamide are commonly used agents with variable results. These agents have been recommended for patients with extensive cutaneous lesions and/or multiple myeloma. Recently, there have been reports of pulsed high dose oral dexamethasone being effective. This has been effective in patients for whom lower dose corticosteroids were ineffective. Intralesional triamcinolone, surgical excision and cryotherapy are options for localized cutaneous lesions. Interestingly, there is often no correlation between resolution of cutaneous lesions and the monoclonal gammopathy.

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Case # 38
Klippel-Trénaunay Syndrome

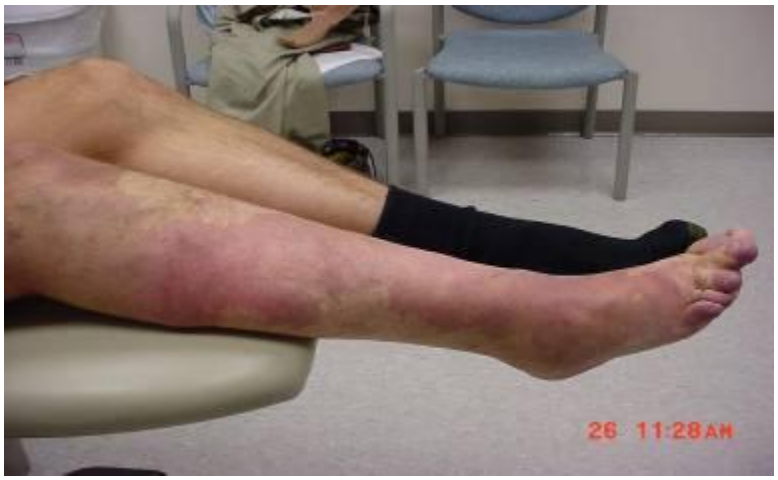
Resident Physicians
Melanie Walter, M.D.
Bishr Al Dabagh, M.D.

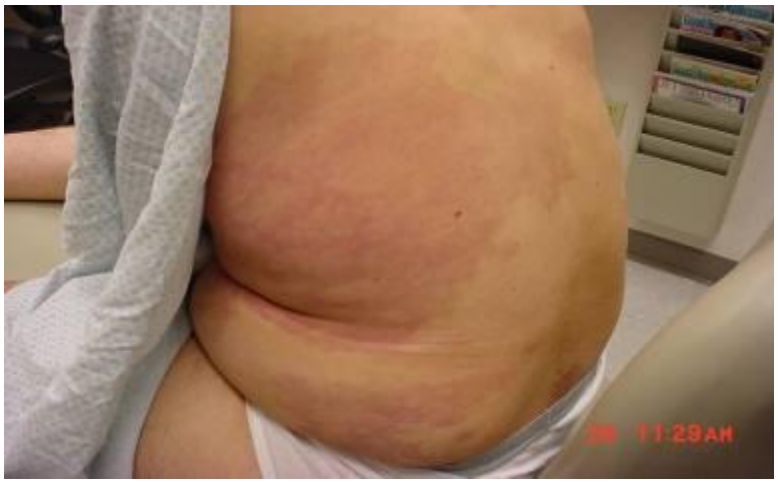
Attending Physician
Claude Burton, M.D.

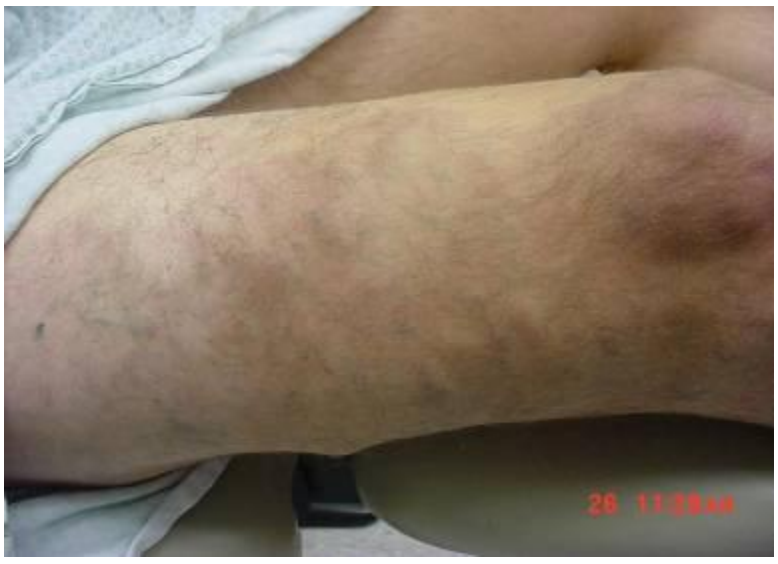
Sites of Interest
Right lower leg.

