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Case 1
Neurofibromatosis type 1

Resident Physician
Josh Wharton, M.D.

Attending Physician
Daniel J. Sheehan, M.D.

History
A 42 year old male with a history of neurofibromatosis type I presented with a 2 week history of tender "moles" on his abdomen. He requested removal due to the pain. Further history revealed he has a child with similar skin findings.

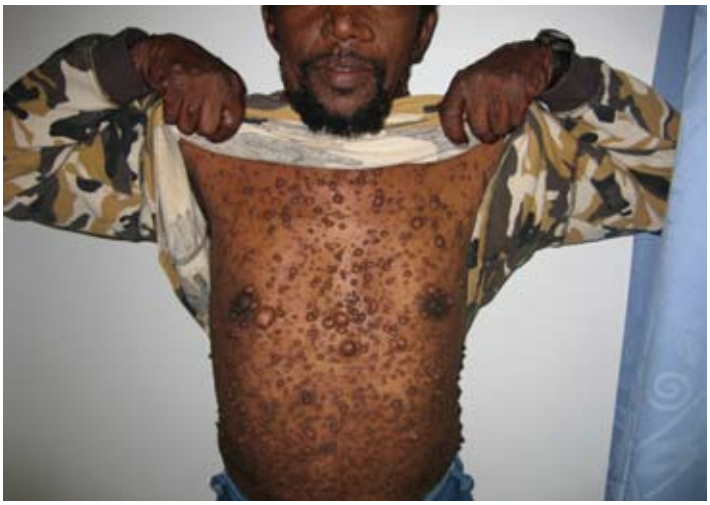
Clinical Findings
Diffuse, soft, flesh-colored papules and nodules cover a large percent of the body. A large, tender subcutaneous tumor measuring 2 x 2 cm is present on the abdomen. On palpation, it resembles a "bag of worms." Yellow-brown, well-defined, dome-shaped elevations project from the surface of the iris. Scattered freckling is noted in the axillary areas.

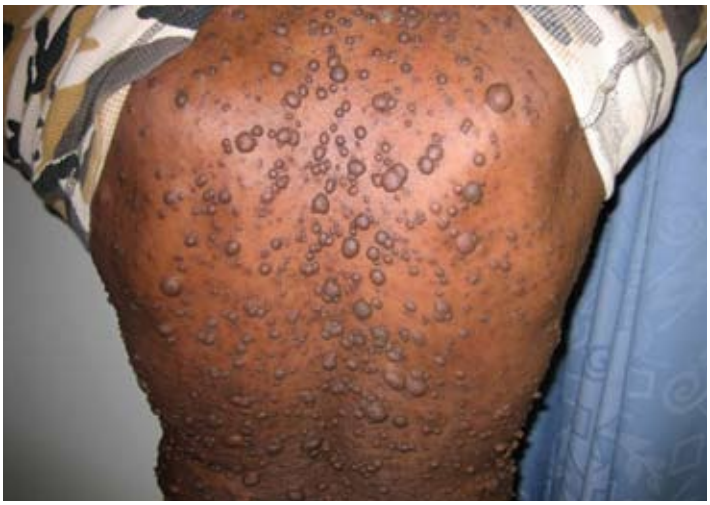
Histopathology
Excisional biopsy revealed elongated spindle cells with nerve fibers embedded in a dense matrix of fibroblasts and collagen. Mast cells were also present. No nuclear pleomorphism or mitotic activity was observed.

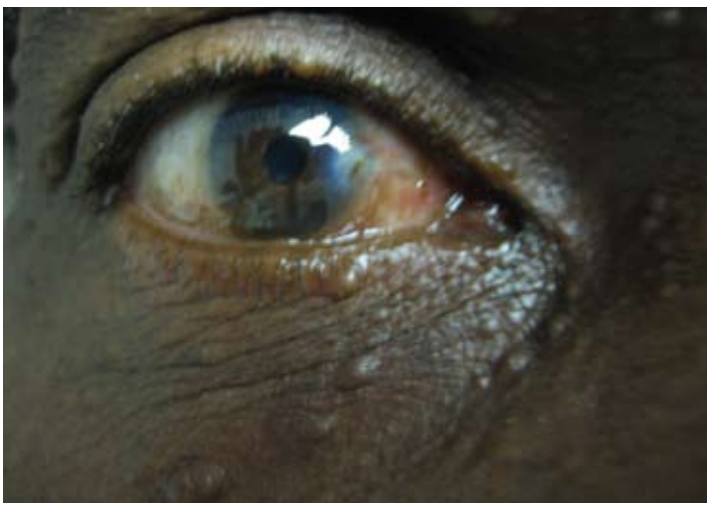
Clinical Course
The large, tender subcutaneous tumor was excised from the patient's abdomen. Although the tumor extended to the lateral and deep margins, the patient's symptoms resolved with the excision.

Discussion
NF-1 (von Recklinghausen's disease) is an autosomal-dominantly inherited syndrome with an estimated birth incidence of 1 in 2500 to 3300 infants. The diagnosis requires 2 or more of the following criteria: 1) 6 or more café-au-lait macules of more than 5 mm diameter in prepubertal individuals and more than 15 mm in postpubertal individuals; 2) two or more neurofibromas of any type or one plexiform neurofibroma; 3) freckling in the axillary or inguinal regions; 4) optic glioma; 5) two or more Lisch nodules; 6) a distinctive osseous lesion, such as sphenoid dysplasia; and 7) a first-degree relative with the disease.

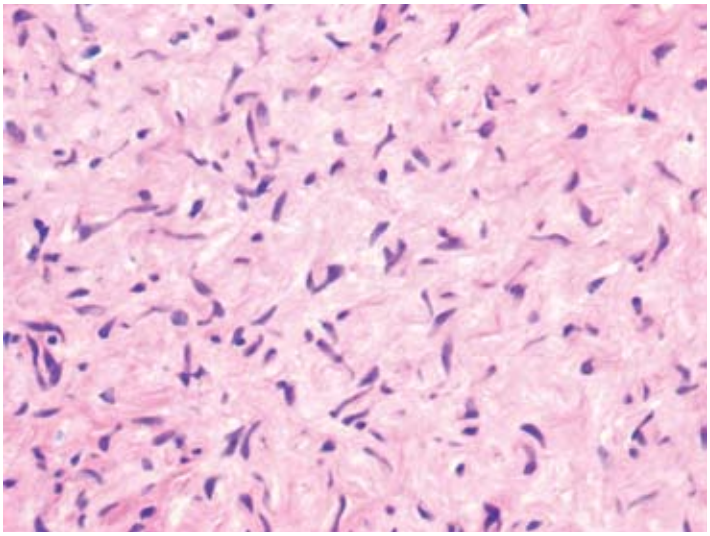
NF-1 is associated with substantial morbidity and mortality, with a decrease in life expectancy of about 15 years compared with the general population. A study by Khosrotehrani et al identified independent factors associated with mortality, which included the presence of subcutaneous neurofibromas, the absence of typical cutaneous neurofibromas, and facial asymmetry. These features can be found with routine clinical exams and may warrant more frequent follow-up. Subcutaneous and/or plexiform neurofibromas excised and found to be dysplastic neurofibromas may be a prognostic factor for transformation to malignant peripheral nerve sheath tumors, which are associated with poor prognosis.







There are currently no guidelines for screening or monitoring patients with NF-1, but the presence of subcutaneous neurofibromas, absence of cutaneous neurofibromas, facial asymmetry, and dysplastic neurofibromas may warrant increased surveillance.



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Case 2
Tuberous Sclerosis

Resident Physician
Allison R. Metzinger, M.D.

Attending Physician
Marshall Guill, M.D.

History
This is a 10 year-old boy who presented at 2 months of age to his pediatrician with a hypopigmented lesion on the forehead. The patient then presented at 4 months of age with new-onset seizures. Imaging was diagnostic of tuberous sclerosis. There is no known family history of tuberous sclerosis or seizure disorders. The patient's medical history is significant for Tourette's, ADHD and aggressive behavior.

Clinical Findings
This boy has several oblong hypopigmented patches on the back and lower extremities. He also exhibits many 1 to 4 mm hypopigmented macules on his extremities. Numerous skin-colored to pink papules are present on both cheeks and nasal ala as well as several skin-colored, firm papules and plaques on the back and left temple.

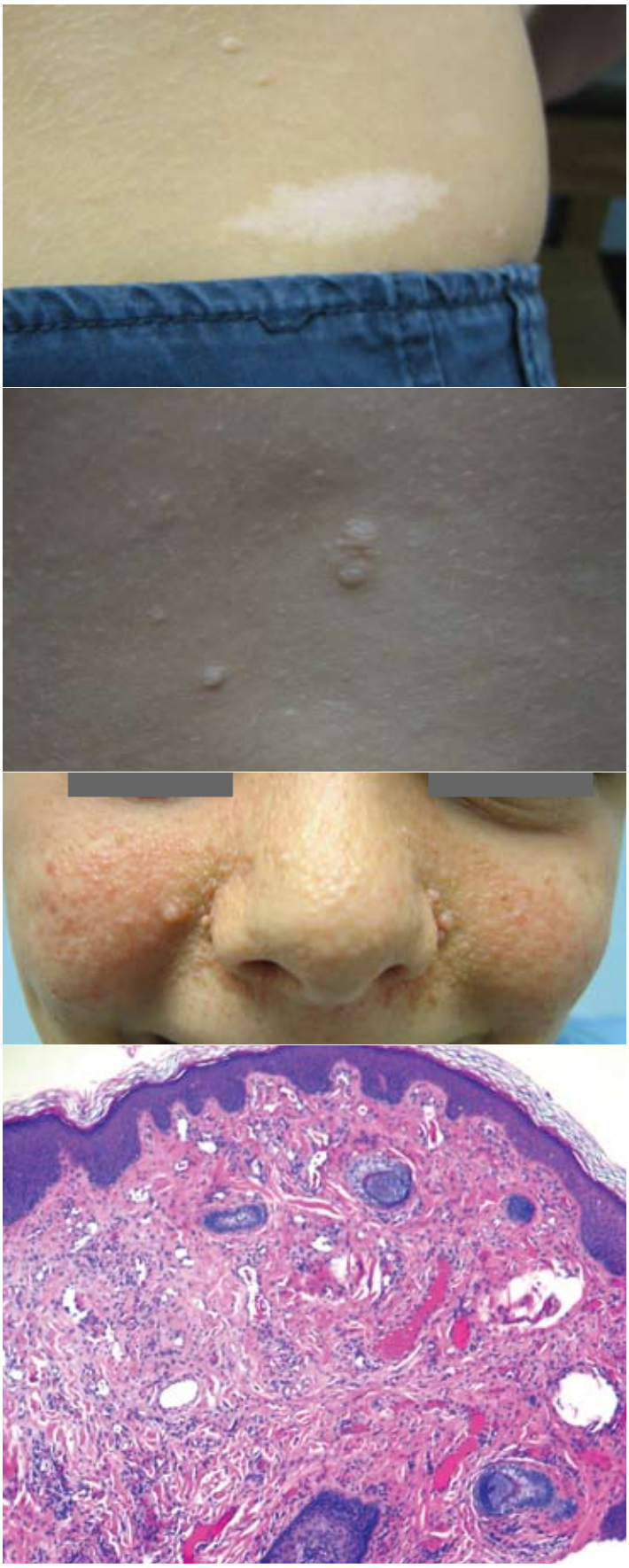
Laboratory/Studies
MRI revealed multiple cortical and subcortical hyperintense areas associated with broadening of the overlying cortex. Subependymal nodules were identified at the margins of both lateral ventricles. Renal ultrasound revealed several cystic structures but no lesions consistent with angiomyolipomas.

Histopathology
Microscopic examination of a frequently traumatized lesion from the left nasolabial fold revealed dermal stellate fibroblasts and dilated vessels consistent with an angiofibroma.

Clinical Course
This patient's seizures are controlled with Oxcarbazepine. His angiofibromas have progressively increased in number and size since the age of 4. One angiofibroma was excised due to frequent traumatization. Other cutaneous lesions are asymptomatic.

Discussion
Tuberous sclerosis (TS) is a multisystem disorder characterized by hamartoma formation. Although autosomal dominant inheritance has been established, two-thirds of cases are caused by sporadic mutations. Two tumor suppressor genes, TSC 1 and TSC 2, are responsible for TS. These genes are located on Chromosomes 9 and 16, and encode hamartin and tuberin, respectively.

Clinical manifestations are variable. The earliest cutaneous feature is hypopigmented macules, which are characteristically shaped like ash leaves. Most patients have "ashleaf macules", primarily on the trunk. Additional cutaneous manifestations include angiofibromas (adenoma



sebaceum), collagenomas (Shagreen patch), molluscum pendulum, fibrous plaque of the forehead, periungal fibromas and confetti-like macules. Patients may also exhibit retinal hamartomas (phakomas), renal hamaratomas (angiomyolipomas, cystic disease, fibroadenomas), cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis, dental enamel pitting and gingival fibromas. Individuals with TS are at risk for gliomas and astrocytomas.

Central nervous system manifestations are the primary cause of morbidity and mortality. Epilepsy occurs in greater than 90% of individuals with TS, with the majority having their first seizure before 2 years of age. Associated mental deficiencies are present in 40% to 50%. Imaging reveals hamartomas and subependymal nodules as early as 6 weeks of age. Seizure can be controlled with anti-epileptic medications.

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Case 3
Large Congenital Melanocytic Nevi/Bathing Trunk Nevus

Resident Physician
Josh Wharton, M.D.

Attending Physician
Jack L. Lesher Jr., M.D.

History
A 13 year old male presented for evaluation of large congenital nevi. He had recently moved to the area from New York to live with his grandmother. The patient maintained that his "moles" continued to enlarge as he grew. He denied associated symptoms and signs such as headaches and seizures, but was bothered cosmetically by a large "mole" on his forehead.

Clinical Findings
Large, hyperpigmented verrucous plaques cover the abdomen and lower back, and extend to the left anterior and posterior upper leg. Numerous brown to black nummular papules are scattered over both upper and lower extremities. Present on the forehead is a 3 cm dark brown plaque. Hypertrichosis is apparent in many of the large plaques.

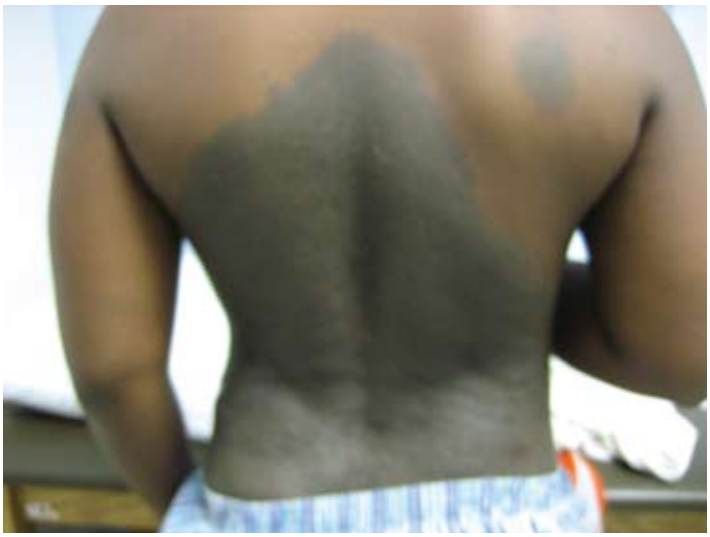
Laboratory/Studies
The patient and grandmother declined MRI of head and spine.

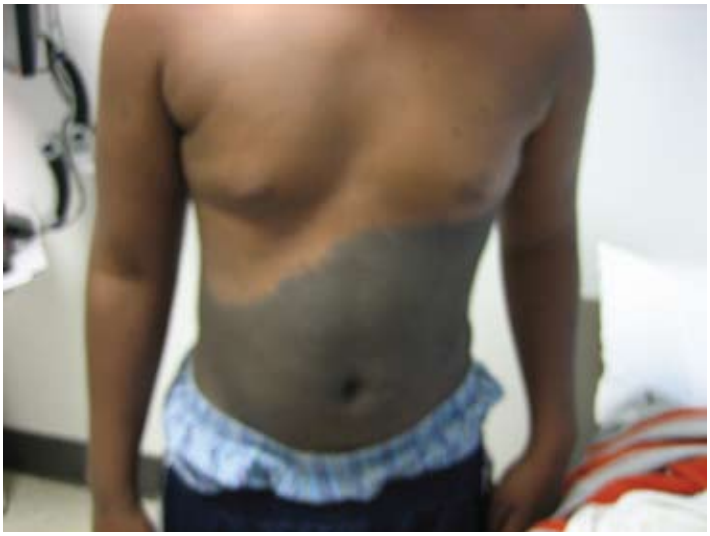
Clinical Course
The patient was referred to plastic surgery regarding possible excision of the large nevus on his forehead. He failed to return for his 6 month follow up appointment.

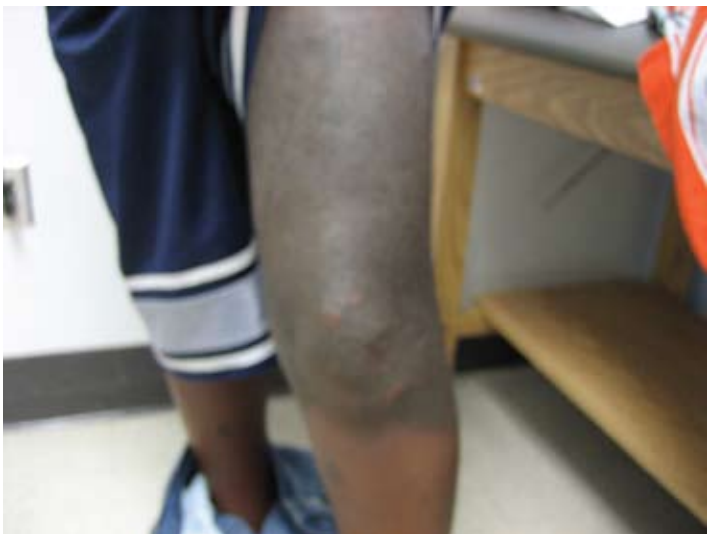
Discussion
Large congenital melanocytic nevi (LCMN) are 20 cm or more in adults (9 cm on the scalp and 6 cm on the trunk in newborns) and often cover large areas of the scalp, trunk, and extremities. The estimated incidence is 0.005%, and they are often accompanied by satellite congenital melanocytic nevi.

These patients are at risk for neurocutaneous melanosis (NCM). One study of 379 patients with LCMN had 26 patients with NCM. Patients with LCMN on the posterior axis had a significantly higher percentage of NCM. In addition, patients with LCMN and more than 20 satellites had a 5.1 fold increased risk for NCM compared with LCMN patients with 20 or fewer satellites. NCM is divided into asymptomatic and symptomatic, with symptoms typically due to increased intracranial pressure. MRI of the CNS to screen for NCM should be considered in neonatal patients with large posterior axis congenital nevi and multiple satellite nevi.

Recent studies have also confirmed substantial melanoma risk associated with LCMN. The risk for the development of MM in patients with LCMN has been reported to range from 2.9% to 18%. In a prospective study of 92 patients with LCMN, the cumulative 5-year life-table risk for the development of malignant melanoma was 4.5%. Compared







to individuals matched for age, sex, and length of follow-up to the 92 study patients, 0.013 would be expected to develop malignant melanoma. Another study revealed 12% of 289 patients with LCMN developed primary cutaneous melanoma, all of which were in an axial location. No melanomas were associated with satellite or extremity nevi. The median age at diagnosis of melanoma was 4.6 years. Up to two-thirds of melanomas arising in LCMN develop in the dermis, subcutaneous fat, or deeper as a distinct nodule.

This patient certainly meets criteria for increased risk of NCM and MM. His lack of neurological symptoms and his age are good prognostic indicators, but do not eliminate his risks. He should be followed for yearly total body skin exams and educated to perform self skin exams.