History
The patient is a 29 year old Caucasian man with a history of extensive right leg vascular malformation present since birth. The lesion is at times painful and swollen, worse with weight bearing / prolonged standing, and occasionally associated with a burning sensation. He has no history of seizures, other neoplasms, GI bleeding, AV fistula or other problems.

Clinical Findings
MRI and leg / pelvic films from 1988 / 89 demonstrated overgrowth of soft tissue and periosteal reaction on side of lesions. MR Venogram and ultrasound of the right lower leg in 2007 demonstrated numerous varicosities as well as absence of the true deep venous system including femoral and popliteal veins. There are numerous competent venous collaterals and minimal shunting. CT of the abdomen in 2007 demonstrated soft tissue attenuation in pelvis and left upper quadrant, suggestive of involvement of the peritoneal cavity with vascular malformation or possible hematomas. Echocardiogram in 2003 demonstrated right atrial and ventricular enlargement. Upper endoscopy has been negative for GI involvement.







Laboratory/Studies
Elevated D-dimer associated with pulmonary emboli and phlebitis. Normal Factor V Leiden, platelet neutralization panel, mixing studies and lupus anticoagulant. Slight elevation of Protein S, but otherwise normal thrombosis panel.

Clinical Course
Complications have included subtle limb length discrepancy, intermittent phlebitis, DVTs, and bilateral pulmonary emboli with resultant chronic warfarin use. The patient has been treated with compression (50-60mmHg to waist), warfarin, anti-inflammatory medications as needed.

Discussion
Klippel-Trénaunay syndrome, first defined in 1900, is comprised of vascular (capillary, venous and lymphatic) malformations with associated overgrowth of the soft tissue and underlying bone on the affected side. In 95% of patients, the lower limb is involved, and rarely there is also associated arteriovenous fistula, in which case the syndrome is designated Parkes-Weber. Over time, the vascular lesions becomes progressively more raised and congested, with associated varicosities, claudication, warmth, swelling and hair changes.

Treatment is aimed at the complications and their prevention, as well as reducing pain and functional impairment and improving cosmesis. Conservative management with compression therapy and pain management are imperative. Surgery is an option if veins are present and not hypoplastic, and more recently foam sclerosant has been used with few complications. Bergan et al, in 2006 used polidocanol foam injections for the treatment of 332 patients, including 9 with KTS, with significant decrease in pain, improved dermatitis and ulcer healing but no cure. Adverse events were rare and there were no reports of pulmonary emboli. Similar results were achieved by Nitecki et al in seven patients treated monthly with an average of 14 treatments.

There have also been several reports in the literature using pulsed dye laser, although typically this has most effect on cosmesis of the port wine component, with little effect on symptoms.

Another novel approach to management is the use of endovascular radiofrequency ablation for treatment of Klippel-Trénaunay syndrome. This method is cost effective and minimally invasive but associated with complications.

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Case # 40
Tuberous Sclerosis

Resident Physician
Elizabeth Naylor, M.D.

Attending Physician
Claude Burton, M.D.

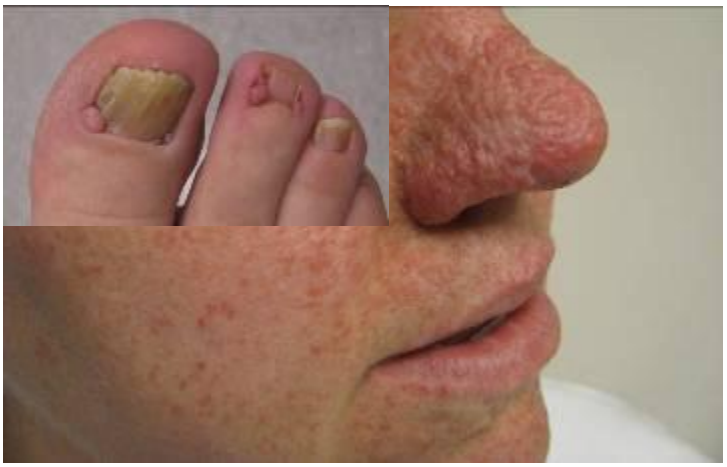
Sites of Interest
Hands, feet, face, back, legs.