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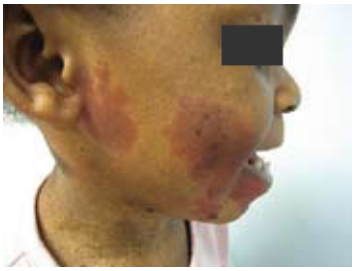
Case 4
Phakomatosis Pigmentovascularis

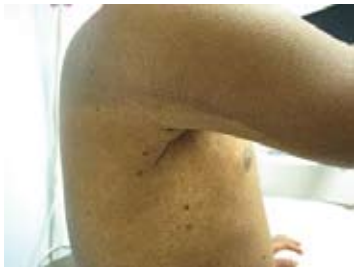
Resident Physician
Travis W. Blalock, M.D.

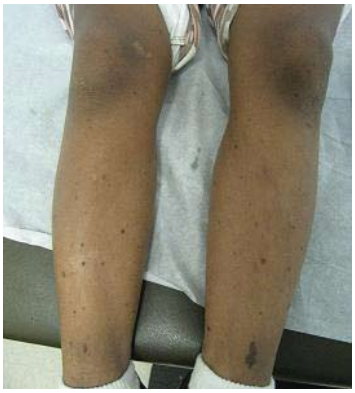
Attending Physician
Jack L. Lesher, Jr., M.D.

History
A 3 year-old adopted female presented for evaluation of a birth mark on her right cheek/neck with a presumed inherited disorder causing multiple lentigines. The patient did not complain or exhibit symptoms of pain or itching, but the foster-parent related problems with patient dental development secondary to associated hypertrophy of the lower jaw. The patient's family history is incomplete, with a suspicion of a positive maternal family history.

Clinical Findings
Well defined red macule is present on the right cheek (Photo #1). Numerous brown macules are scattered diffusely over trunk and extremities along with some scattered hypopigmented macules interspersed (Photo #2-3). There is hypertrophy of the right lower jaw with associated hyperpigmentation. A hyperpigmented to violaceous plaque with surrounding red macule is present on the right cheek. Head shape is mildly brachiocephalic. The eyes appear up slanting with medial canthal bridging.







Clinical Course
The patient was referred to Pediatric Genetics for evaluation. Patient was also referred to Pediatric Dentistry for dental evaluation and possible correction. They believed that the vascular lesion was not affecting the patients gingiva, although they note that she does have an under-developed maxilla.

Discussion
Phakomatosis Pigmentovascularis is a rare congenital association of a vascular malformation with an extensive pigmentary nevus, either of melanocytic or epidermal origin. The origin of this hereditary anomaly is explained by the didymosis phenomenon, more commonly known as the twin spotting phenomenon. This phenomenon describes the causative event as an early post-zygomatic crossover and recombination of two different autosomal recessive mutations on separate homologous chromosomes.

The division of this type of malformation has traditionally been based on the type of pigmentary component of the lesion (type I-IV). The further subdivision classifies the disease based on whether or not extracutanous manifestations or lesions are present (subtype a vs. subtype b). The extracutanous manifestations vary from inconsequential to very severe, including, but not limited to, laryngeal and subglottic anomalies, eczema, scoliosis, ocular anomalies, anemia, malignant polyposis, mental development delays, retardation, epilepsy, and cerebral atrophy. One study estimates the incidence of extracutanous manifestation as high as 50%. The most common classification scheme is displayed below, though additions to the classification have been made, as found in the Journal of American Academy of Dermatology article referenced below.

Classical Classification of Phakomatosis Pigmentovascularis		
	Vascular Component	**Pigmentary Component**
Type I	Port wine stain	Epidermal nevus
Type II	Port wine stain	Dermal melanocytosis
Type III	Port wine stain	Nevus spilus
Type IV	Port wine stain	Dermal melanocytosis and nevus spilus

The diagnosis of this lesion is primarily clinical. Treatment such as pulsed dye laser and a pigmented lesion laser (i.e. Q-switched laser) for the melanocytic component are moderately effective in treating the lesions. However, as long as there are no systemic complications, Phakomatosis Pigmentovascularis runs a benign course without any treatment necessary.

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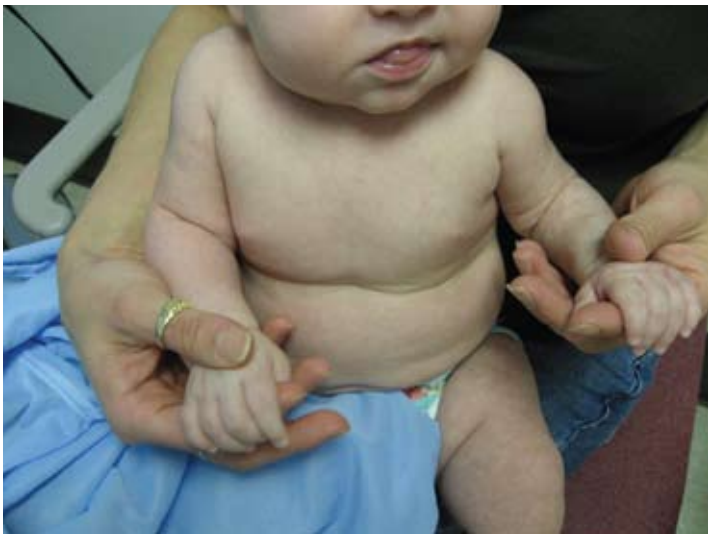
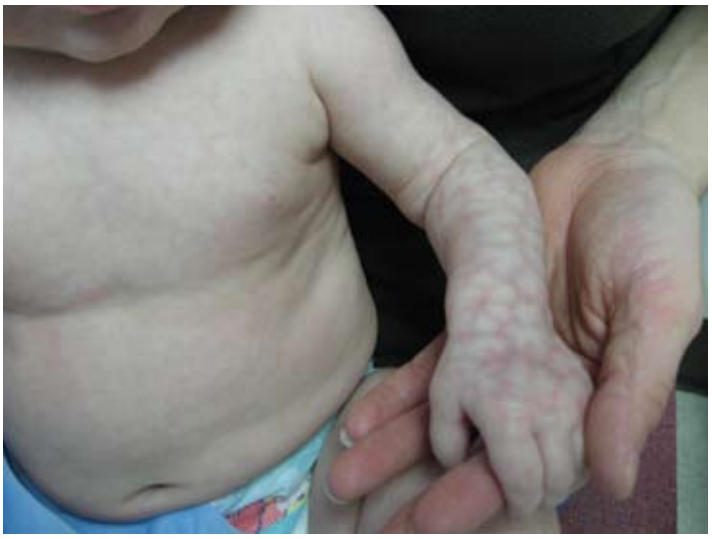
Case 5
Cutis Marmorata Telangiectatica Congenita

Resident Physician
Allison Brown, M.D.

Attending Physician
Jack L. Lesher, Jr., M.D.

Referring Physician
Scott Chapell, M.D.





History
The patient is a 2-month old female seen for evaluation of left arm atrophy and increased vessel size prominence. She has no other health problems and has had a normal development up to this point. She was born full term and no complications or abnormalities were noticed at that time. The patient does note that the reticulated pigmentation worsens with cold temperatures.

Clinical Findings
Limbs have a prominent superficial venous network. Arms are of equal length, but left arm has a decreased circumference.

Clinical Course
The patient was referred to pediatric cardiology, ophthalmology, and orthopedics due to potential systemic abnormalities including eye, cardiac, and bone/soft tissue. Orthopedics found a fully functional left upper extremity with no sensory or motor defects. They recommended periodic screening for scoliosis, as this can sometimes be associated with cutis marmorata telangiectatica congenita. The patient continues to be followed by dermatology and some lightening of the vessels has been observed as she has aged. The slight left-sided hemiatrophy persists but the patient currently has full functional use of that arm.

Discussion
Cutis Marmorata Telangiectatica Congenita (CTMC) is a congenital phlebectasia that is characterized by violaceous reticulated dark purple lesions usually in a segmental distribution most commonly affecting one limb and the corresponding quadrant of the trunk. Occasionally, atrophic depressions may ulcerate, especially if they are over the joints, resulting in scarring. The most dramatic changes tend to occur in the fist year and the lesions taper thereafter. This entity becomes more apparent when blood flow to the affected area is increased, such as by vigorous activity or crying. Cold also accentuates the lesions.

Up to 50% of patients have been reported to have other associated abnormal findings, such as nevus flammeus, varicosities, macrocephaly, hypoplasia and hypertrophy of soft tissue and bone. Unusual associations are with generalized congenital fibromatosis, premature ovarian failure, Arnold-Chiari type I malformation, and rectal and genital anomalies. These lesions have been associated with Mongolian spots as type 5 phacomatosis pigmentovascularis, and have been reported in association with the Adams-Oliver syndrome (limb abnormalities, scalp defects, skull

ossification defects). Lastly, CMTC has been described in infants with neonatal lupus erythematosus.

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Case 6
Sturge-Weber Syndrome

Resident Physician
Allison R. Metzinger, M.D.

Attending Physician
Loretta S. Davis, M.D.

History
This 23 year-old male was noted at birth to have a violaceous plaque over the right face. At 8 months of age, the patient presented with focal seizures. His facial plaque has remained asymptomatic throughout his life. Right-sided hemihypertrophy worsened during puberty but has been stable since that time. The patient's medical history is significant for developmental delay and obstructive sleep apnea.

Clinical Findings
This young man has a violaceous plaque on the right face in the distribution of the right V1 and V2 branches of the trigeminal nerve. There is associated right-sided hemihypertrophy extending to the right neck, right upper trunk and right arm. Gingival hyperplasia and prominent vasculature of the right eye conjunctiva are also present. Cranial nerves I – XII are intact.

Laboratory/Studies
MRI of the head revealed right hemispheric hemiatrophy, diffuse angiomatous leptomeningeal enhancement thoughout the right cerebral hemisphere convexity, asymmetric enhancement of right choroid plexus and leptomeningeal enhancement of the brainstem to the right of midline. Mucosal lesions are noted at the level of the tonsillar fossa. Calvarium hypertrophy is present on the right side.

Clinical Course
The patient's seizures are controlled with Phenytoin and Phenobarbital. He underwent palatopharygoplasty at age 11 to treat obstructive sleep apnea.

Discussion
Sturge-Weber Syndrome (SWS) is a rare, sporadic syndrome occurring in 1 per 50,000 live births. It is characterized by a unilateral capillary malformation in the V1 distribution of the trigeminal nerve, leptomeningeal angiomatois and a choroid malformation. The capillary malformation is present at birth and may extend to other dermatomes. When extending to V2 regions, gingival and maxillary hypertrophy may be associated.

Neurological manifestations occur in the majority of patients with SWS. Epilepsy occurs in 75% to 90% of patients, with 75% of these patients having seizures within the first year of life. Mental retardation occurs in 50% to 65% of patients with SWS. Patients with more extensive neurological involvement are at higher risk for developmental delay and mental retardation. Hemiplegia occurs in 30% and headaches are common in adults. Glaucoma is the most common ocular finding. It is associated with a choroid malformation. Two-thirds of patients present with glaucoma at birth, but it has been reported to arise in adulthood.

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Case 7
Epidermolytic hyperkeratosis

Resident Physician
Betsy R. Cooke, M.D.

Attending Physician
Loretta S. Davis, M.D.

History
A thirty-two year old female reported blisters on her legs as a child and a life long history of rough, dry skin. She remembers being on erythromycin for infections when she was younger. Her father, grandfather, and sister all had similar skin problems although some had worse disease than others. She had been on isotretinoin in the past with improvement in pruritus. Her affected sister was doing well on acitretin. She first presented to our clinic one year ago.

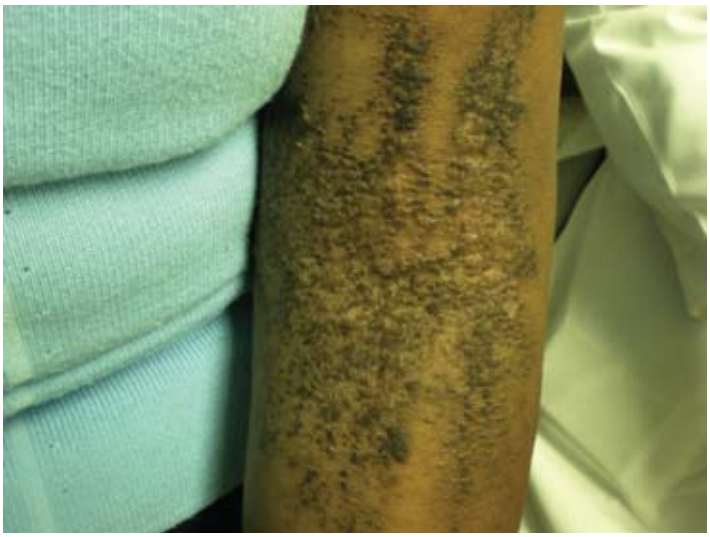
Clinical Findings
There is diffuse skin thickening with hyperkeratosis. Verrucous plaques are present on the arms, legs, and trunk. Corduroy-like hyperkeratosis is present in the antecubital fossae. The patient's palms are fissured with a contracture of the 4th right digit. The skin lesions have a foul-smelling odor.

Clinical Course
The patient was started on isotretinoin and received a four month course with overall improvement. Her course was cut short as insurance, despite numerous appeals, would no longer pay for the medication. Because the patient is of "child-bearing potential," acitretin therapy has been withheld. She was then started on Vitamin A therapy at 50,000 units daily. She does feel the Vitamin A has helped her skin.

Discussion
Epidermolytic hyperkeratosis, also known as bullous congenital ichthyosiform erythroderma, occurs in 1 of every 100,000-300,000 live births. The mode of inheritance is autosomal dominant but 50% of cases are sporadic indicating new mutations. The disease manifests itself at or shortly after birth with erythema, blisters, and superficial ulcerations. In the newborn period, denuded areas can lead to fluid and electrolyte imbalances. Sepsis is a major concern.

The flexural areas are initially involved. With age, blistering decreases while hyperkeratosis and scaling become more prominent. Scales can be dark brown, gray, or white. The warty scales are increased over flexor surfaces but can also be found on the palms and soles. Secondary bacterial colonization and infection can occur producing a foul odor. Although rare, digital contractures like that seen in our patient can occur.

Mutations in genes for keratins 1 and 10 are responsible for epidermolytic hyperkeratosis. These keratins are expressed in the suprabasal layers of the epidermis. Due to the variety of mutations that can occur, there are variable phenotypes and severities of this disease.



In the newborn period, patients may need to be placed in the intensive care unit so that fluid and electrolyte imbalances and any superinfection can be treated. Care should be taken in handling the neonate so as to prevent blister formation. As a child and an adult, treatment is also symptomatic. Emollients should be applied to aid in softening the skin. Bathing with antibacterial soaps can help lessen colonization, and these patients may require topical or oral antibiotic treatment. Systemic retinoids are useful in improvement of the hyperkeratosis. Low doses must be used however to prevent side effects such as skin fragility, increased blistering, and delayed healing.

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Case 8
Keratitis-Ichthyosis-Deafness (KID) Syndrome

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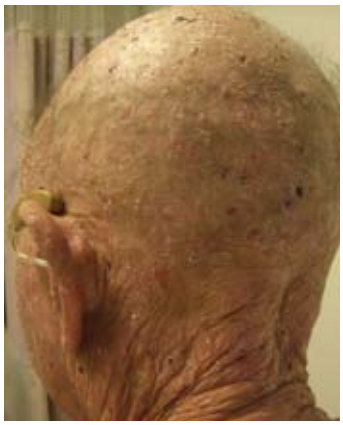
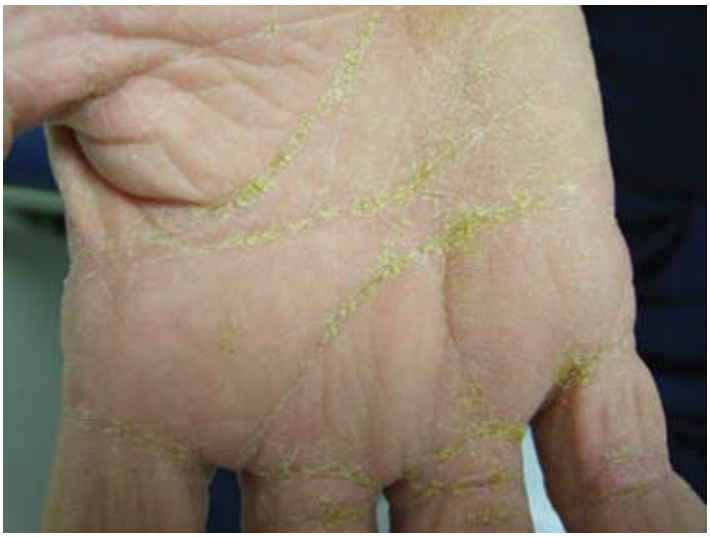
Attending Physician
Jack L. Lesher, Jr., M.D.

Referring Physician
Dennis Doud, M.D.





History
A fifty-eight year old female was referred for treatment of her hyperkeratotic skin lesions a year and a half ago. She had been treated in the past with PUVA, multiple topical agents, and other oral medications. Her main complaint was the plaques on the soles of her feet that were tender and would crack. She had been seeing ophthalmology for corneal neovascularization and scarring. Her sister reported the patient had hearing loss since birth and was almost deaf.

Clinical Findings
The patient wears a hearing aid in her left ear. There are erythematous crusted patches over the scalp with alopecia. Eyebrows and eyelashes are also absent. Her face, neck, upper back, and lower legs have erythematous, ichthyotic patches and plaques. Hyperkeratotic, adherent plaques with fissures are present on palms and soles.

Histopathology
No biopsy specimen was obtained.

Clinical Course
The patient was treated with topical corticosteroids, topical antifungals, and keratolytics. She has required multiple courses of antibiotics for superinfections. Recently, she was started on acitretin and can tolerate 25 mg daily. There has been improvement in the hyperkeratosis. The patient also had a squamous cell cancer removed from her lateral canthus area. Her scalp has improved with topical imiquimod treatment. She continues to follow up with ophthalmology for the corneal neovascularization.

Discussion
KID syndrome is a rare (about 70 cases reported) congenital disorder of ectoderm. It is characterized by vascularization of the cornea, ichthyosiform eruption, and sensorineural deafness. The skin findings develop in the first 3 months of life and have features of erythrokeratodermia rather than being typical of classic ichthyosis. Verrucous, leathery plaques can be found on the central portions of the face, scalp, elbows, and knees. The keratitis is of later onset and is progressive in contrast to the sensorineural deafness which is congenital and non-progressive.

Other findings include hyperkeratosis of the palms and soles, nail dystrophy, and alopecia. The alopecia may only involve the eyebrows, eyelashes, and scalp or may be universal. KID syndrome patients are more susceptible to cutaneous bacterial, viral, and fungal infections but an underlying immune problem has not been clearly defined.

The mode of inheritance is thought to be mostly sporadic but cases of familial transmission have been reported. A missense mutation in the GJB2 gene that encodes connexin 26, a gap junction protein, is thought to be responsible for the disorder.

Treatment can be difficult and requires a multidisciplinary approach. Reports of acitretin clearing the hyperkeratotic lesions provide a promising new treatment option. Also, squamous cell carcinomas have been reported in this population (as in our patient) and periodic dermatologic monitoring is required. The patient's keratitis should be monitored by ophthalmology and referral to an otolaryngologist should be considered for evaluation for cochlear implants.