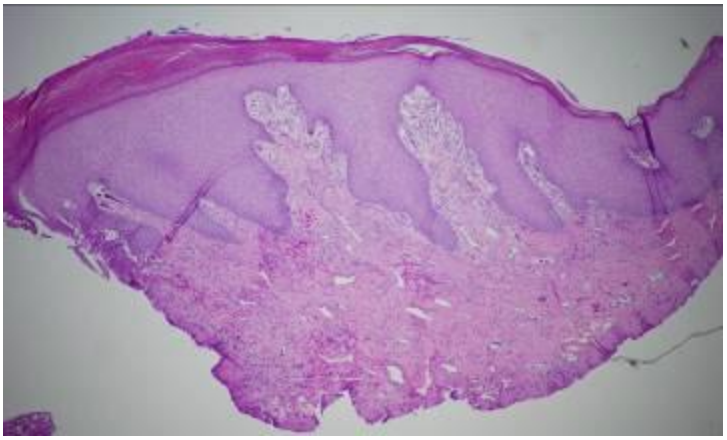
History
42 y/o female followed for a long history of tuberous sclerosis diagnosed at age 3 after presenting with facial angiofibromas. Pt has since developed hypomelanotic macules, progression of her facial angiofibromas, periungual fibromas. Pt was also found to have large renal angiomyolipomas, history of spontaneous retroperitoneal bleed, seizure disorder, hepatic angioma, pulmonary lymphangioleiomyomatosis, intracranial calcifications, hypertension, dental pits, and a right eye astrocytic hamartoma.

Clinical Findings
There are multiple dental pits. Hypopigmented macules are present on the back and legs. Pedunculated, skin colored papules are present periungually on the fingers and toes. Erythematous papules are also noted on the face.

Histopathology
Biopsy of a periungual papule demonstrated perifollicular fibrosis and a proliferation of blood vessels.

Clinical Course
The patient is currently being treated with podophyllin 25%. In the past, she has been treated with several lasers (2940nm, 595nm, 585 nm laser). She has taken part in a clinical trial at the University of Cincinnati involving rapamycin and embolization of her angiomyolipomas. Pt noted minimal change in her facial angiofibromas while on rapamycin. She is now awaiting renal transplant.





Discussion

Tuberous Sclerosis(TS) is an autosomal dominant disorder caused by mutations in TSC1 (chromosome 9q34) and TSC2 (chromosome 16p13), the genes that encode hamartin and tuberin, respectively. 75% of cases are sporadic. One of the first manifestations is often hypopigmented macules, including the well known "confetti" or "ash-leaf" types.

Recent literature has focused on rapamycin, a mTOR (mammalian target of rapamycin) inhibitor, as a potential therapy for both cutaneous and systemic manifestations of TS. The genes implication in this disorder normally suppress mTOR, making rapamycin a logical choice for therapy. In addition, rapamycin is known to decrease the production of VEGF. A recently published case noted the reduction of total volume of renal angiomyolipomas, an improvement in renal function, and a reduction in facial angiofibromas in a patient on low dose rapamycin (1mg/day) for 12 months.[2] Improvement of facial angiofibromas has also been noted with topical rapamycin.[3,4]

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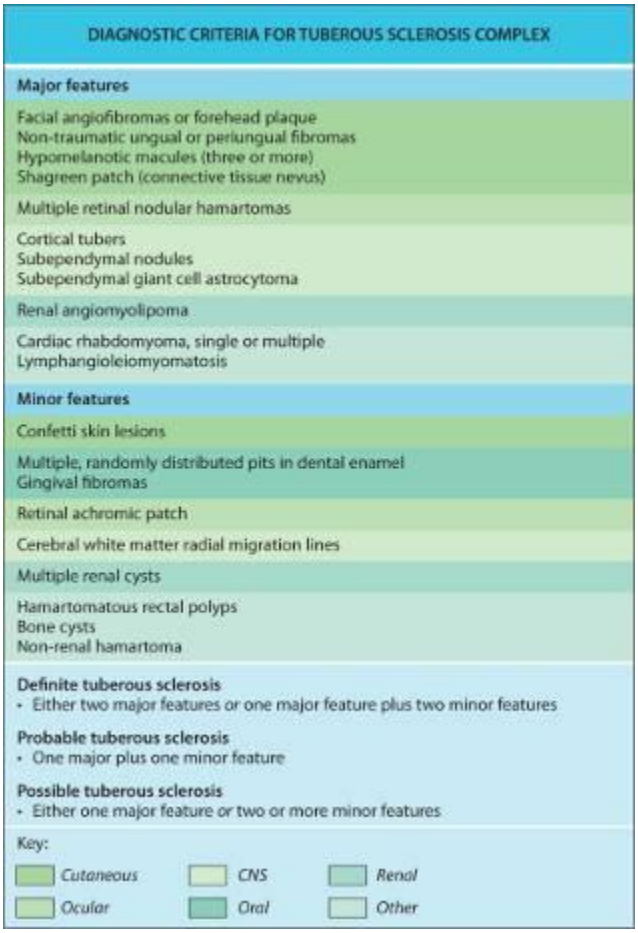

Case # 42
Orofacial Granulomatosis

Resident Physician
Holly Bartell, M.D.

Attending Physician
Adela Cardones, M.D.

Sites of Interest
Periorbital.

History
This is a 53-year-old gentleman who presented for evaluation of profound bilateral eyelid swelling. Five years ago he developed progressive severe swelling of his upper and lower eyelids with marked obstruction of his vision. He denied having ulcerations in the eyes or mouth. No triggering factors were identified. There were no associated systemic symptoms, in particular no GI abnormalities.

Clinical Findings
Well developed gentleman in no acute distress. Soft, skin colored plaques involving the upper and lower eyelids. Significant overhanging of his eyelids impeded his line of vision. There was no cervical, supraclavicular, or axillary lymphadenopathy.

Laboratory/Studies
Angiotensin converting enzyme – normal
ANA + 1:40 (speckled pattern)
PPD - Negative

Histopathology
Chronic perivascular inflammation and granulomatous inflammation within and adjacent to vascular spaces. (Figure 2) D2-40, an immunostain for lymphatics, showed the granulomatous inflammation within lymphatics (figure 3), and CD68 stain confirmed the histiocytic nature of the cells within lymphatics. (not shown)

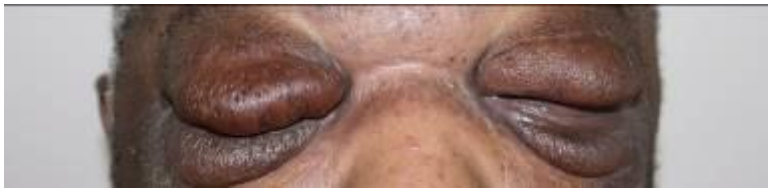
Figure 1

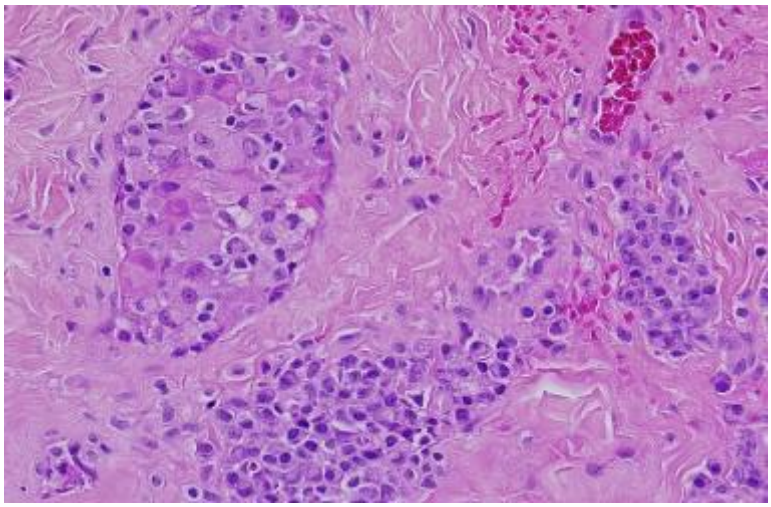
Figure 2

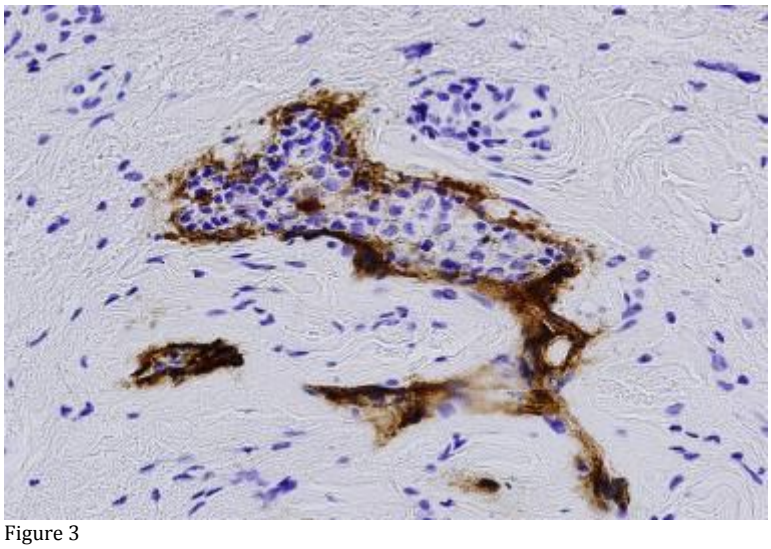
Figure 3

Clinical Course
Over the past 5 years he has had multiple treatments including surgical reduction, short tapering courses of prednisone, oral methotrexate (15-20mg/week), and low dose oral thalidomide (50 mg po daily). He has also been given concurrent intralesional and topical steroids. None of these treatments have offered significant improvement in his eyelid swelling. We are planning on starting him on a trial of infliximab infusions in the near future.

Discussion
Orofacial granulomatosis (OFG) is an uncommon immunologically mediated disorder clinically characterized by recurrent or persistent swelling of the orofacial tissues and oral mucosal ulceration together with a spectrum of other orofacial features.[1] The chronic inflammation of OFG is often characterized by the presence of granulomas in the subepithelial stroma, however, noncaseating granulomas are not always detected.[2]