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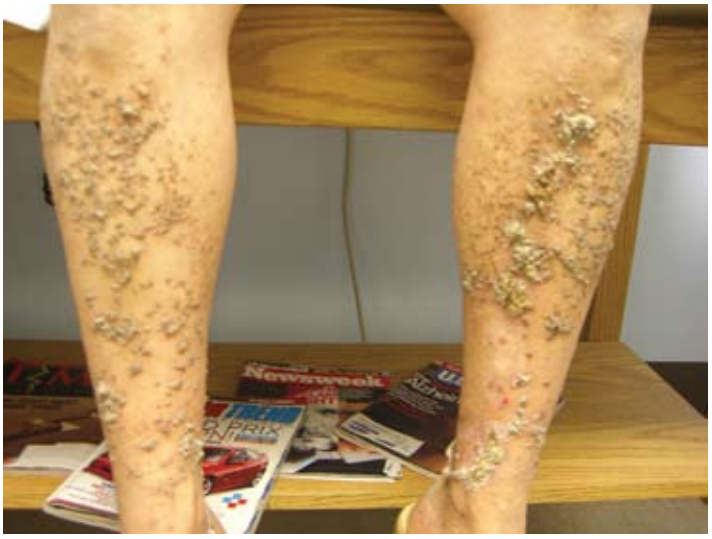
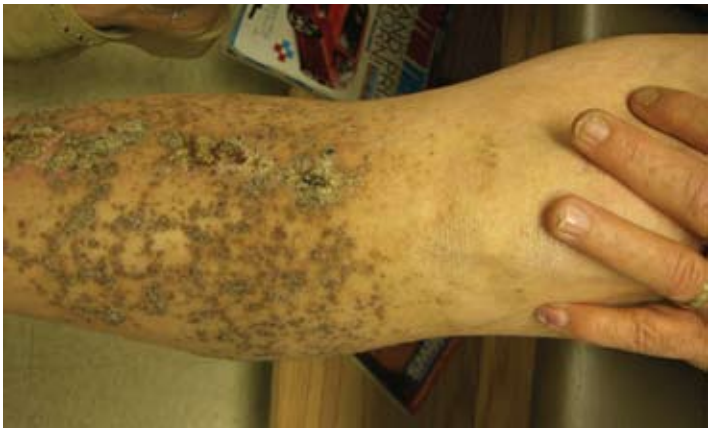
Case 9
Darier's Disease

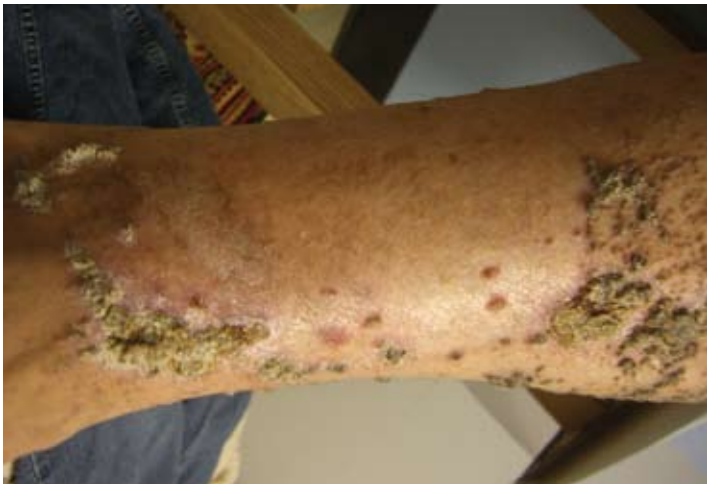
Resident Physician
Jeannette Hudgens, M.D.

Attending Physician
Jack L. Lesher, Jr., M.D.

Referring Physician
Arthur Klein, M.D.







History
A 51 year-old female presented with a long history of multiple hyperkeratotic lesions on her trunk and legs. She complains of recurrent flaring of her disease which causes drainage and significant pain affecting her quality of life. The patient was previously seen by another dermatologist who had tried multiple topical treatments. She then underwent dermabrasion to an isolated area on her left leg which continues to remain clear.

Clinical Findings
The patient has numerous brown, hyperkeratotic papules on the back, mid chest, and abdomen with coalescing plaques on her bilateral lower legs. There is a well defined area of almost complete clearing on her left anterior lower leg corresponding to treatment with dermabrasion.

Histopathology
Histopathology of Darier's disease reveals acantholysis and dyskeratosis. Two different types of dyskeratotic cells are observed, corps ronds and corps grains. The epidermis shows papillomatosis and hyperkeratosis and there is a perivascular inflammatory infiltrate in the superficial dermis.

Discussion
Darier's disease is an autosomal dominant disorder characterized by brown, crusted, malodorous lesions with a follicular distribution. Suprabasilar acantholysis and apoptosis results from abnormal function of the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2, also known as ATP2A2). This leads to abnormal intracellular Ca^{2+} signaling of the endoplasmic reticulum and mitochondria necessary for efficient cell-to-cell adhesion. The disease usually begins around puberty with a seborrheic distribution and involving the flexures. The lesions often become confluent forming a papillomatous mass that is frequently malodorous. This is likely due to secondary infections with yeast, dermatophytes and bacteria. Almost all patients have nail changes that include red and white longitudinal lines or ridging, subungual hyperkeratosis, and V-shaped notches. Clinical differential diagnosis includes Acrokeratosis Verruciformis of Hopf, Grover's disease, Pemphigus vegetans, Blastomycosis-like pyoderma, and Hailey-Hailey disease.

Treatment options include emollients, corticosteroids, retinoids, and antibiotics and antifungals which help treat the malodor. Isotretinoin and acitretin have been very effective treatments, but patients usually relapse after cessation. Surgical treatments include excision followed by

grafting, dermabrasion, CO_2 laser, and erbium:YAG laser. These treatments have provided more long-term remission.

Dermabrasion was used in our patient which has provided continued local remission for three years. The areas treated are sharply demarcated from the untreated areas. Due to loss of insurance, she could not follow up for further treatments.

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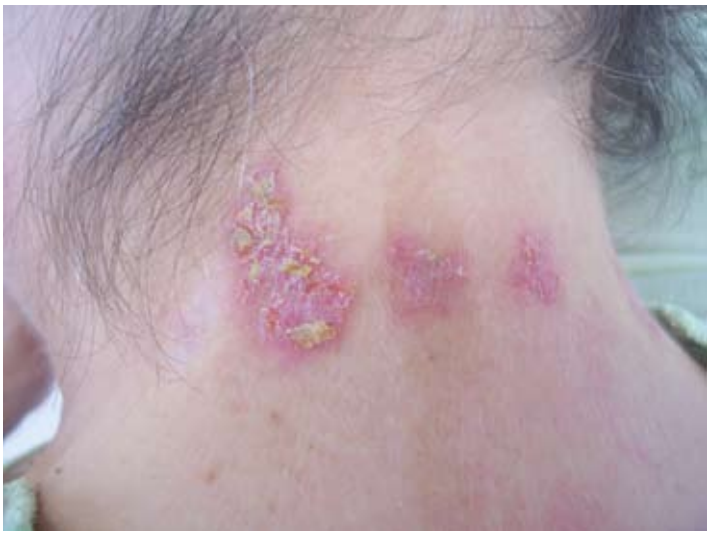
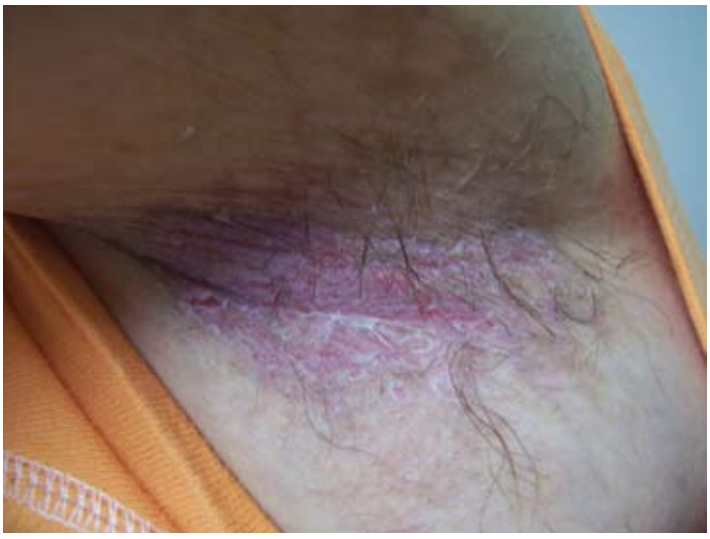
Case 10
Hailey-Hailey Disease

Resident Physician
Allison Brown, M.D.

Attending Physicians
Daniel Sheehan, M.D.
Lorretta Davis, M.D.

Referring Physicians
Omar Ali, M.D.
John Reeves, M.D.



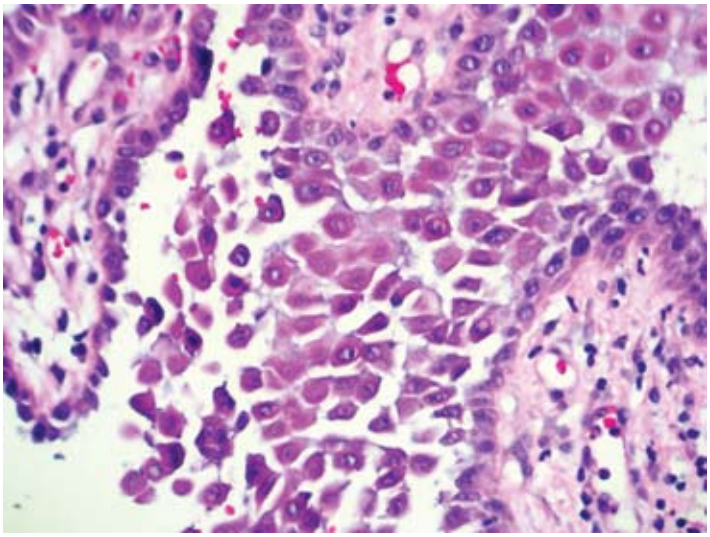


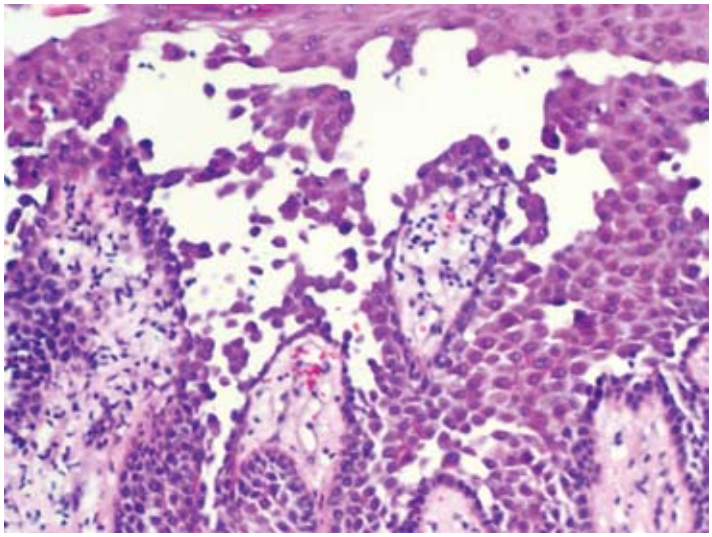
History
The patient is a 52-old female who presents with a 20+ year history of a pruritic rash in the groin, under breasts, on posterior neck on upper back, and on posterior lower extremities. The patient did have biopsy-proven Hailey-Hailey disease prior to referral in 10/2005. She had been treated with several topical steroids, acitretin, azathioprine, and prednisone prior to referral.

Clinical Findings
The patient has macerated erythematous patches and papules coalescing into plaques in groin creases, axillae, under breasts, on her posterior neck, upper back, and on her bilateral popliteal fossae.

Histopathology
Biopsy shows acantholysis diffusely within the epidermis. There are large areas of dyscohesion with single or groups of acantholytic cells likened to a 'dilapidated brick wall'.

Clinical Course
After the patient failed conservative therapies with topical antibiotics, topical steroids, and oral antibiotics, cyclosporine 300 mg po qd was started in 2006. The patient had an excellent response to the cyclosporine, but experienced elevated creatinine.





The patient flared once the cyclosporine was discontinued and was started on adalimumab 40 mg q o w, doxepin po 30-100 mg qd, and numerous treatments with oral clindamycin, cephalexin, doxycycline, hibiclens and topical bactroban for methicillin-senstitive staph aureus. After several painful flares, azathioprine 100 mg bid was started in 11/2006, and oxycodone and acetaminophen added for pain. Triamcinolone injections to the neck and lidocaine/epinephrine to the axillae were performed in 08/2007. The lesions improved and subsequent injections were done. CO2 laser treatments (at settings 175 Hz, 15w) were done on the bilateral axillae on 11/07, with no subjective improvement. Calcipotriene cream and tacrolimus 0.1% ointment were added to the axillae in 12/2007. Azathioprine was stopped in 01/08, and mycophenolate mofetil 500 mg bid increasing to 1 g bid was started. Mycophenolate mofetil was discontinued in 04/2008 due to non-response, and cyclosporine 300 mg qd was re-started.

The patient is a smoker and her blood pressure was in the 150s/80s at home and in the office. She has a history of being non-compliant with hypertension medications and follow-ups with her primary care physician. The patient has reported that cyclosporine is the only treatment that has ever improved her lesions significantly. Unfortunately, her creatinine has begun to rise, and we have started to decrease her cyclosporine dose. She is presented in the hope of suggestions for treatment.

Discussion

Hailey-Hailey disease is characterized by recurrent bullous and vesicular dermatitis of the sides of the neck, axillae and flexures, which may become generalized. The scalp, antecubital and popliteal fossae or trunk are less frequently involved. Inframammary lesions are common in women. The primary lesion is a flaccid vesicle on an erythematous base or on normal skin which ruptures easily and may be overlooked. Development of chronic, moist, malodorous vegetations and painful fissures is common. Healing occurs without scarring, leaving post-inflammatory hyperpigmentation.

Hailey-Hailey disease is inherited in an autosomal-dominant matter, but 30% of patients express new mutations. The genetic defect is in a calcium ATPase (ATP2C1) on chromosome 3q21. Acantholysis is likely mediated through impaired calcium sequestration resulting in the depletion of intraluminal Golgi Ca^{2+}. Lesions tend to recur at sites of prior involvement, and may be triggered by trauma, bacterial or fungal infections, or other dermatoses.

Complete remissions and flares are common, and the clinical course in an individual patient is difficult to predict. Some patients report lessening of the lesions as they progress in age but others state their disease worsens with age.

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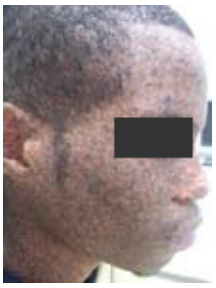
Case 11
Xeroderma Pigmentosum

Resident Physician
Travis W. Blalock, M.D.

Attending Physicians
Daniel J. Sheehan, M.D.
Jack L. Lesher, Jr., M.D.



History
A teenage male presented for chronic care for his known skin disorder, which had resulted in multiple diagnoses of skin cancer. The patient's mother noted a full term pregnancy with no obvious problems. At birth, the patient's skin was "normal". Sometime during the first year of life, the patient began developing what the mother thought to be freckles. Over the first few years of life, the patients irregular patches of light and darkly pigmented areas increased. At the age of 11, the patient developed a mass on his right medial canthus, which was diagnosed as a primary conjunctival squamous cell carcinoma. The patient underwent a right orbital exenteration. Over the subsequent 7 years, the patient developed and was treated for multiple skin malignancies, despite conscientious attempts at sun protection and avoidance.

Clinical Findings
There are diffuse irregular patches of interlaced hyperpigmentation and hypopigmentation on face, scalp, trunk, and all extremities.

Laboratory/Studies
PET CT (3/21/2008): Study was ordered secondary to complaints of chronic headaches, but revealed no evidence of active disease or metastasis relating to prior ocular squamous cell carcinoma.

Histopathology
06/06/2001

- Squamous cell carcinoma of right conjunctiva with orbital invasion

08/22/2005

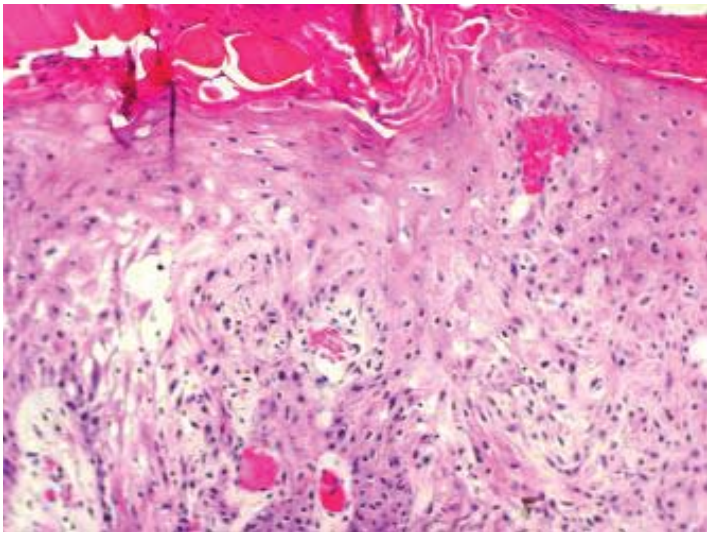
- Atypical intra-epidermal melanocytic proliferation consistent with residual in situ malignant melanoma, Clark level 1 and nodular basal cell carcinoma of right scalp skin

04/17/2006

- Residual in situ malignant melanoma, Clark 1 of forehead skin
- Basal cell carcinoma, nodular pattern and an atypical junctional melanocytic proliferation consistent with an early evolving in situ malignant melanoma of the nose

08/13/2007

- Nodular basal cell carcinoma, pigmented type of left eyebrow



- In situ malignant melanoma and pigmented actinic keratosis of left forehead x 2
- In situ malignant melanoma, pigmented actinic keratosis, and focal squamous cell carcinoma in-situ of left forehead
- Nodular basal cell carcinoma with foci of squamous differentiation as well as foci of prominent clear cells on right nasal ala

10/08/2007

- Basal cell carcinoma, nodular type of nasal bridge
- Atypical melanocytic neoplasm most consistent with an evolving melanoma in-situ of left third finger

Clinical Course
The patient continues UV avoidance and sun protective measures. He continues to have multiple skin and neurological evaluations every 3-6 months. The patient remains on acitretin (25mg) for chemoprophylaxis and has received intermittent treatment with topical retinoids.

Discussion
Xeroderma Pigmentosum is an autosomal recessive genodermatosis resulting in a defective thymidine dimer

excision repair mechanism. Clinically, this abnormal repair mechanism results in skin that is very sensitive to ultra violet (UV) damage with the development of numerous benign, premalignant, and malignant cutaneous neoplasms. Most often, these occur very early in childhood with development of squamous cell carcinoma, basal cell carcinoma, or melanoma. These patients also develop significant ocular pathology, most notably in the region of the eye with UV exposure (ectropion, corneal opacity, ocular neoplasm in 40% of patients). Others develop neuropathic sequelae that results in the evolution of severe neurodegeneration. Treatment is championed by protection from 'sun' exposure. Topical retinoids can be used to prevent neoplasms, but seem to only suppress them while the treatment is continued. Gene therapy remains an active area of research for potential treatment.

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Case 12
Pachyonychia Congenita

Resident Physician
Susan Corey, M.D.

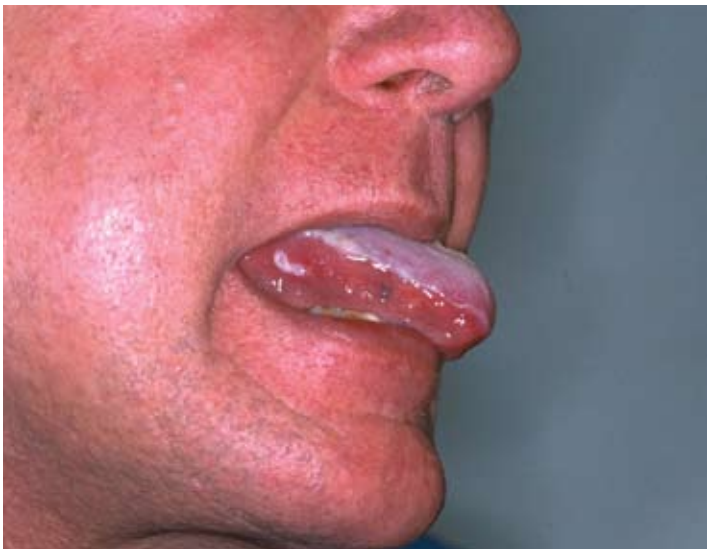
Attending Physician
Loretta Davis, M.D.

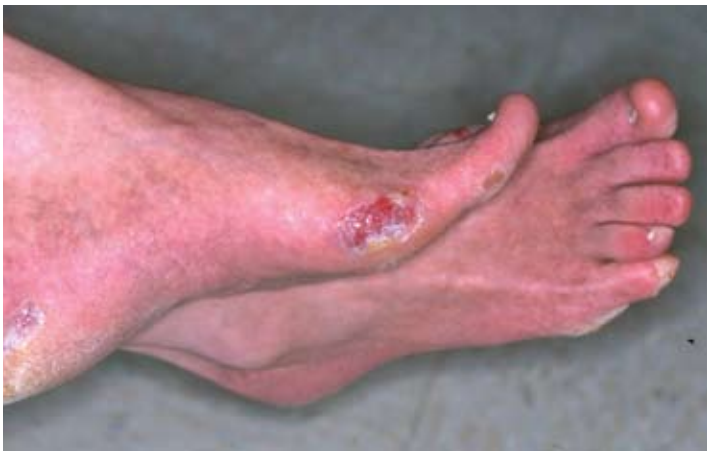
History
This patient is a 63-year-old male who developed nail discoloration and thickening as a young infant. At around the age of four, the patient began to experience blistering of his hands and feet and increased thickening of his nails. He saw one physician who attempted nail avulsion. Soon afterwards, he was noted to have small papules on his elbows and knees. During the 1960s, he was seen by dermatologists at the Mayo Clinic and at Johns Hopkins and given the diagnosis of Epidermolysis Bullosa Simplex. In the 1970s, he developed asymptomatic white patches on his tongue. He then presented to the dermatology clinic at the Medical College of Georgia in the late 1980s or 1990s and was diagnosed with pachyonychia congenita Type I. The patient has an affected daughter and grandson, whose nails are shown in the last picture. The daughter has undergone genetic testing confirming this diagnosis.

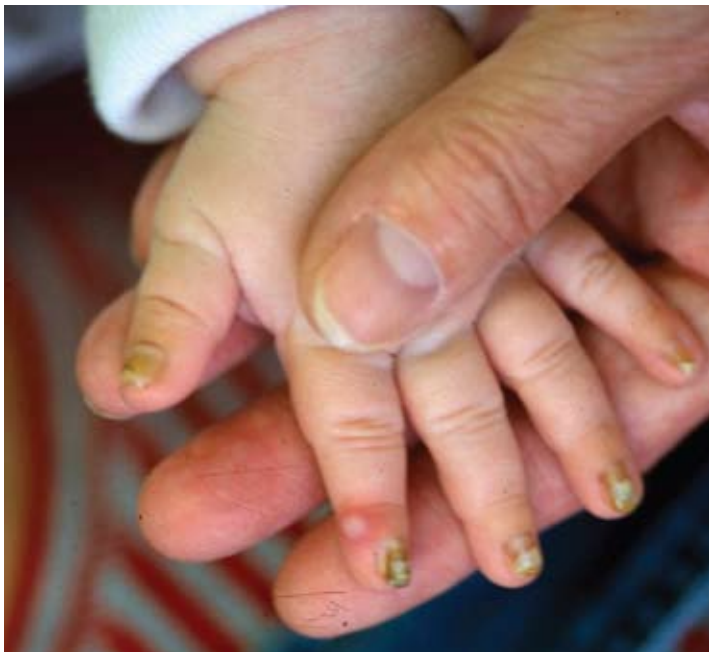
Clinical Findings
Hyperkeratotic plaques with occasional intact tense blisters occur mainly over the heels and plantar aspects of the metatarsal joints. Multiple small follicular papules are present on the patient's elbows and forearms. White plaques can be seen on the tongue.

Clinical Course
Since establishing care at the Medical College of Georgia, the patient's major concern continues to be recurrent painful blisters on his feet that become secondarily infected requiring intermittent courses of antibiotics. He has used multiple topical agents to help with the hyperkeratosis and to prevent infection. Obtaining a handicapped-parking permit has greatly aided in limiting blister formation as has his current 'cutaneous cocktail' of mupirocin ointment, ciclopirox gel, and sodium sulfacetamide lotion. Also of note, the patient has recently been diagnosed with minimal change renal disease by renal biopsy, which is not known to be associated with pachyonychia congenita.

Discussion
Pachyonchia congenita type I is a rare, usually autosomal dominant, disease that presents with predominately nail, skin, and mucosal findings. Keratin 6a and 16 are mutated. Nails and toenails of an affected patient are thickened with yellow subungal debri, and chronic paronychia is often present. Patients also get palmar and plantar hyperkeratosis and hyperhidrosis. Painful friction blisters occur under callosities on the soles and lateral feet and may become secondarily infected. Follicular keratotic papules may occur on the buttocks and and dorsal extremities. Oral leukoplakia is common. But unlike in dyskeratosis congenita, it does not







predispose the individual to malignancy in the area. While corneal cataracts and corneal dystrophy are rare in patients with pachyonychia congenita, the eyes should be monitored as corneal dystrophy can lead to patient blindness.

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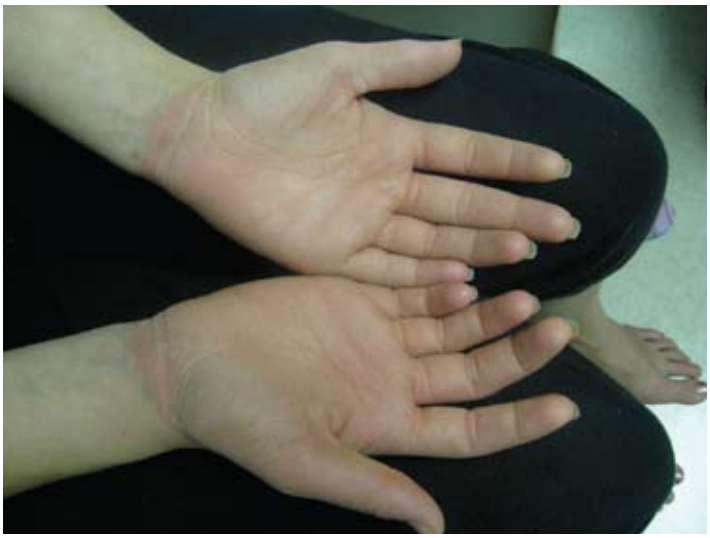
Case 13
Diffuse Nonepidermolytic Palmoplantar Keratoderma (considering Unna Thost vs. Sybert/Greither)

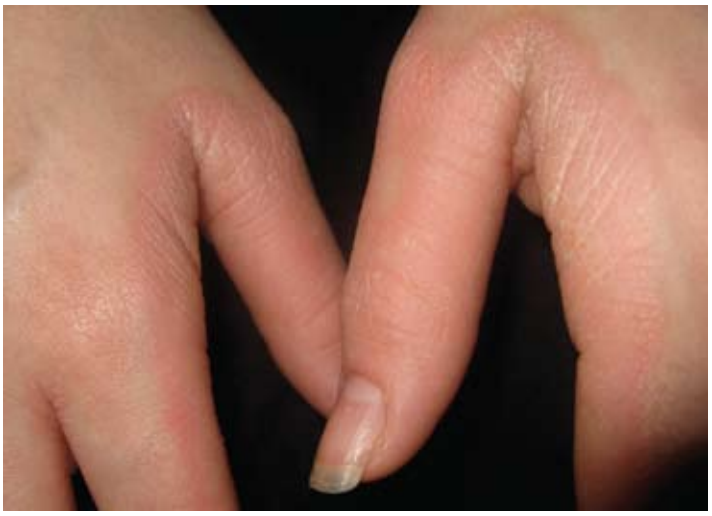
Resident Physician
Betsy Cooke, M.D.

Attending Physician
Jack L. Lesher, Jr., M.D.

History
An eleven year old female presented for treatment of a rash on her hands and feet since birth. The patient is adopted, and her adoptive mother states this rash was noted in the patient's records. The patient was bothered by the slight redness that covered her palms and soles. She also reported increased sweating and odor of these areas particularly her soles. There was no stinging or itching of the lesions. She had used topical corticosteroids in the past with no improvement. Her adoptive mother stated she was otherwise healthy except for frequent urinary tract infections. The patient denied hearing, vision, or dental abnormalities. She first presented to our clinic two months ago.

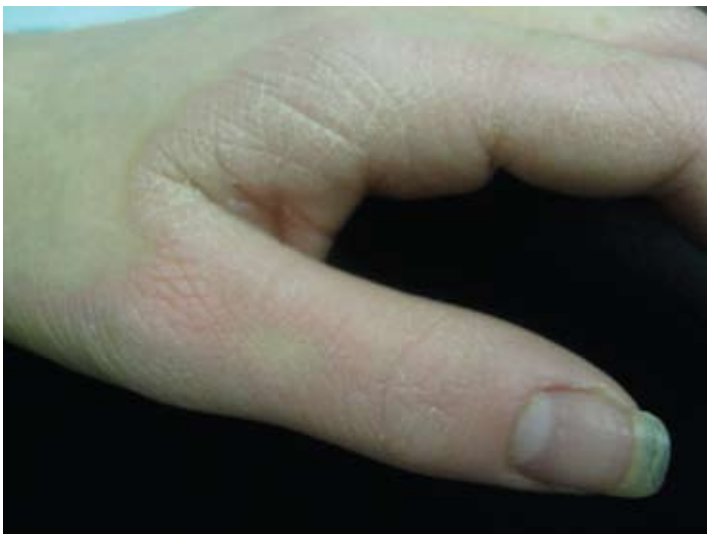


Clinical Findings
The patient is a healthy appearing preteen female. There are well demarcated slightly erythematous and scaly plaques on the palms and soles that extend to the dorsum of these areas (transgrediens). She has no other skin lesions on exam. Her fingernails have unusually oriented longitudinal ridges. The patient's teeth are grossly normal.



Histopathology
Punch biopsies were performed of the left and right hands. Both specimens demonstrated hyperkeratosis, hypergranulosis, and epidermal hyperplasia consistent with nonepidermolytic keratoderma.

Clinical Course
The patient was originally prescribed erythromycin solution and ketoconazole cream to be used twice daily on her feet. Ammonium lactate cream was also recommended for use on her hands. At a recent appointment, the patient felt the ketoconazole cream improved the odor and sweating of her feet. Tretinoin 0.05% cream was added for use on palms and soles at this visit.



Discussion
Hereditary palmoplantar keratodermas (PPK) are a varied group of diseases that are characterized by marked thickening of the palms and soles. PPK of Sybert, also known as Greither's disease, is an autosomal dominant form of diffuse nonepidermolytic PPK. Patients have hyperkeratosis, scaling, and erythema of the palms and soles, and hyperhidrosis is an associated feature. Dorsal extension onto the hands and feet (transgrediens) is present, and the skin over the Achilles tendon is characteristically involved. Hyperkeratotic plaques can be found on the knees and elbows. Classically, the disease starts in the first few years of life although onset shortly

TABLE 1. *Differential Diagnoses of Greither PPK*

	Greither PPK	Unna–Thost PPK	Vorner PPK	Mal de Meleda PPK
Onset	After 2 years	Before 2 years	Before 2 years	Before 2 years
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Transgrediens	Yes	No	No	Yes (50% of cases)
Hyperhidrosis	Yes	Yes	Yes	Yes
Constrictive bands	No	No	No	Yes
Nail involvement	Rare	Rare	Rare	Frequent
Epidermolytic hyperkeratosis	No	No[a]	Yes	No
Involution	Possible after fifth decade	No	No	No
Genetic abnormality	Unknown	Keratin 1 mutation in some families (15)	Keratin 9 mutations (16)	Unknown

[a]It has been demonstrated that members of the same family of the patients originally described by Thost showed epidermolytic hyperkeratosis.

after birth has been described. Extracutaneous findings are not associated with Greither's disease. It was suggested that Greither's disease and erythrokeratodermia variabilis were due to the same mutation on chromosome 1, but this was not confirmed in other studies.

Both Unna-Thost PPK and Greither's disease have autosomal dominant inheritance and are generally considered to be nonepidermolytic PPK's. In contrast, Unna-Thost type of PPK tends to start earlier in life than Greither's disease, and it is not transgrediens. Only rarely is there hyperkeratosis of the knees and elbows in Unna-Thost but this skin finding is a described feature of Greither's.

While our patient has many features of Greither's disease, she does not possess the hyperkeratosis of the knees and elbows. It is possible she may develop this later. It is also unclear as to the time frame of when her keratoderma developed.

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Case 14
Combined Porphyria

Resident Physician
Susan Corey M.D.

Attending Physician
Jack L. Lesher Jr M.D.

History
This patient is a 19 year-old male who has a seventeen-year history of photosensitivity and "tea-colored" urine, and an approximately ten-year history of hypertrichosis and sclerodermoid skin changes. He also had erythrodontia that began in early childhood, but this became imperceptible after a dental whitening procedure. No immediate members of his family are known to have similar symptoms. However, a distant relative may have had congenital erythropoietic porphyria.

Clinical Findings
The patient has crusted papules on the dorsal hands and forearms with intermittent vesicles. He also has hypertrichosis of the face, dorsal hands and forearms and mild sclerodermoid skin changes in a photo distribution.

Laboratory/Studies
The table below depicts the patient's twenty-four-urine screen. The patient had a RBC porphyrin level of 459 µg/L (ref range 1.0 to 5.6µg/L), and a zinc protoporphyrin level of 279 (ref range 30-70). On routine laboratory tests, the patient was noted to have mild anemia (13.8), and persistently elevated bilirubin (1.5-1.7). All other lab values were within normal limits. Tests for hepatitis A, B, and C were all negative. Enzyme testing revealed red blood cell uroporphyrinogen III synthase (UROS) activity of 18 relative units (ref range >75), and a RBC uroporphyrin decarboxylase (UROD) activity level of 0.23 (ref range >1.0 normal, 0.80-0.99 marginal).

Porphyrin	Result (µg)	Reference Range (µg)
Total porphyrin	16,844	3.3 - 29.5
Urophorphyrin	12,559	3.3 - 29.5
Heptacarboxyporphyrin	310	<6.8
Hexacarboxyporphyrin	121	<0.9
Pentacarboxyporphyrin	601	<4.7
Coproporphyrin	3,252	<155

Clinical Course
The patient has done well with protective attire, diligent sunscreen use, and topical corticosteroids. He more recently was given topical tretinoin to try. Pt has been referred to gastroenterology and hematology for further management and work-up of his elevated bilirubin and anemia,

respectively. Our patient has not seen these specialists yet.

Discussion
Our patient showed deficiencies of both uroporphyrinogen III synthase and of uroporphyrin decarboxylase. Deficiency of uroporphyrinogen III synthase classically causes congenital erythropoietic porphyria (CEP). CEP is a rare autosomal recessive disorder with variable age of onset and clinical severity. Most patients present in early childhood with severe photosensitivity. Other common symptoms include erythrodontia, hypersplenism, hemolytic anemia, thrombocytopenia, and increased unconjugated bilirubin. Severe cases may be fatal in utero from hydrops fetalis, while others have a very mild phenotype and may present in adulthood with anemia and skin changes similar to porphyria cutanea tarda (PCT). Phenotype is most likely related to amount of residual uroporphyrinogen III synthase activity.

Hepatoerythropoietic porphyria(HEP) is caused by a deficiency of uroporphyrin decarboxylase throughout body tissues. Deficiency of this enzyme may also be seen with autosomal dominant inherited forms of porphyria cutanea tarda; however, elevated erythrocyte zinc protoporphyrins do not occur with inherited PCT. HEP is a very rare autosomal

recessive disease with common symptoms of photosensitivity, hypertrichosis, milia, vesicles, anemia, and scarring. Patients with hepatic erythropoietic porphyria may have mild to severe phenotype as with congenital erythropoietic porphyria. Common laboratory abnormalities in HEP include elevated urine porphyrins (mainly uroporphryin and hepta-carboxyl) with some coproporphyrins and hexa-carboxyl porphyrins.

In summary, evaluation of our patient supports that he may have a mild form of both CEP and HEP. Further testing may be warranted to confirm these diagnoses and to monitor the patient for any associated problems.

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Case 15
Epidermolysis Bullosa Simplex

Resident Physician
Allison R. Metzinger, M.D.

Attending Physician
Jack L. Lesher, Jr, M.D.

History
This 2 year old female presented to clinic at 14 months of age with complaints of blisters beginning at 3 months of age. Blisters were initially present on the feet, hands and diaper area. Since the patient began walking, lesions have been limited to the feet and diaper areas. The patient has difficulty walking at times due to plantar blisters. The patient's father, paternal grandfather, paternal uncle and several other paternal relatives have similar findings.

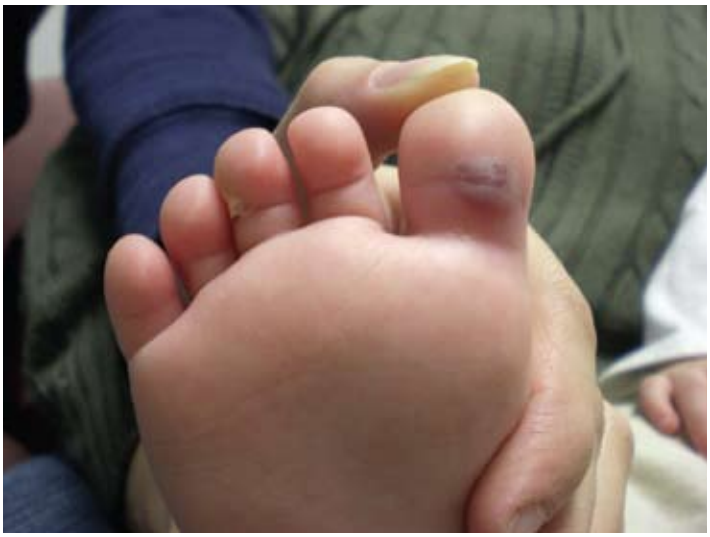
Clinical Findings
The patient is a well-nourished, well-developed toddler with several intact bulla on both plantar surfaces.

Clinical Course
The patient was diagnosed with Epidermolysis Bullosa Simplex, likely of the Weber-Cockayne type. The parents are diligent in their efforts to minimize trauma. Open lesions are treated with mupirocin ointment.

Discussion
Epidermolysis bullosa simplex (EBS) is an inherited blistering disorder. The Weber-Cockayne, or localized, type is the most common and least severe type of EBS. It is an autosomal dominant disorder caused by a defect in keratin 5 or 14. These defects result in a suprabasilar separation with subsequent blister formation. Onset is typically in early childhood with lesions occurring in areas of increased friction and pressure. Exacerbation is caused by hot environmental conditions and extending periods of walking. Hyperhidrosis may be associated. Scarring and milia formation are rare, occurring in only 15% of patients. Focal palmoplantar keratoderma develops by adulthood in some patients. Extracutaneous involvement is absent.

Diagnosis can be made clinically in many cases of limited EBS. However, if the diagnosis is uncertain, transmission electron microscopy or immunofluorescent mapping may be utilized to determine the type of epidermolysis bullosa. Electron microscopy determines the level of split, and immunofluorescent mapping reveals the altered antigen. As a result, these studies can differentiate between EBS, Junctional EB and Dystrophic EB. However, they cannot always differentiate between the subtypes.

Treatment focuses on avoiding exacerbating factors such as trauma, prolonged walking and exposure to heat. Regular use of anhydrous aluminum chloride application to the hands and feet can reduce appearance of new blisters. Patients must also be diligent regarding wound care in order to prevent infection. Appropriate cultures and antibiotics are used at the earliest sign of infection.