The clinical features of OFG are identical to orofacial manifestations of Crohn's disease, although in contrast to the latter there is no consistent evidence of concurrent inflammatory bowel disease. The clinical features of OFG may also mimic orofacial manifestations of sarcoidosis. It is probable that OFG represent a spectrum of disease that ranges from localized granulomatous inflammation of the lips (granulomatous cheilitis, Miescher cheilitis), through orofacial swelling with mucosal ulceration to disease with neurologic deficit and lingual fissuring (Melkersson-Rosenthal syndrome).[3]

OFG does not seem to be associated with any significant hematologic abnormalities or serologic evidence of systemic inflammation, other granulomatous disorders, or gastroenterological involvement. A recent retrospective study of 49 patients with OFG showed that combined therapy (topical plus intralesional corticosteroids or systemic agents) was more frequently associated with partial/complete control of the facial manifestations of OFG than topical therapy alone. This analysis also suggested that OFG responds slowly to treatment with 50% of the patients achieving complete resolution of the orofacial swelling within 3 years of treatment and only 25% of them doing so within the first year of therapy.[4]

Infliximab is approved for use in severe and refractory rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis, as well as for recalcitrant Crohn's disease. Interestingly, in the latter condition, it appears to work as well in cases of orofacial involvement. With respect to the relationship between Crohn's disease and OFG, infliximab has recently been used successfully for treatment of OFG, suggesting that TNF-α may play a central role in the pathogenesis of OFG.[5]

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Case # 43
En Coup De Sabre Linear Scleroderma with Parry-Romberg Syndrome

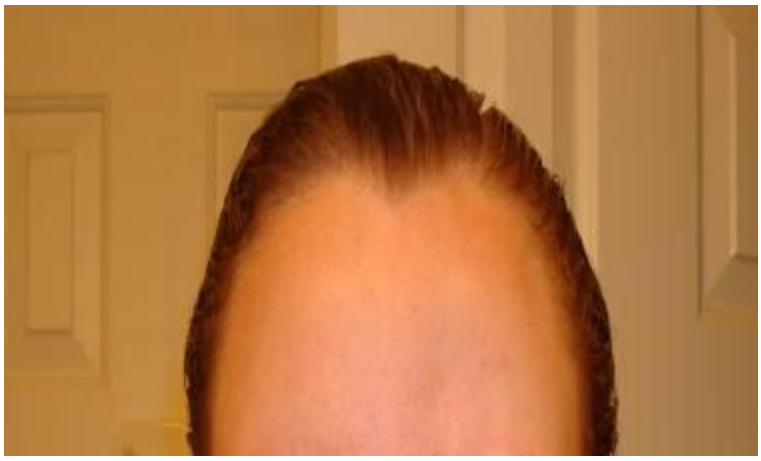
Resident Physicians
Melanie Walter, M.D.
Bishr Al Dabagh, M.D.

Attending Physician
Neil Prose, M.D.