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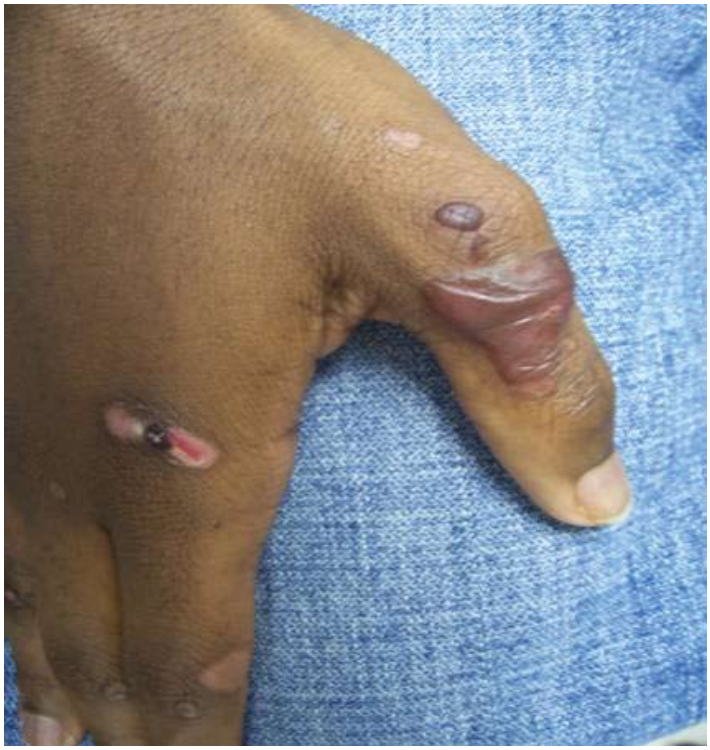
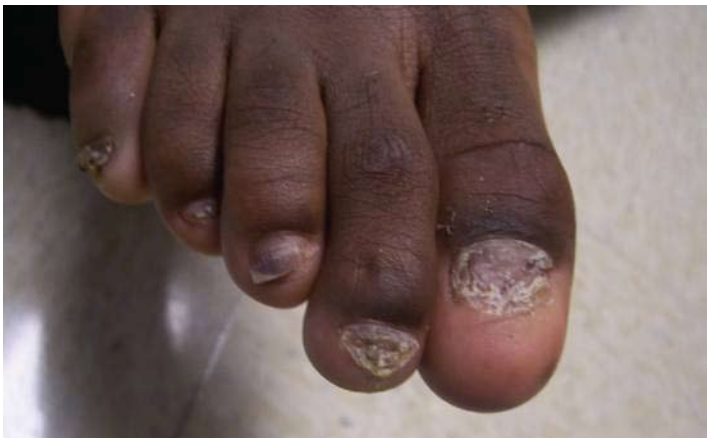
Case 16
Epidermolysis Bullosa Acquisita

Resident Physician
Greg Simpson, M.D.

Attending Physician
Loretta S. Davis, M.D.
Daniel J. Sheehan, M.D.





History

An 18 year old previously healthy male presented 2 years ago for evaluation of tense blisters appearing on bilateral hands. The disease progressed to include painful tense blisters of the feet, knees, and buttocks, and blisters and ulcerations of his oral mucosa. The lesions formed in areas of trauma or other inciting events, such as arthropod bites. The patient failed to see major improvement with super-potent topical corticosteroids, minocycline, or dapsone, and was hospitalized secondary to pneumonia while on mycophenolate mofetil. Mycophenolate mofetil was restarted and has been titrated with fairly good control when regimen is adhered to. At this time he occasionally flares, usually with trauma, but is able to participate in normal activities.

Clinical Findings

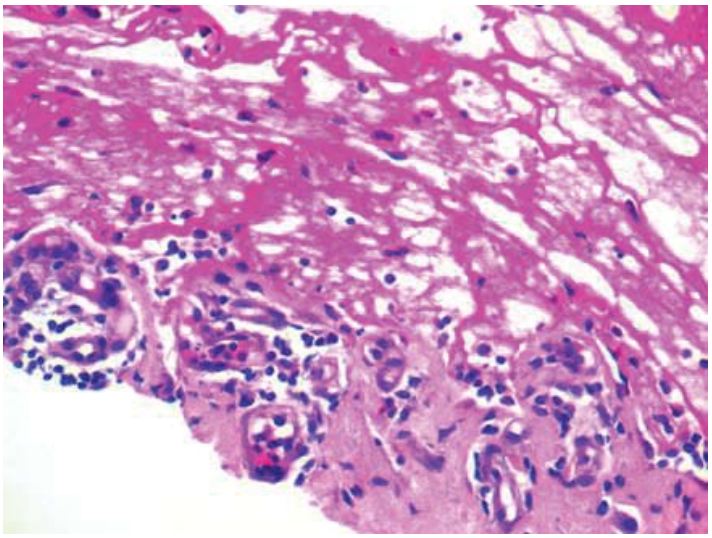
Bilateral hands show multiple flaccid bullae, erosions, scarring milia, and hypopigmented, erythematous scarring. Anterior lower legs show multiple hyperpigmented patches and flaccid bullae.

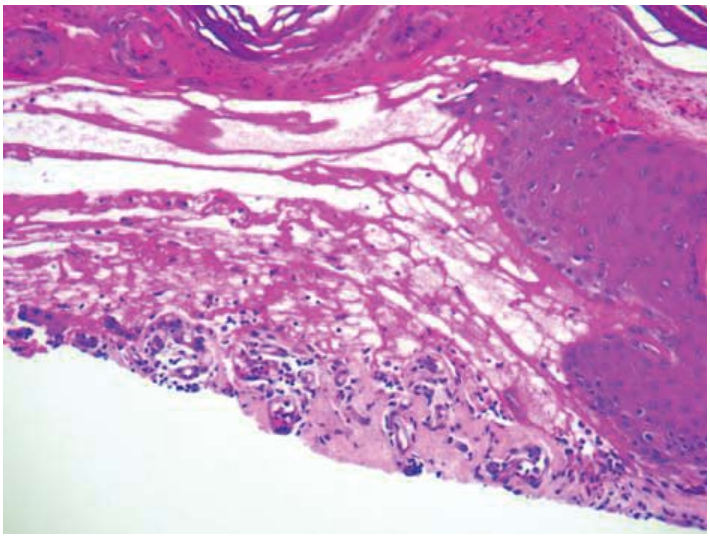
Laboratory/Studies

DIF revealed linear staining along the basement membrane zone with IgG and C3. Collagen Type IV stained very weak and only focal positivity was seen in the blister base and roof.
ANA was <1:40.
Rheumatoid factor was <20.0 IU/mL.

Histopathology

Normal acral type cornified layer with a blister roof that consists of necrotic epidermis. The blister is filled with





serous and hemorrhagic exudate and a few inflammatory cells including a few neutrophils. There is advanced re-epithelialized blister base and subtle vacuolar alteration with early dermo-epidermal separation is seen. A sparse predominantly lymphocytic inflammatory cell infiltrate is present.

Clinical Course

The patient has failed topical steroids, minoccyline (due to dizziness and change in personality), and dapsone. At this time, he is taking Mycophenolate mofetil 3G BID and has recently had his first PO prednisone taper. As he is an active youngster, it has been difficult to curtail his activities and faithfully remain on any systemic regimen. He has learned to deal with his disease over the years and is much more wary of trauma exacerbating his condition and pitfalls of his activities

Discussion

Epidermolysis Bullosa Acquisita is a chronic, sub-epidermal blistering disease of the skin that manifests itself in trauma-prone areas such as the elbows, hands, knees, feet and buttocks. IgG autoantibodies can target 2 different areas on Type VII collagen, the major component of anchoring fibrils that connect the basement membrane to the dermis. The nature of the disease leads to skin fragility, secondary scarring and restriction of movement in the trauma-prone areas. There is a strong association with inflammatory bowel disease, so patients should be watched closely for development of GI symptoms. EBA usually presents in older individuals (50's) but has been reported in all ages, including a 3 month old. Treatment should focus on control of new blister outbreaks with adequate immunosuppression, education on inciting events such as trauma, keeping a close watch on gastrointestinal symptoms and oral involvement, and possible new therapies such as rituximab (anti-CD20) or other biologic agents. Patients with EBA can expect a normal life span with hopeful minimization of scarring sequelae.

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Case 17
Porokeratosis of Mibelli

Resident Physician
Sarah K. Josephson, M.D.

Attending Physician
Jack L. Lesher Jr, M.D.
Daniel Sheehan, M.D.

History
A seventy-one year old male presented with a large red plaque on his left shoulder. He stated the lesion had been present since 1957. It began as a small lesion that had progressively enlarged over time.

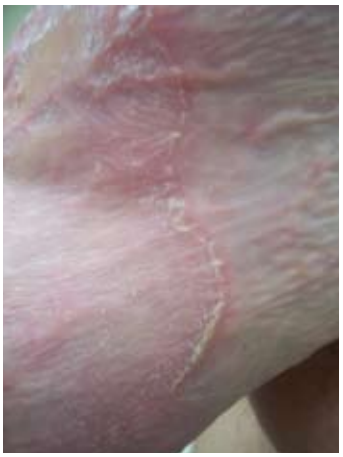
Clinical Findings
He has a large, 19 x 22 centimeter, erythematous plaque with a raised peripheral scale and a central area of depression on his left shoulder that extends down to his elbow, with an adjacent depressed scar.

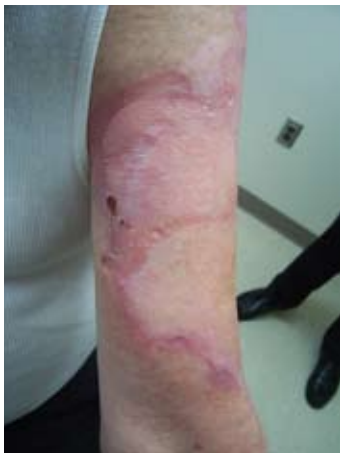
Laboratory/Studies
The lesion was KOH negative.

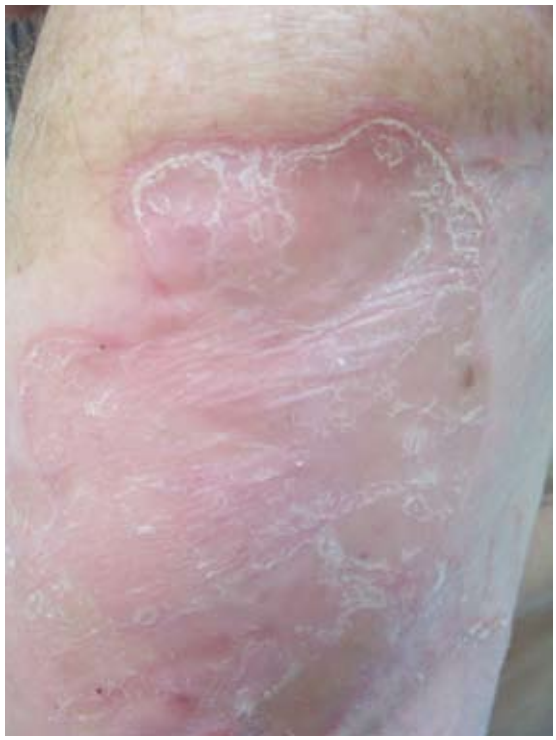
Histopathology
Biopsy revealed a very focal parakeratotic column formation with an absence of the granular layer beneath. PAS stain was negative.

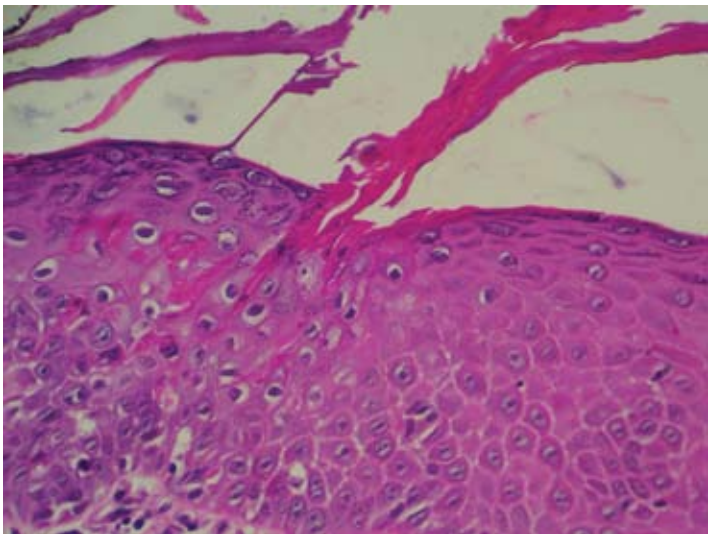
Clinical Course
Upon further questioning he had previously been diagnosed with porokeratosis of Mibelli, biopsy confirmed, at an outside hospital. He also had a history of a squamous cell carcinoma (SCCA) originating within the lesion, hence the depressed scar described as above. He was being treated with acitretin 25 mg by mouth daily, which was increased to 50 mg daily. He later stopped acitretin secondary to side effects, including hair loss, dryness and peeling. He had also previously undergone treatment with a CO2 laser without improvement. He later completed 6 weeks of tretinoin 0.05%, followed by a month long course of fluorouracil cream with some success. He had no further expansion of the lesion and experienced thinning of the existing lesion. He later completed a course of imiquimod 5% cream, without much improvement. Approximately one and a half years into his treatment course after presenting to us, he developed a second SCCA within the area of porokeratosis. At this time an excision was performed. He is currently being treated with imiquimod 5% cream under occlusion.

Discussion
Porokeratosis is a heterogeneous group of disorders that is inherited sporadically or as an autosomal dominant disorder. At least five types of porokeratosis have been recognized in the literature. Classic plaque-type porokeratosis of Mibelli, disseminated superficial actinic porokeratosis (DSAP), linear porokeratosis, porokeratosis palmaris, plantaris, et disseminata, and punctate porokeratosis. This case is an example of classic plaque-type porokeratosis, originally described by Mibelli in 1893.









Porokeratosis of Mibelli is a rare condition, usually beginning during infancy or childhood as an asymptomatic, small, hyperkeratotic papule that gradually expands peripherally, over years, to form a large plaque with typical central depression. Eventually, it develops a well-defined, circinate, keratotic collar. The center can be hyperpigmented, hypopigmented, atrophic, and/or anhidrotic. Lesions may occur anywhere on the body, but the extremities are the most frequently involved.

Two theories exist regarding the pathogenesis of porokeratosis. Reed proposed that it is an expanding mutant clone of keratinocytes. The finding of abnormal DNA ploidy in keratinocytes of porokeratosis supports this theory. Chemotherapy, organ transplantation, AIDS immunosuppression, PUVA treatment, UVA or chemical exposure all appear to trigger porokeratosis in genetically predisposed individuals. Tatnall and Sarkanay report a case of porokeratosis in a 63 year old male following treatment with prednisolone and azathioprine for chronic active hepatitis. A second theory suggests that dermal lymphocytes may be directed against an unidentified epidermal antigen and subsequently release mediators causing mitosis of epidermal cells.

Histologically, the classic finding in porokeratosis is the cornoid lamella, a thin column of tightly packed parakeratotic cells, extending from an invagination of the epidermis through the stratum corneum. It corresponds clinically to the raised hyperkeratotic border. Under the cornoid lamella, the granular layer is markedly diminished, or possibly absent.

Cryotherapy, topical 5-fluorouracil (5-FU), topical retinoids in combination with 5-FU, oral retinoids, topical imiquimod, CO2 and other lasers, shave excision, curettage, linear excision, and dermabrasion have all been attempted in the treatment of porokeratosis. Montes-De-Oca-Sanchez, et al. report the successful use of imiquimod 5% cream in the management of porokeratosis of Mibelli in the axilla of a 12-year-old. They suggest the area of application, large hydrated skin folds, enhanced the efficacy of therapy.

Due to the risk of malignant transformation, the search for an effective treatment is of great importance. The development of squamous cell carcinoma, Bowen's disease, and basal cell carcinoma has been reported within the lesions of all variants of porokeratosis, except the punctate form. A higher risk of malignant degeneration exists in older patients, lesions of longstanding duration, and linear porokeratosis. It has been suggested that oral retinoids may have an inhibitory effect on cutaneous carcinogenesis in porokeratotic lesions. However, one must be aware that relapses usually follow upon discontinuation of therapy. This case presents an example of plaque-type porokeratosis resistant to multiple treatments with evidence of malignant degeneration within the lesion.

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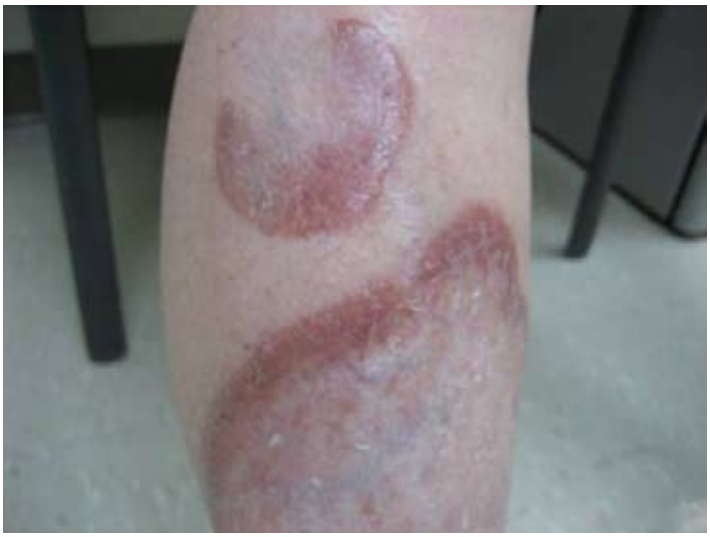
Case 18
Necrobiosis Lipoidica

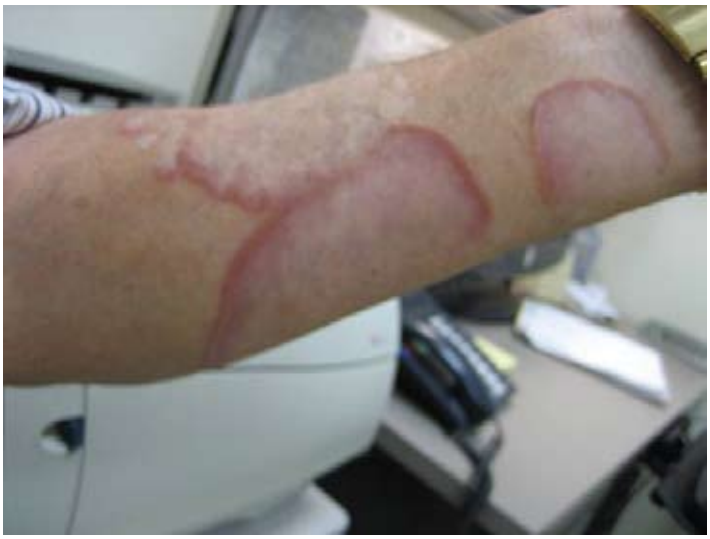
Resident Physician
Greg Simpson, M.D.

Attending Physician
Jack Lesher, M.D.

History
A 60 year old male presented for evaluation of an upper and lower extremity slowly expanding rash of many years duration. He reported a decreasing amount of pain with the lesions after many years of unsuccessful topical and intralesional therapy. The eruption began as telangiectatic plaques on his lower extremities that spread throughout his lower extremities and eventually included bilateral forearms. He has a past medical history of diabetes mellitus type 2 that is controlled with insulin therapy.

Clinical Findings
Lower extremities show multiple yellow-brown annular plaques with central atrophy and thickened violaceous borders. Upper extremities show serpiginous, annular and semi-annular, brown and violaceous plaques with raised borders.





Histopathology
Biopsy reveals interstitial and palisaded granulomas that involve the dermis and subcutaneous tissue with a predominantly lymphocytic infiltrate and perivascular plasma cells. The epidermis is mildly atrophic.

Clinical Course
Originally the patient was treated with high potency topical corticosteroids and intralesional steroid injections which helped the symptoms but did not affect the clinical picture. Years later, topical Calcineurin inhibitors and topical retinoids were added to the regimen but these have been unsuccessful as well.

Discussion
Necrobiosis Lipoidica is a chronic, cutaneous disease which is often recalcitrant to treatment. Approximately 2/3 of patients with this disease have Diabetes Mellitus (majority having Type 1), 12-15% have glucose intolerance, and over half of the remaining affected have a family history of glucose intolerance. While the cause of NLD remains unknown, immunologically mediated vascular disease has been hypothesized as the primary cause of the collagen alterations. Other theories speculate on the role of microangiopathic vessel changes seen in DM and elevations in plasma fibronectin, factor VIII related antigen, and alpha-2 macroglobulin levels. Many consider NLD to be a primary disease of collagen with electron microscopy showing a loss of cross-striations of collagen fibrils and variation in diameter of individual fibers. The differential of NLD includes granuloma annulare and sarcoidosis (which do not normally exhibit the same degree of atrophy and telangiectasias), necrobiotic xanthogranuloma (which tend to form peri-orbitally and have a paraproteinemia), and diabetic dermopathy and stasis dermatitis which tend to be more macular and hyperpigmented. The major histopathologic differential is granuloma annulare which tends to have more patchy discrete granulomas than NLD's diffuse dermal extension. NLD tends to have more giant cells, plasma cells, vascular changes and collagen degeneration than GA. This case presents an example of how difficult treatment of NLD can be, the association of this chronic skin disease with diabetes mellitus, and the long term evolution of cutaneous lesions of NLD.

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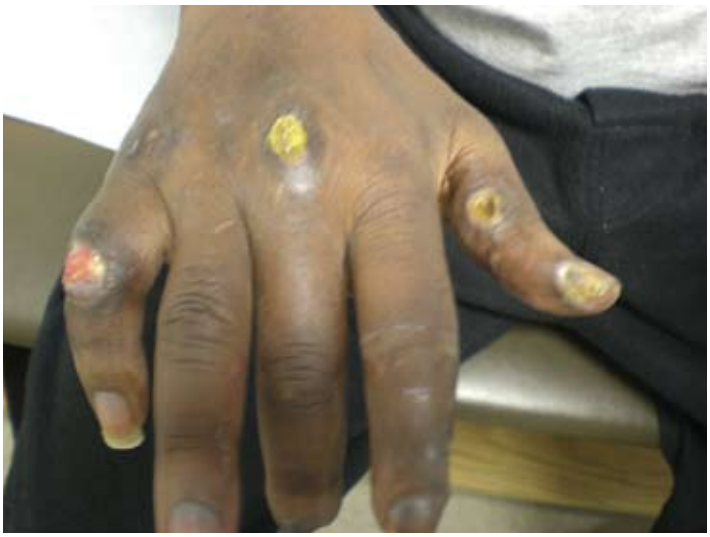
Case 19
Dermatomyositis/Overlap Connective Tissue Disease

Resident Physician
Jeannette Hudgens, M.D.

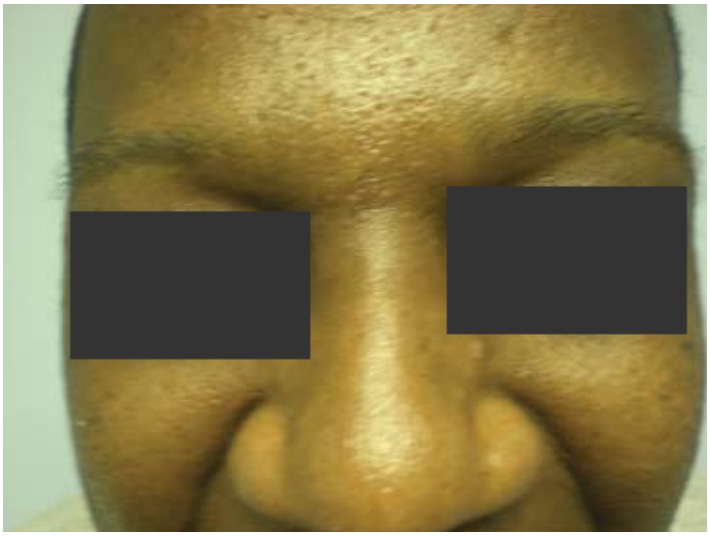
Attending Physicians
Loretta Davis, M.D.
Daniel Sheehan, M.D.

Referring Physician
Bruce Goeckeritz, M.D.



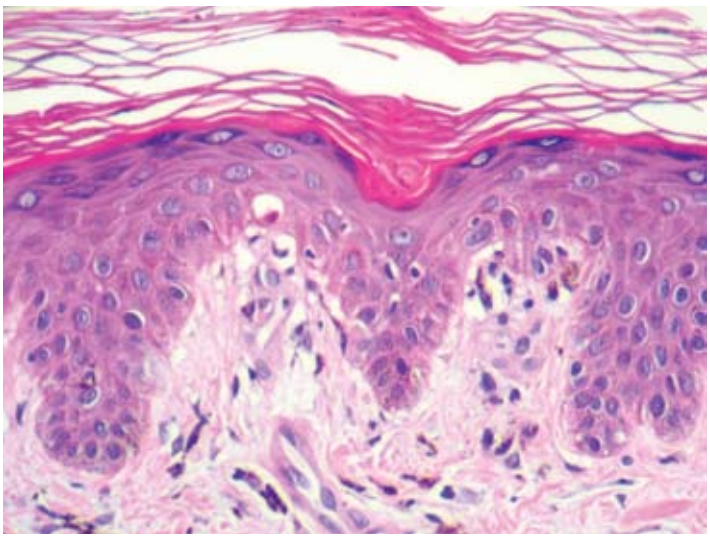
History
A 40 year-old male with a past medical history of hypertension was admitted to the MICU for dyspnea and hypoxemia. He reported fever, chills, 40lb weight loss, arthralgias and ulceration of his hands and elbows that started 6 months prior. The arthralgias involved the knees, hands, and shoulders.

Clinical Findings
Swelling of the eyelids was originally noticed and improved with prednisone therapy. Hyperpigmented, slightly thickened plaques on bilateral elbows and wrists and multiple violaceous to hyperpigmented ulcerations on the dorsal MP joinst and fingertips were impressive. Striae were diffusely present over his abdomen, axillae, and groin.



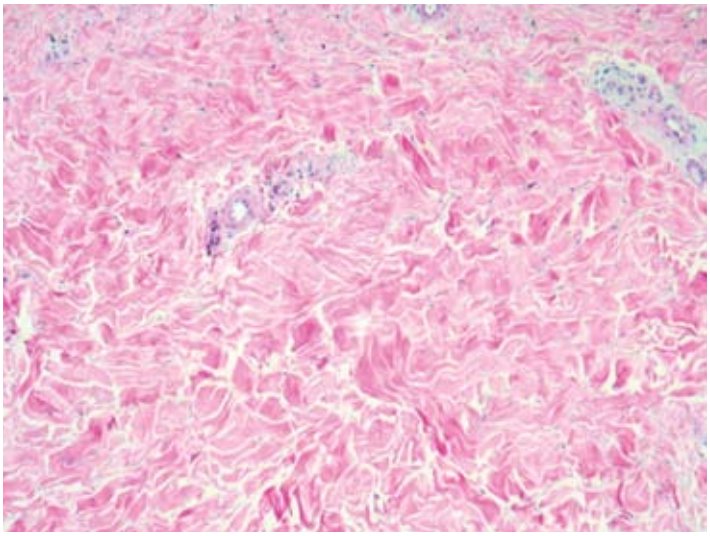
Laboratory/Studies
Rheumatoid factor is elevated at 21.3IU/ml. He has an elevated ESR at 62mm/hr and CRP at 2.58mg/dL, and a slightly elevated SS-A at 1.1U. Lupus anticoagulant is weakly positive. The patients extensive negative work-up includes ANA, Smith Ab, SS-B, U1RNP, SCL-70, ds-DNA, Centromere Ab, CCP Ab, ANCA-T, ANCA-M, anticardiolipin antibodies, Beta 2-Glycoprotein 1 antibodies, and cryoglobulin. He also tested negative for HAV, HBV, HCV, and HIV. The PFTs showed a restrictive pattern. Chest CT showed ground-glass-like process with dense fibrotic changes. Transbronchial biopsy revealed features of chronic interstitial pneumonia and fibrosis without granulomas or other features of sarcoidosis.

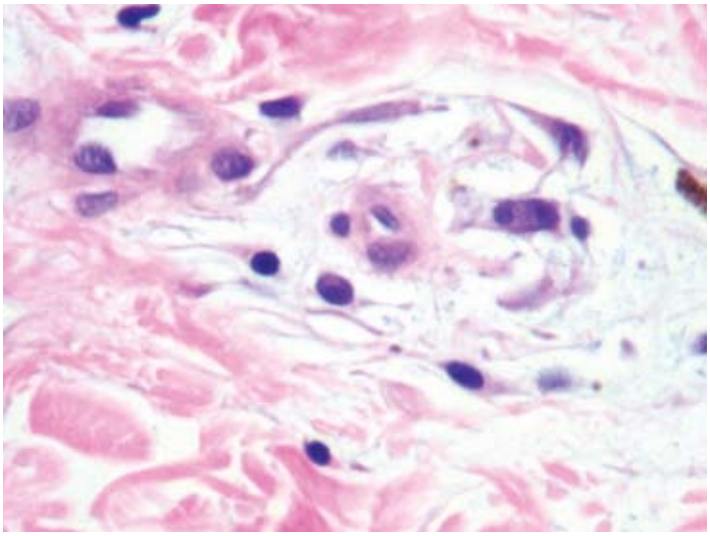
Histopathology
Biopsy of a plaque on right wrist showed changes consistent with lichen sclerosis et atrophicus and morphea overlap. Biopsy of the hand showed changes consistent with adjacent ulceration without definitive evidence of vasculitis.



Clinical Course
Lung function improved with prednisone and azathioprine therapy. Cyclophosphamide was begun prior to discharge, but was discontinued when it became unavailable per the manufacturer due to insurance and financial reasons. The patient continued to follow up with Rheumatology and Dermatology with worsening of his cutaneous ulcerations on prednisone and Imuran. Periocular violaceous erythema and several darkly hyperpigmented plaques on the knees were noted later in his course. A skin biopsy of the knee showed vacuolar interface dermatitis with dyskeratotic

keratinocytes and pigmentary incontinence consistent with dermatomyositis. He continued to deny any muscular weakness or fatigue. Cyclophosphamide 100mg qday was reinitiated. All serologies have been negative, including an infectious workup and autoimmune workup. The patient has no clotting disorder. His disease remains active with impressive digital ischemia.





Discussion

Our patient has been a diagnostic dilemma. It is difficult to make a case for autoimmunity when his ANA and related antibodies have all been negative. In addition, he has no anticardiolipin antibodies and his beta 2 glycoprotein 1 is negative. He does have a weakly positive lupus anticoagulant. This may suggest a predisposition for clot formation or it may be a false positive. His inflammatory disorder shares features of several autoimmune illnesses, including systemic sclerosis and dermatomyositis. This raises the possibility of an "overlap-like illness" yet to be determined.

Dermatomyositis is characterized by inflammatory skin disease and myositis. Amyopathic dermatomyositis occurs with subclinical or absent myopathy. The skin findings usually begin with erythema and edema of the face and eyelids, notably referred to as the heliotrope sign. Periocular edema and later hyperpigmentation was observed in our patient's clinical course. Extensor surfaces of the extremities can be pink or violaceous with atrophy or overlying scale. 'Mechanic's hands' refer to hyperkeratosis, scaling, fissuring and hyperpigmentation over the fingertips, lateral thumbs and palms. It has been reported in 70% of patients with antisynthetase antibodies. Rarely, ulcerations in flexural areas or over pressure points can be quite persistent. Ulceration in early stages of disease has been reported to be associated with a poor prognosis and higher incidence of cancer.

Sclerodermatomyositis refers to an overlap of DM and sclerodermatous changes. Anti-Ku and anti-PM/scl antibodies may be present in this subgroup. Interstitial lung disease is frequently the cause of death. The development of pulmonary disease correlates well with the presence of anti-Jo1 antibodies and other antisynthetase antibodies, such as anti-PL-7, anti-PL-12, anti-DJ, and anti-EJ. However, up to 69% of patients with interstitial lung disease are seronegative for the anti-Jo-1 antibody. The serology work-up in our patient was negative, but antisynthetase antibodies were not obtained.

Of note, the patient claims that his symptoms began after exposure to an unknown caustic cleaning chemical.

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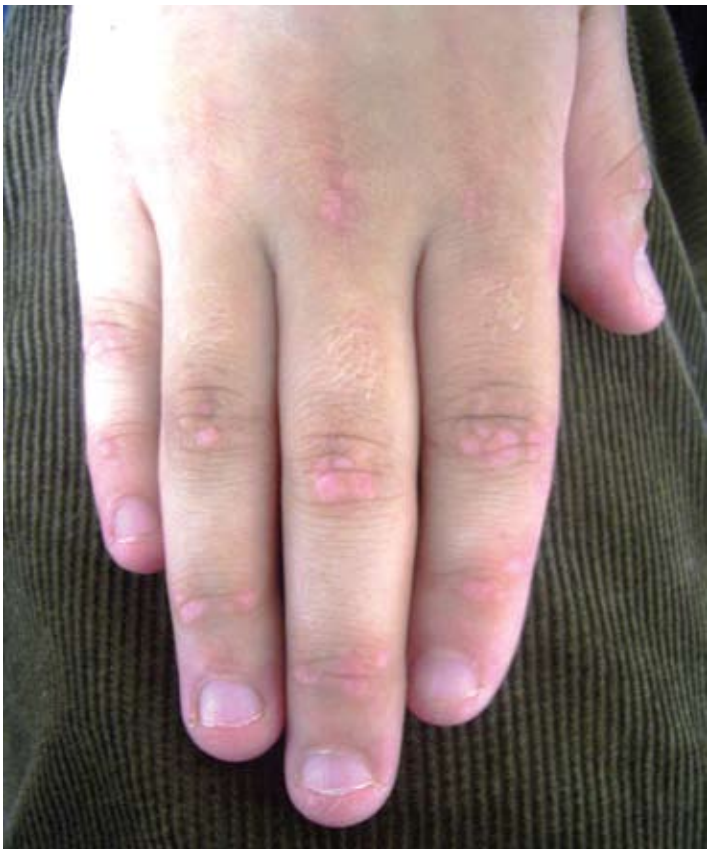
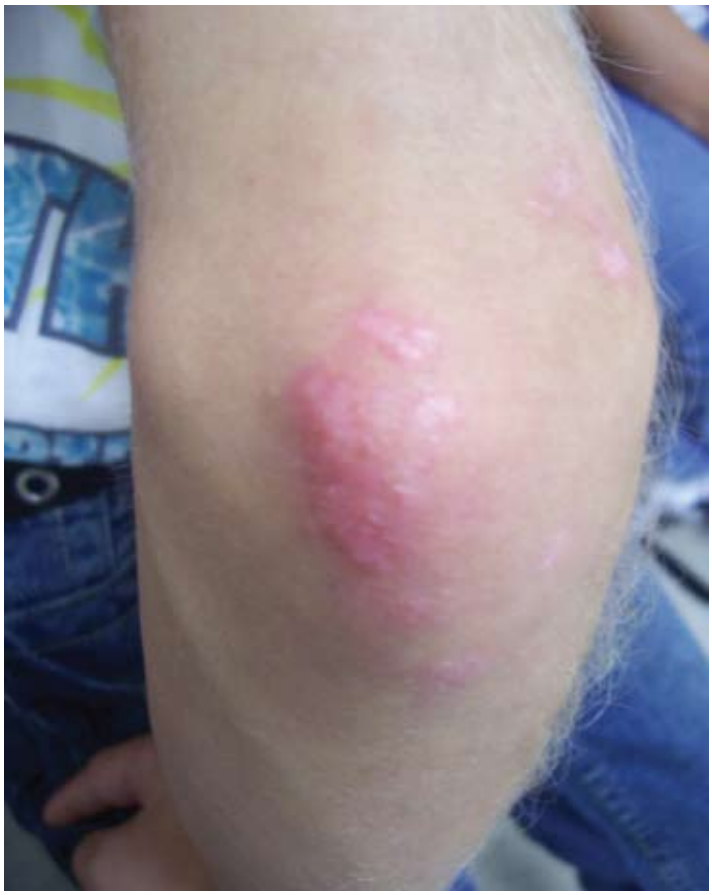
Case 20
Juvenile Dermatomyositis

Resident Physician
Jeannette Hudgens, M.D.

Attending Physician
Daniel Sheehan, M.D.

Referring Physician
Rita Jerath, M.D.





History
The patient originally presented as a 3 year-old previously healthy female. She began with an erythematous rash typical of dermatomyositis, along with intermittent low-grade fevers. She did not experience any muscle weakness, but her original dermatologist found an elevated CPK and aldolase. She was sent to Rheumatology and a muscle biopsy was consistent with Dermatomyositis.

Physical Examination
The patient presented with violaceous macules below her eyes bilaterally, and violaceous flat topped papules on the MCP and DIP joints, wrists, elbows, knees, and ankles bilaterally.

Laboratory/Studies
She had a positive ANA at 1:640 with a speckled pattern. PM-Scl antibody, anticardiolipin antibodies, histone, Jo-1, Scl-70, Sm, SSA, SSB, and U1RNP were all negative. CK and aldolase have remained WNL while under our care.

Histopathology
A muscle biopsy done on 10/15/01 showed perivascular lymphocytic infiltrates and perimysial lymphocytic infiltrates. Focal perifascicular atrophy with basophilic fibers was also seen.

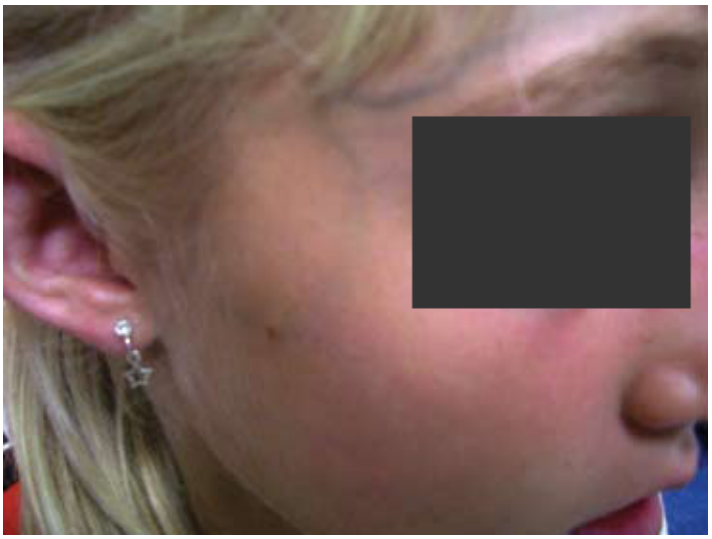
Clinical Course
The patient was diagnosed with Juvenile Dermatomyositis at 3 years of age. She responded well to oral steroids and tapered off later that year. The rash recurred and she was restarted on oral prednisone, IV methylprednisolone, methotrexate, and pimecrolimus topical. A few years later she improved and was again tapered off prednisone and methotrexate. Erythema again appeared on her knuckles, elbows and knees, which could not be controlled with pimecrolimus and clobetasol. Hydroxychloroquine was then started last year. Due to continued inadequate control, methotrexate was restarted along with monthly IVIG and methylprednisolone infusions with good response.

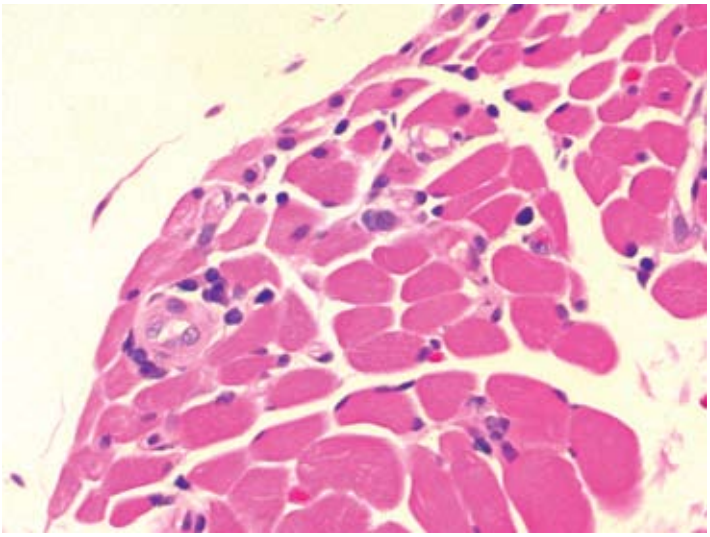
Discussion
Unlike many other muscle diseases of childhood, juvenile dermatomyositis is responsive to treatment. Many can make a good recovery if diagnosed early and treated aggressively. The median age of onset of juvenile dermatomyositis is 6.8 years and may have a slight female predominance. Calcinosis cutis and small-vessel vasculitis are more prevalent in children with dermatomyositis than adults. Chronic inflammation

affects the muscles and skin, but also often involving the gastrointestinal tract. Less frequently, cardiac muscle, joint, renal and cerebral involvement can occur. The onset of disease is usually insidious, which contributes to delay in diagnosis. Patients exhibit progressive proximal muscle weakness and symmetrical tenderness. The characteristic rash consists of periorbital violaceous patches or edematous plaques that spread onto the nasal bridge. Patients also frequently get scaly erythematous patches over the knuckles, elbows, knees, medial malleoli and shawl areas that wax and wane with photosensitivity.