History
The patient is a 22 year old woman with a linear atrophic forehead plaque since childhood, gradually increasing over time, with associated hair loss. This has been accompanied by loss of sensation in the V1 and V2 distribution and severe debilitating left-sided headaches.. She has a history of typical migraines with her menses since ~7th grade, but those associated with her left face are different. They are associated with nausea, vomiting, dizziness, eye pain, diplopia, tinnitus and occasional shortness of breath. They also have increased in duration (6-7 hours), frequency (daily) and severity during times of active forehead plaque expansion.

Clinical Findings
Depressed linear plaque on the left forehead with extension into scalp and to orbital rim, with associated loss of eyebrow. There is slightly diminished sensation in the V1 and V2 distribution. Left nasal ala, and lesser so left cheek, are hypoplastic. Facial expression is symmetric.

Laboratory/Studies
MRI of brain (2007) showed no involvement. MRI of brain (2009) showed 9 mm nonenhancing fat containing mass in the left ethmoid compatible with a nasal dermoid cyst. CT (2008) revealed mild asymmetric atrophy of the left sided frontalis musculature. ANA 1:160. Normal eye exam in 2007.



Clinical Course

The patient struggled most over time with the expansion and severe headaches associated with the facial plaque. She failed Imitrex, Maxalt, Axert and Relpax (triptans), Trileptal (oxcarbazepine), gabapentin and Lyrica, and Relafen (nabumetone). She was using Percocet with some success but complained of drowsiness. She then received IV solumedrol pulse therapy with good improvement in symptoms and ability to decrease narcotics. Gradually the headaches returned with worsened severity. Methotrexate was added but she developed significant GI distress. Both drugs were stopped and she underwent several supraorbital nerve blocks, the success of which was short lived. She then had radiofrequency ablation several times which helped for up to six weeks but the symptoms gradually recurred each time. More recently she failed Tegretol and Cymbalta, had little success with a second course of IV solumedrol, and tried a peripheral nerve stimulator which was too cumbersome. Finally, she has been maintained on Savella (milnacipran) and switched to Cellcept with great improvement in symptoms and apparent lack of progression of skin disease.

Discussion

Linear scleroderma of the "en coup de sabre" pattern most frequently involves the forehead and can be associated with significant cosmetic and functional deficits. It is more common in children than adults, and females more than males. Parry Romberg Syndrome, on the other hand, refers to hemifacial atrophy of the skin and tissue below the forehead. Neurologic deficits are common to both conditions and most frequently involve seizures. Migraines and focal motor or sensory deficits have also been described. There is some debate in the literature over whether these are two distinct conditions or a spectrum of disease with some overlap. A large review by Tollefson, *et al* demonstrated that of 41 patients with en coup de sabre scleroderma, 36.6% also had hemifacial atrophy. Conversely, of 28 patients with Parry Romberg syndrome, 53.6% also had en coup de sabre lesions. Further, patients with one or the other had similar neurologic deficits, biopsy results and response to similar treatment as one another. They speculated that both conditions may share a similar pathogenesis.

Many treatments have been used with variable success, including d- penicillamine, cyclosporine, UV light, vitamin D analogs, low dose methotrexate and pulse corticosteroid therapy. More recently, a study demonstrated success in ten patients treated with mycophenolate mofetil after failure of other modalities. There have not been reports of use of dermal fillers for en coup de sabre plaques.

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Case # 44
Dermatomal Sclerodermoid Graft-vs-Host Disease

Resident Physician
Holly Bartell, M.D.

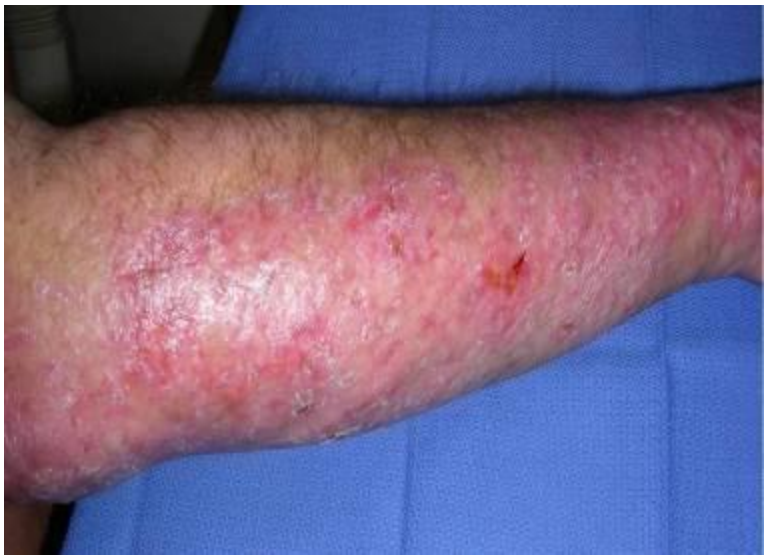
Attending Physician
Navjeet Sidhu-Malik, M.D.