If there is any doubt about the diagnosis, a muscle biopsy is necessary. Endothelial cell damage with swelling, cell necrosis and regeneration may be seen early. Later, an inflammatory infiltrate develops around blood vessels of the perimysium and extending into the endomysium. The infiltrate initially contains neutrophils, and later lymphocytes, histiocytes, and plasma cells. Fibrin thrombus may occlude the lumen causing regional ischemia throughout the muscle. DIF shows deposits in the intima of blood vessels from muscles biopsies.

Patients with juvenile dermatomyositis do not have an increased risk of malignancy as in their adult counterparts. Less than 5% of children have a positive nRNP autoantibody, but there has been an association with HLA-DR3 and –B8.





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Case 21
Linear Morphea

Resident Physician
Jeannette Hudgens, M.D.

Attending Physician
Frances Florentino, M.D.

Referring Physician
Sidney P. Smith III, M.D.

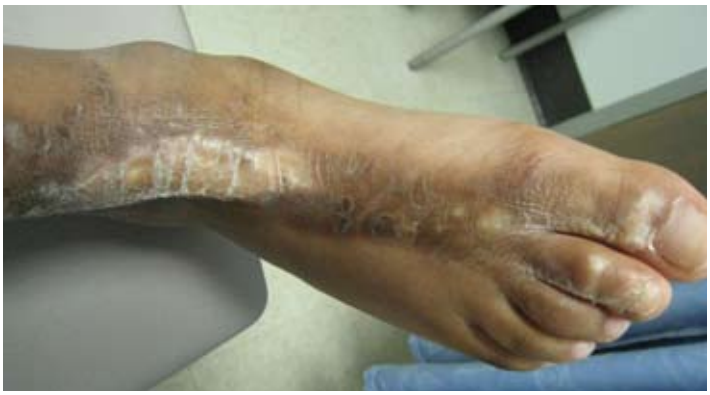
History
A 7 year-old black female with a history of asthma, presented with a one year history of progressive indurated lesions on the right leg. The lesions started as alligator-type appearing skin with more fibrotic scarring on the dorsal aspect of the right foot. The lesions have since progressed up the right leg, abdomen, and arm. She reports diminishing range of motion in her right ankle causing a gait deformity. The patient has also had intermittent fevers and itching of lesions. Previous treatments with topical steroids caused burning without improvement in skin lesions.

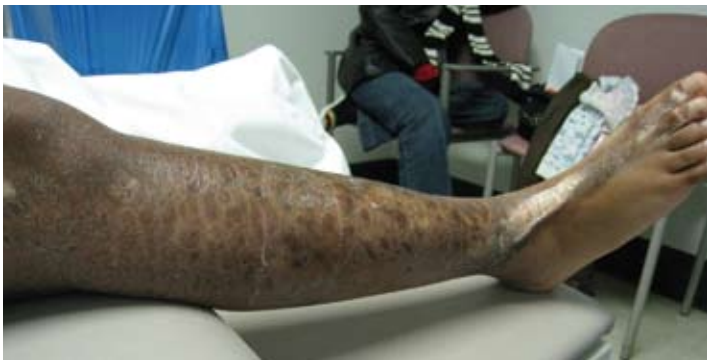
Clinical Findings
The patient presented to our facility with linear, hyperpigmented, indurated plaques with overlying 'fish-like' scale on right leg. There is a depigmented, thick, indurated plaque over right ankle with decrease range of motion. She also has hyperpigmented indurated plaques on right flank, buttock and gluteal cleft.

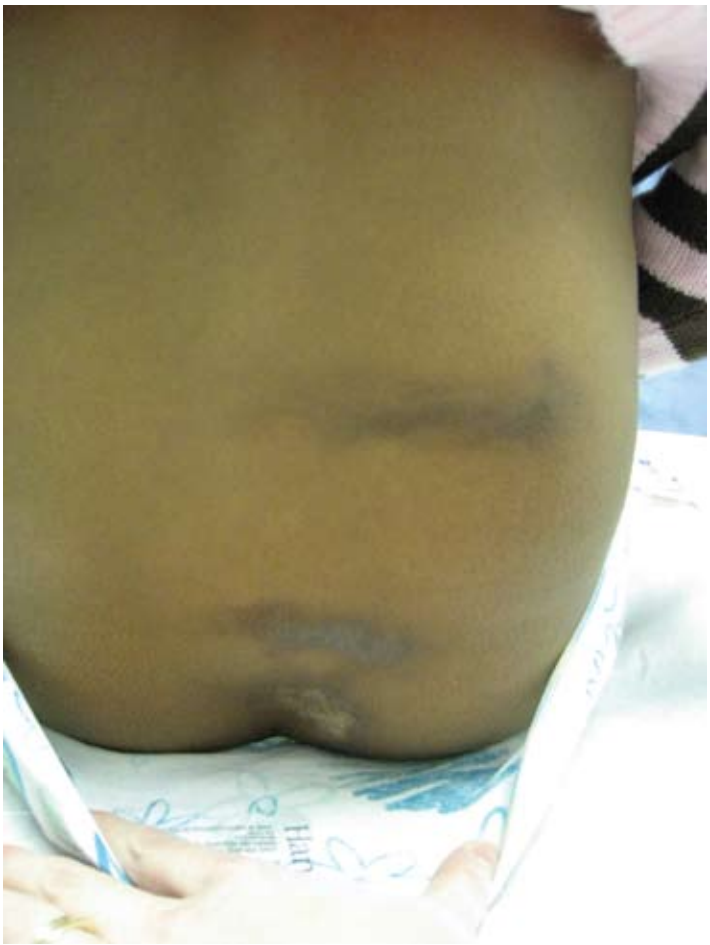
Laboratory/Studies
ANA is positive at 1:640 with a speckled pattern and PM-Scl Ab is positive. She has an elevated IgA at 346mg/dL and IgG at 1870mg/dL. U1RNP is elevated at >8.0U. Initially CRP was elevated at 2.59mg/dL. The negative work-up includes normal C3 and C4, Histone Ab, Scl70, SSA, SSB, ds-DNA, ESR.

Histopathology
Early biopsy showed signs consistent with ichthyosis: mildly atrophic epidermis, hyperpigmentation of basal keratinocytes, thickened layer of compact orthokeratosis overlying a normal to diminished granular layer.

Clinical Course
As her disease progressed, the diagnosis of linear morphea was made and the patient was referred to a pediatric rheumatologist who started prednisone and methotrexate. The current doses are 15mg PO BID and 0.9ml SQ qwk (22.5mg) respectively. She has also received weekly methylprednisolone 1gm IV infusions x 3 for recent flare-ups. The patient began to shows signs of response with halting progression of new lesions. However, she was recently admitted to an outside hospital for decreased O_2 saturation. With a history of asthma, she was placed on home oxygen, which has since been discontinued.







Discussion

Linear morphea is an autoimmune inflammatory sclerosing disease that often begins during the first decade of life. Linear lesions may extend the length of the extremities and may follow lines of Blaschko. Plaques are usually unilateral, but bilateral lesions have been reported. Progression may result in abnormal limb development, hemiatrophy, or flexion contractures that can result in permanent functional disability and disfigurement. Melorrheostosis may also occur with dense linear cortical hyperostosis of long bones. If the involvement is limited to the extremities, spontaneous improvement may occur. The course usually lasts 3-5 years, but many patients experience quiescence followed by reactivation of their disease. Anti-ssDNA antibodies are common. Physical therapy may be helpful in preventing contractures and frozen joints.

Initial oral corticosteroid treatment and long-term methotrexate administration has been shown to stabilize or improve patients with aggressive disease. Our patient has extensive disease affecting the entire right lower extremity, and developed a flexion contracture of her right ankle prior to presentation. In addition to oral corticosteroids and methotrexate, weekly IV methylprednisolone has been required. She is also actively involved in physical therapy to prevent further abnormal limb development.

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Case 22
Linear Morphea

Resident Physician
Jeannette Hudgens, M.D.

Attending Physician
Jack L. Lesher, Jr., M.D.

History
An 8 year-old female with Asperger Syndrome, presented two years ago with a one year history of a white lesion on her lower right leg. The lesion was asymptomatic. She has a paternal grandmother with lupus/scleroderma.

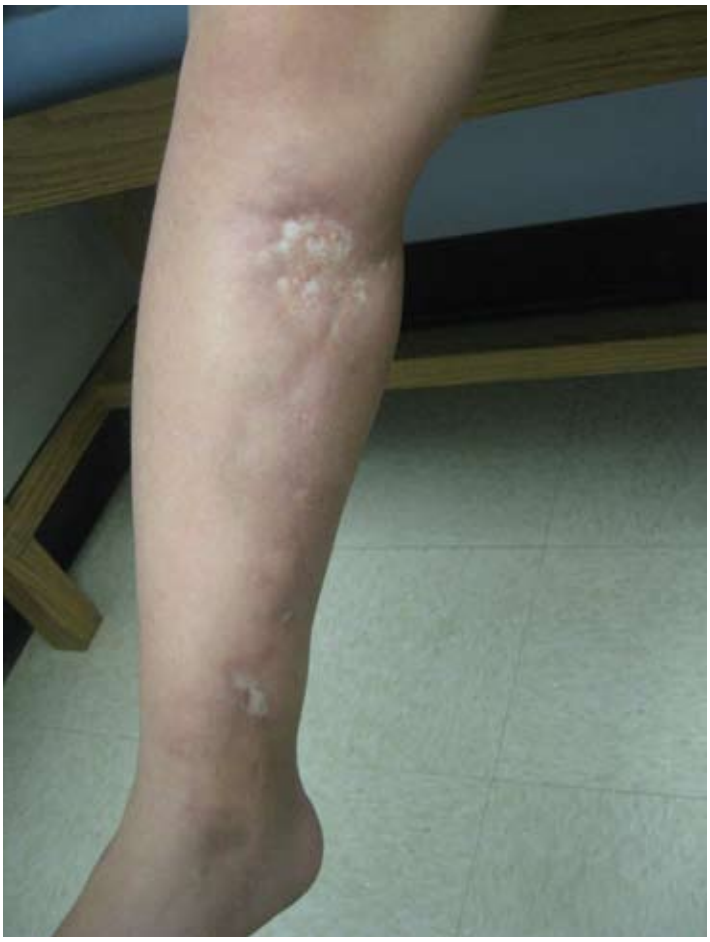
Clinical Findings
There is a hypopigmented plaque with irregular borders and surrounding violaceous discoloration on the right lower leg, and 2 smaller hypopigmented lesions below.

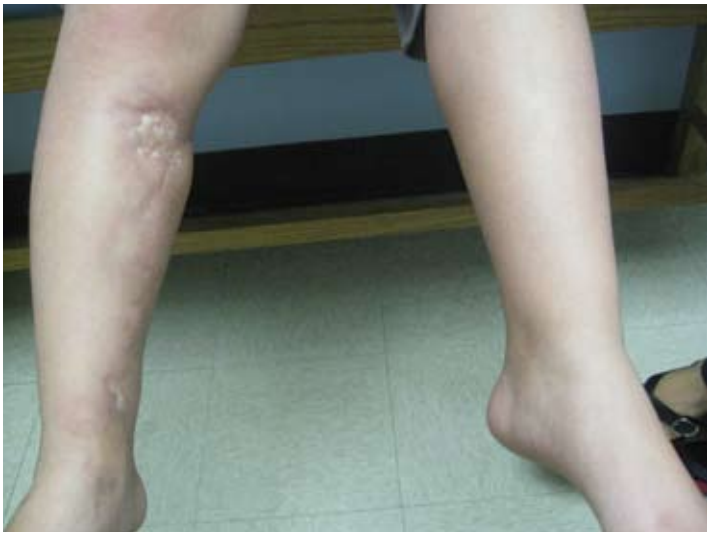
Laboratory/Studies
ANA was negative at <1:40. The negative work-up includes normal C3 and C4, Rheumatoid factor, anticardiolipin antibodies, Centromere Ab, ds-DNA Ab, Histone Ab, Jo-1 Ab, PM-Scl, Scl70, SM, SSA, SSB, and U1RNP.

Clinical Course
Erythema improved with betamethasone dipropionate, but the patient could not tolerate calcipotriene. She later developed striae on her right thigh and right superior lower leg. Calcipotriene was again tried with resolution of lesions on her thigh. She was then started on total body UVA twice weekly in 11/06. After 6 months of treatment no active lesions were noted and light therapy was discontinued. New lesions shortly developed despite topical tacrolimus, tretinoin, and triamcinolone. UVA was restarted twice weekly in 11/07, but the patient continue to acquire new lesions. Patient was referred to pediatric rheumatologist who is currently considering MTX. She was also referred to pediatric dermatology.

Discussion
Linear morphea is an autoimmune inflammatory sclerosing disease that often begins during the first decade of life. Linear lesions may extend the length of the extremities and may follow lines of Blaschko. Plaques are usually unilateral, but bilateral lesions have been reported. Progression may result in abnormal limb development, hemiatrophy, or flexion contractures that can result in permanent functional disability and disfigurement. Melorrheostosis may also occur with dense linear cortical hyperostosis of long bones. If the involvement is limited to the extremities, spontaneous improvement may occur. The course usually lasts 3-5 years, but many patients experience quiescence followed by reactivation of their disease. Anti-ssDNA antibodies are common. Physical therapy may be helpful in preventing contractures and frozen joints.

Initial oral corticosteroid treatment and long-term methotrexate administration has been shown to stabilize or improve patients with aggressive disease. Our patient's





disease has been limited to one extremity without signs of abnormal limb development, hemiatrophy, or flexion contractures. She has had positive response to UVA in the past, but lesions recently flared despite this therapy.

References

1. Christen-Zaech S, et. al. Pediatric morphea (localized scleroderma) review of 136 patients. *J Am Acad Dermatol*. 2008 Sep;59(3):385-96.
2. Vandana Mehta, et. al. Generalized linear scleroderma in childhood. *Dermatology Online Journal* 13 (3) 34.
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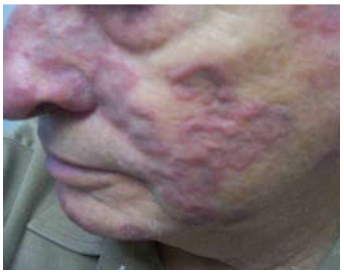
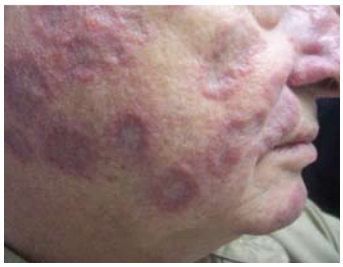
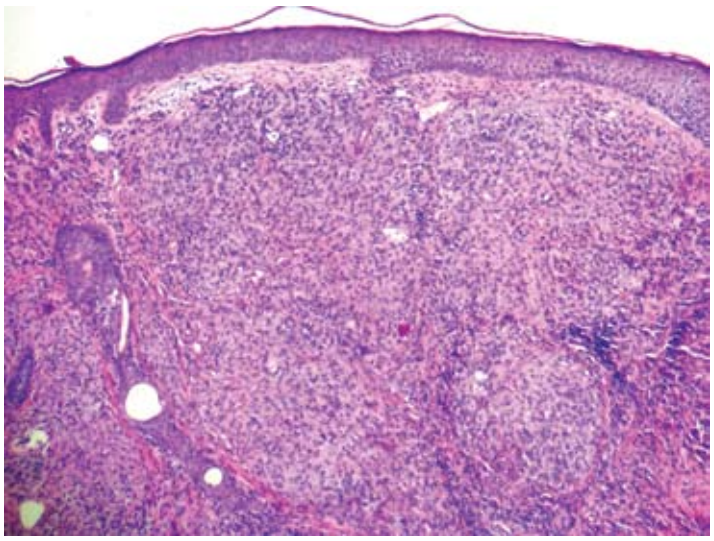
Case 23
Sarcoidosis

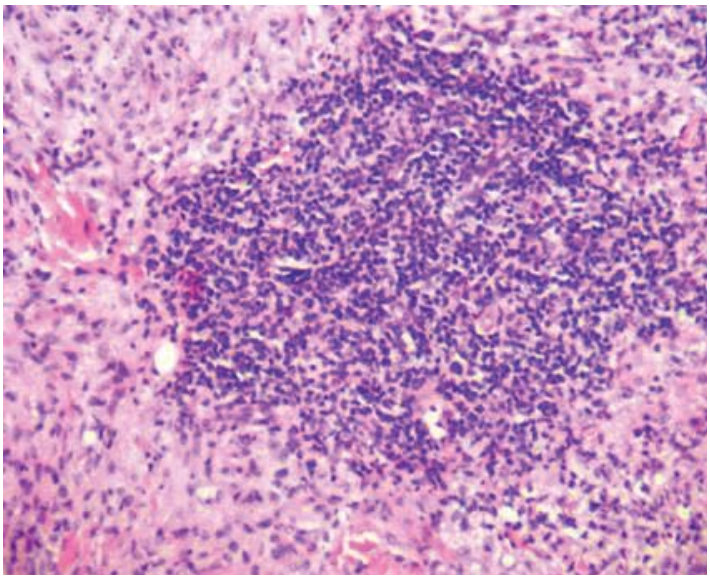
Resident Physician
Greg Simpson, M.D.

Attending Physicians
Loretta Davis, M.D.
Marshall Guill, M.D.









History
A 68 year-old male presents with a 4 year history of an asymptomatic facial rash that has been stable for the last 3 years. It spread to cover his entire face but has not involved the scalp, neck or any other areas of his body. It is slightly photosensitive but is not pruritic or painful. These lesions have been unresponsive to topical steroids, topical metronidazole, topical erythromycin, minocycline, doxycycline, and minimally responsive to systemic corticosteroids prescribed for joint pain.

Clinical Findings
The patient has red, indurated, peripherally raised plaques covering >50% of the face.

Laboratory/Studies
CXR showed fullness in mediastinal region. CT scan showed borderline lymph node in precarinal region, but this was not suspicious for systemic sarcoid. ACE was 11 unit/L (Normal 7-46 unit/L)

Histopathology
Biopsy revealed a granulomatous dermatitis consistent with sarcoidosis.

Clinical Course
This patient has failed multiple topical antibiotics, minocycline, doxycycline, steroids and has maintained adequate photoprotection. He was started on methotrexate and titrated to 15 mg PO Qweek with a slight improvement. hydroxychloroquine was recently added to the regimen, and work-up for systemic sarcoidosis is negative. Methotrexate was increased to 25mg PO Qweek. He has yet to have a follow-up evaluation on the regimen. The patient is in the process of signing up for VA coverage so that a trial of adalimumab can be initiated if necessary.

Discussion
Sarcoidosis is a systemic granulomatous disease with an elusive etiology that commonly affects the lungs, lymph nodes, skin, and eyes. Those affected appear to have a genetic predisposition to granuloma formation, with an exposure or "trigger" setting off the cascade. Studies have indicated an increased female to male ratio in cutaneous sarcoidosis, and more severe disease in African Americans and people of Scandinavian descent. Essential histologic findings of specific skin lesions include noncaseating epithelioid cell granulomas in the dermis or infrequently in the subcutaneous tissue. However, sarcoidosis remains a diagnosis of exclusion with the need to eliminate infectious and other depositional etiologies. The treatment for patients with sarcoidosis is

complicated due to the variable nature of the disease process. Patients sometimes recover spontaneously with complete resolution of cutaneous nodules or with a minimal residual effect. Corticosteroids remain popular while other options such as hydroxychloroquire, methotrexate, minocycline, isotretinoin, thalidomide, and allopurinol have had some success. Recently, the TNF-α biologic agents infliximab, etanercept, and adalimumab have had success in treating systemic and cutaneous manifestations of this disease. Treatment should focus on limiting cutaneous lesions and evaluating the patient for progression of systemic disease.