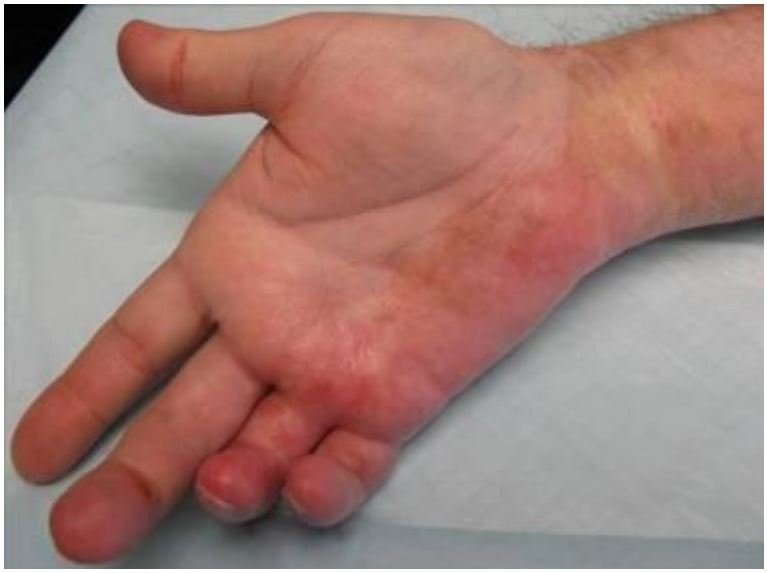
Sites of Interest
Right arm, dorsal hand and palm.

History
47-year-old Caucasian male with polycythemia vera underwent a sibling HLA-matched peripheral blood stem cell transplant in July 2004. Approximately three weeks after the transplant he developed pruritic scaly erythematous plaques on his upper back, shoulders and forearms which was histologically proven to be graft versus host disease (GVHD). He was treated over the next 2 years with cyclosporine, prednisone and topical triamcinolone 0.1% cream which maintained him at a grade I GVHD despite tapering doses of immunosuppressants. In November of 2006, he was clinically diagnosed with herpes zoster on the right arm and treated with a 4 week course of acyclovir 800 mg five times a day. He was first seen by dermatology for a new skin rash on the right arm.

Clinical Findings
Physical exam revealed confluent erythematous macules with lichenification and exfoliative scale confined to the C7-C8 dermatome of the right upper arm, forearm, hand and fingers. He also displayed severe hyperalgesia in the affected area.

Histopathology
A 4 mm punch biopsy on the right forearm confirmed GVHD.


Sclerodermoid, chronic GVHD limited to the C7-C8 dermatomes of the right arm.


Severe contractures of fourth and fifth digits of the right hand, secondary to dermatomal, sclerodermoid, chronic graft-versus-host disease.

Clinical Course
Over the next two years he had progressive induration limited to the right C7-C8 dermatomes. Repeat biopsy revealed sclerodermoid GVHD. He was treated for chronic GVHD by his hematology oncology team with cyclosporine, Rituxan and psoralen plus ultraviolet light which offered no improvement.

Discussion
GVHD occurs in 40-50% of patients who undergo an allogeneic HLA matched transplant. It occurs as a result of mature donor T cells clonally expanding in an antigen-specific manner after inadvertently labeling the host HLA as foreign.

There have been several reports in the literature of a close association between herpes VZV and the onset of chronic GVHD. While chronic lichenoid GVHD has been reported in a dermatomal distribution in skin previously affected by VZV infection, sclerodermoid GVHD in a dermatomal distribution has only been described as a personal observation.[1, 2] Even in skin without a history of past VZV infection, case reports present dermatomal, lichenoid, chronic GVHD arising de novo; however, the authors attributed these cases to subclinical VZV infection, supported by the equal frequency of clinical and subclinical VZV infection in this patient population.[3-5]

The mechanism by which herpes viruses may trigger GVHD remains unclear. One common theory suspects the viral-infected cells may have an altered antigen presentation thereby making the affected areas susceptible to GVHD. The most widely accepted theory is that the herpes virus alters the surface antigenicity of keratinocytes marking them as targets for donor effector cells. Other possible mechanisms include: viral induction of HLA class II antigen expression molecules on keratinocytes, or a cross-reaction of antibodies directed towards viral antigens with host HLA molecules.

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Case # 45
Facial Segmental Hemangioma treated with Propranolol

Resident Physicians
Diana Mcshane, M.D.
Kristen Rice, M.D.

Attending Physician
Jane Bellet, M.D.

Sites of Interest
Face, scalp.

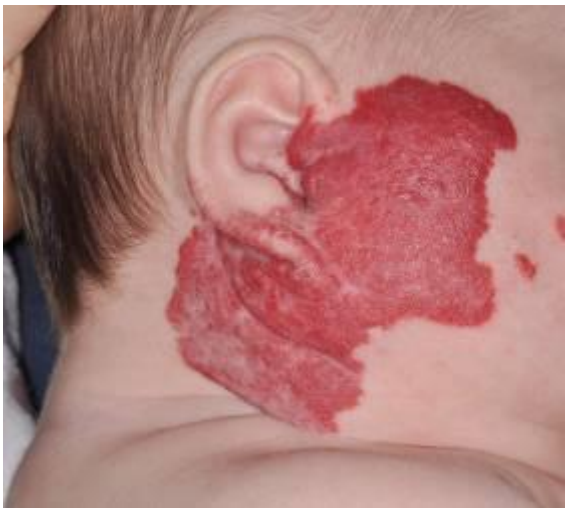
History
Full term infant born with hypo-pigmented macules on the right face that developed into a segmental hemangioma with beard distribution.

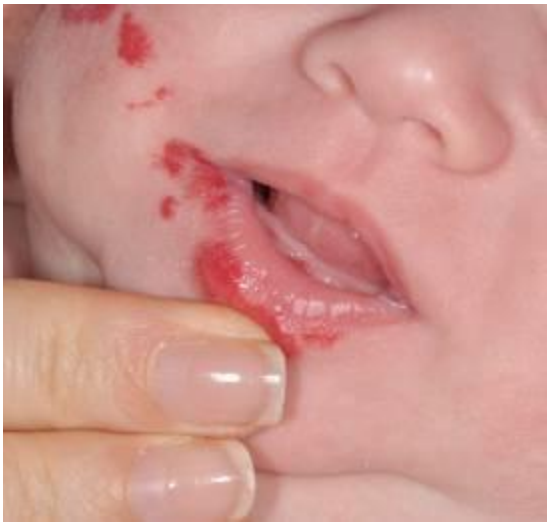
Clinical Findings
Erythematous vascular thick plaque on R cheek, lip, gingiva and ear. CTA B, RRR, no M/R/G, no stridor or SOB.

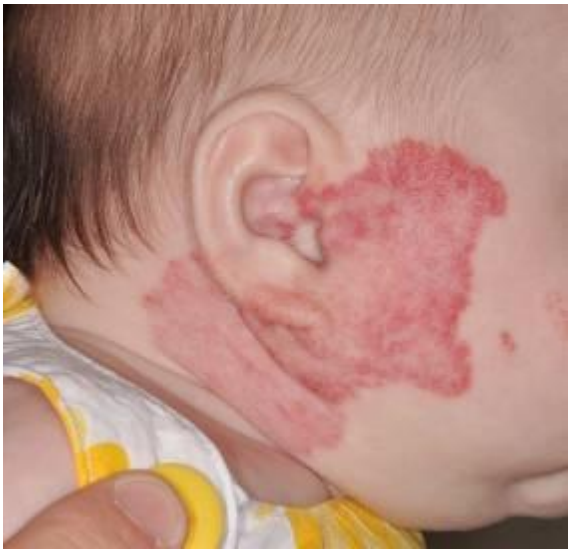
Laboratory/Studies
Head/Neck MRI/MRA; Echo, EKG normal.

Clinical Course
Started prednisolone (1mg/kg/day) until brain MRI/MRA completed. MRI nl, initiated propranolol → 2mg/ kg/day and noted rapid improvement.

Discussion
Facial segmental hemangiomas require investigation for PHACE syndrome (Posterior fossa malformations, Hemangioma-segmental distribution, Arterial lesions-in neck or brain, Cardiac- often aortic coarctation, Eye abnormalities) and if present in a beard distribution, consider potential for airway involvement. Propranolol is quickly emerging as the preferred medication for infantile hemangiomas requiring treatment.







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