References

1. Tchernev G. "Cutaneous Sarcoidosis: The Great 'Imitator.' Etiopathogenesis, Morphology, Differential Diagnosis, and Clinical Management". *Am J Clin Dermatol*. 2006; 7(6) 375-382
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Case 24
Verrucous Sarcoidosis

Resident Physician
Greg Simpson, M.D.

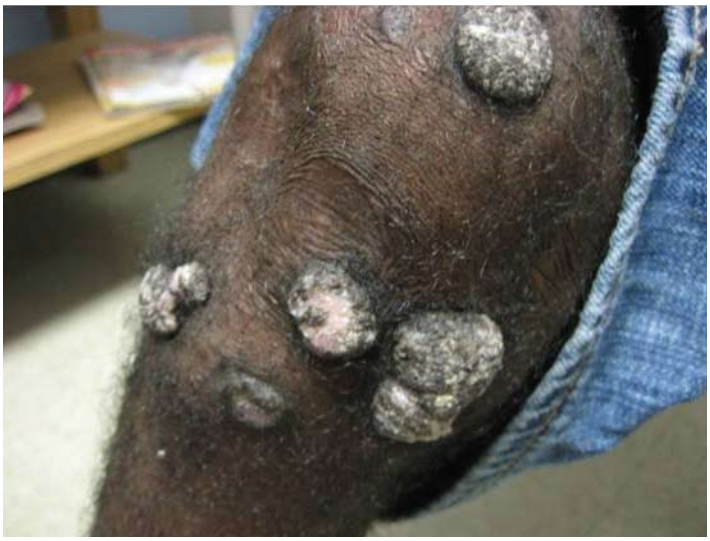
Attending Physician
Jack Lesher, M.D.

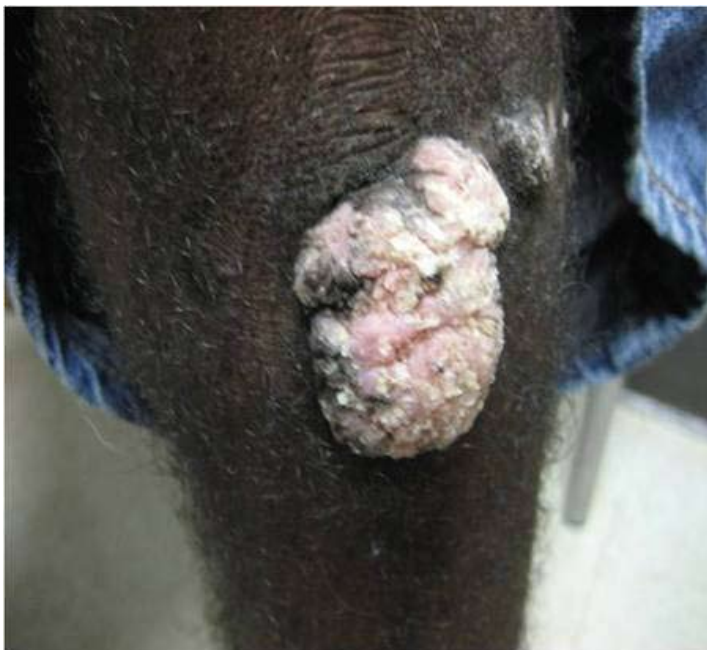
History
A 31 year old male presented with multiple 0.5-3.0 cm verrucous nodules on bilateral knees and dorsal right foot. He has a history of Pott's disease (tuberculosis of the spine) at the age of 5 which was treated with surgery and systemic medication. The lesions appeared around the time of the surgery and have grown slowly since then. The patient is paraplegic and has been confined to a wheelchair since his childhood. He has attempted no treatment, medical or surgical, on the lesions.

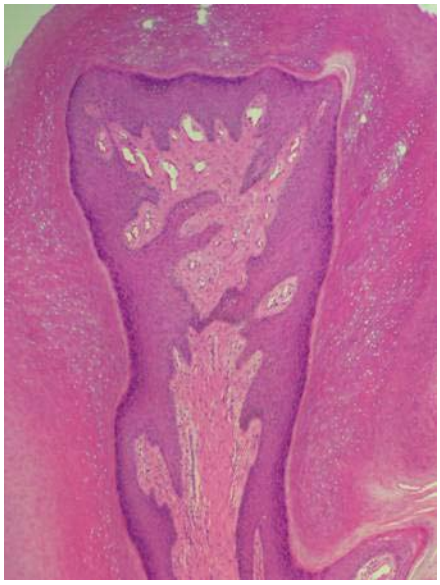
Clinical Findings
The patient has multiple, verrucous, exophytic nodules and tumors (1-3 cm) on bilateral knees and right 1st metatarsal joint.

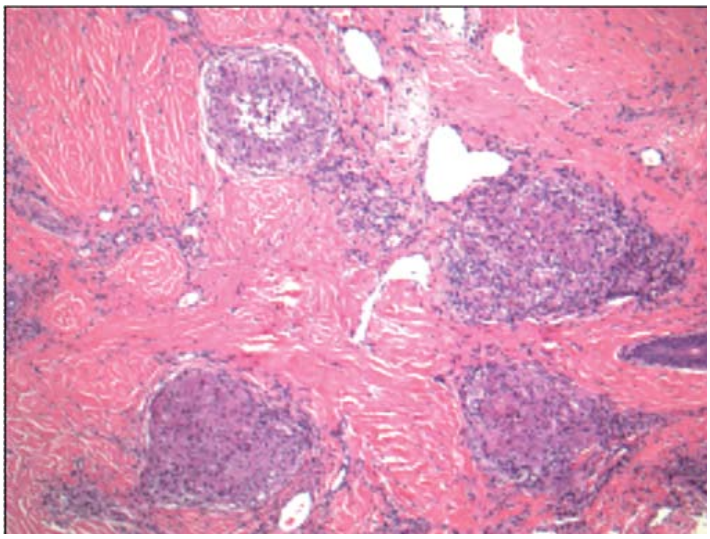
Laboratory/Studies
Angiotensin converting enzyme level was 91 unit/L (Nl-7-46). Chest X Ray showed no evidence of granulomas or hilar adenopathy. Fungal culture showed Candida glabrata.

Histopathology
Microscopic examination reveals a prominent pseudoepitheliomatous epidermal hyperplasia with downgrowths of follicular structures containing neutrophilic infiltrates extending into the dermis. There is a prominent mixed perivascular infiltrate consisting of lymphocytes, histiocytes, as well as prominent eosinophils and plasma cells. There are granulomas in the dermis surrounded by a lymphoplasmacytic infiltrate. Giant cells are prominent in the granulomatous areas. In addition, an interface pattern with a lichenoid lymphohistiocytic









infiltrate is noted along some of the epithelial downgrowths into the dermis. No polarizable foreign material is identified. Specimens were negative with both Acid Fast and Gomori Methenamine Silver staining.

Clinical Course

This patient has lived for over 25 years with these verrucous nodules which are asymptomatic (secondary to lack of sensation). He has never attempted any sort of topical treatment or manual removal of these at home. Considering his history of spinal tuberculosis and resulting sequelae (paraplegic and possibly these lesions), we performed excisional biopsy on a few lesions for histopathology, PCR, and culture. He has responded well to these treatments and has regrown less than 10% of the original lesions.

Discussion

Verrucous sarcoidosis is a rare specific cutaneous lesion. It was first reported as warty nodules with a histology that demonstrated sarcoidal granulomas and an acanthotic, hyperkeratotic epidermis. Our patient illustrated similar verrucous lesions accompanied by the classic periocular papules of sarcoidosis. Due to this patient's history of tuberculosis of the spine, our goal was to prove that cutaneous mycobacteria was not the causative agent. A small study by Li et al. showed that 80% of his study patients with a previous diagnosis of cutaneous sarcoidosis, had evidence of mycobacteria in the lesions by PCR. Histopathology, PCR, and culture were all negative for mycobacteria in our patient. Considering the unusual nature of these lesions, we are treating them by shave removal. At this time, he has no internal manifestations, so we have not felt a need to escalate our treatment to systemic medications.

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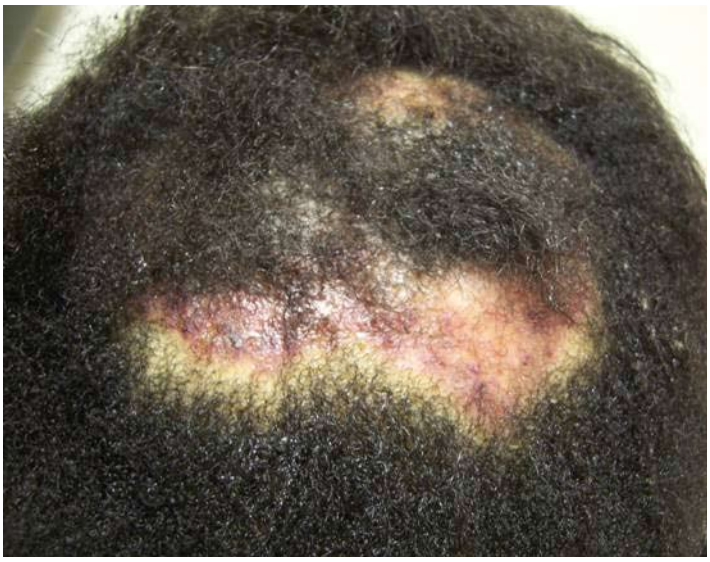
Case 25
Sarcoidosis

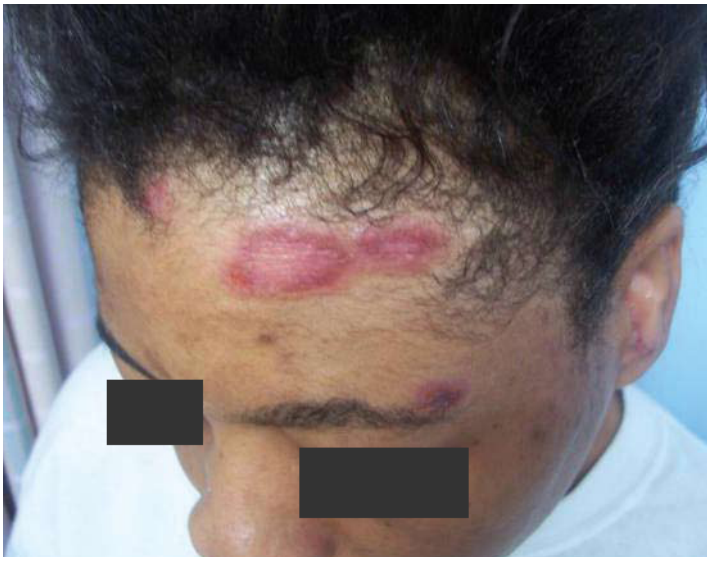
Resident Physician
Greg Simpson, M.D.

Attending Physician
Daniel Sheehan, M.D.



History
The patient is a 37 year old female with an eight year history of systemic sarcoidosis who presented with new onset scalp, face, and neck lesions of one month duration. Her sarcoidosis was discovered secondary to pulmonary complications, but has spread to include her liver and spleen, which has been removed. The scalp plaques were slightly pruritic, spreading relatively quickly and accompanied with a scarring alopecia. She was minimally responsive to topical steroids, systemic steroids, antimalarials, and minocycline and continued to form new plaques. She was started on adalimumab at 40 mg SQ Q14 days to which she has had some improvement.

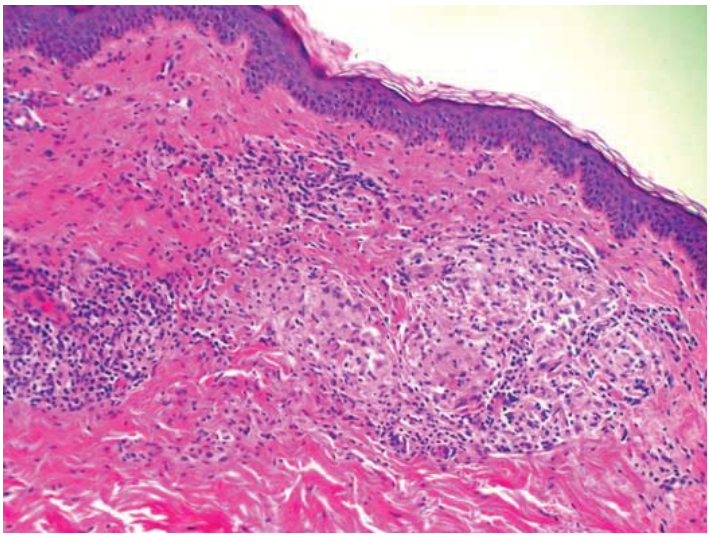
Clinical Findings
The patient has multiple violaceous plaques to scalp (with alopecia), and scattered violaceous papules and plaques on forehead, neck.

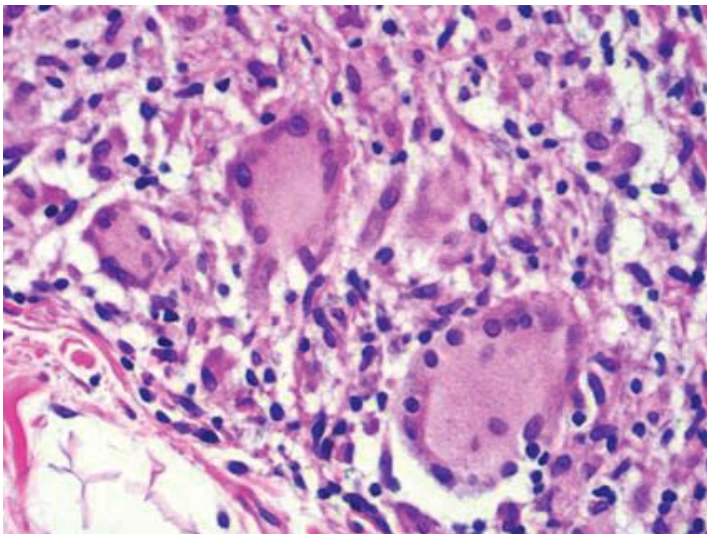


Laboratory/Studies
ANA was 1:80. Ro/SSA was negative. La/SSA was negative. CXR showed stable mediastinal lymphadenopathy. PPD was negative.

Histopathology
Non-caseating granulomas were in the dermis. Organism stains (GMS,AFB) were negative.

Clinical Course
This patient has failed topical steroids, systemic steroids, antimalarials, and minocycline, while continuing to develop new lesions. We elected to start her on adalimumab at 40 mg SQ Q 14 days for this granulomatous process. She has shown noticeable improvement in her scalp plaques and a lack of progression of any of her facial and neck lesions.





Discussion

Sarcoidosis is a systemic granulomatous disease with an elusive etiology that commonly affects the lungs, lymph nodes, skin, and eyes. Those affected appear to have a genetic predisposition to granuloma formation, with an exposure or "trigger" setting off the cascade. Studies have indicated an increased female to male ratio in cutaneous sarcoidosis, and it affects African Americans and people of Scandinavian descent more severely than it does Caucasians in America. Essential histologic findings of specific skin lesions include noncaseating epithelioid cell granulomas in the dermis or infrequently in the subcutaneous tissue. However, sarcoidosis remains a diagnosis of exclusion with the need to eliminate infectious and other depositional etiologies. The treatment for patients with sarcoidosis is complicated due to the variable nature of the disease process. Patients sometimes recover spontaneously with complete resolution of cutaneous nodules or with a minimal residual effect. Corticosteriods remain popular while other options such as hydroxychloroquine, methotrexate, minocycline, isotretinoin, thalidomide, and allopurinol have had some success. Recently, the TNF-α biologic agents infliximab, etanercept, and adalimumab have had success in treating systemic and cutaneous manifestations of this disease. Treatment should focus on limiting cutaneous lesions and evaluating the patient for progression of systemic disease.

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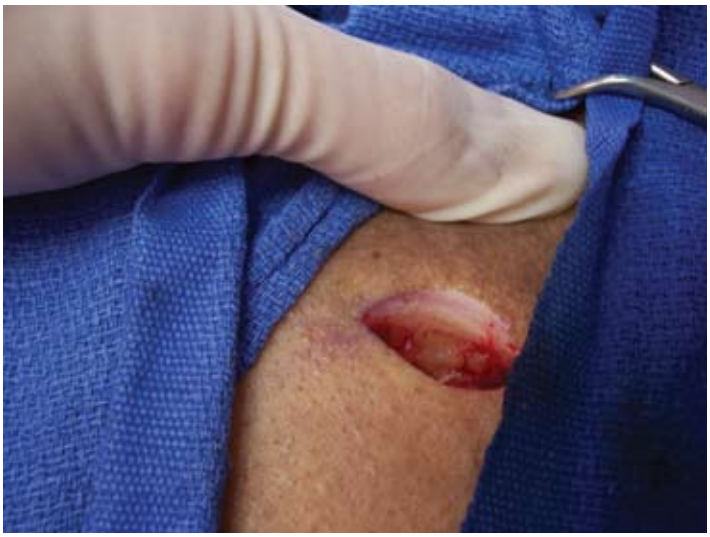
Case 26
Scleredema

Resident Physician
Sarah K. Josephson, M.D.

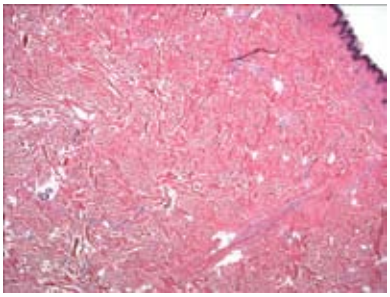
Attending Physician
Jack L. Lesher, Jr. M.D.
Daniel J. Sheehan, M.D.

History
A sixty-five year old female presented for evaluation of noted progressive thickening of the skin on her back and arms. Upon further questioning, she admitted to a change in her skin color and complained that the area itched. On review of systems, she admitted to a chronic cough and shortness of breath. Otherwise her review of systems was negative. Her past medical history included non-insulin dependent diabetes mellitus, glaucoma, and hypertension.

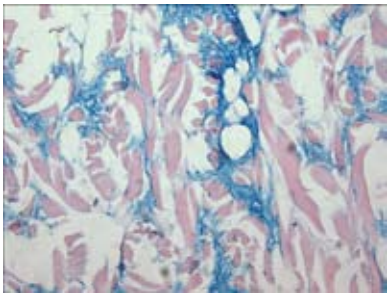
Clinical Findings
On physical exam, she has indurated, woody, hyperpigmented, coalescing thick plaques on the central upper back and proximal arms.



Laboratory/Studies
Chest x-ray demonstrated cardiomegaly and pulmonary venous hypertension with probable chronic interstitial lung disease. Laboratory studies revealed a normal hemoglobin and white blood cell and platelet counts were within normal limits. Immunology revealed a negative Scl-70, but an ANA > 1:640. TSH and Free T4 were within normal limits. SPEP was positive for a small cathodic gamma protein "spike".



Histopathology
Biopsy revealed massive thickening of the dermis with only scant inflammatory infiltrate. In the deeper portion of the dermis, there are increased spaces between collagen bundles, some of which are occupied by a thin, wispy blue material that was highlighted by a colloidal iron stain, indicating mucin. These findings were felt to be consistent with scleredema.



Clinical course
The patient was treated with triamcinolone 0.1% ointment twice daily.

Discussion
Scleredema is characterized by symmetrical, diffuse induration of the upper body caused by a thickening of the reticular dermis and deposition of mucin. Diabetes mellitus is thought to be a pathogenetic factor. Streptococcal hypersensitivity, paraproteinemia and lymphatic injury may also play a role.

There are three types of scleredema having variable prognosis and treatment. The first type, scleredema adultorum of Buschke, is usually preceded by a streptococcal respiratory infection. The skin of the cervicofacial region hardens with progression to the trunk and proximal limbs, resulting in an expressionless face and difficulty opening the mouth or swallowing. It usually resolves in a few months. The second type shares similar clinical features with the first, but is characterized by a more subtle onset, no preceding illness, an association with a monoclonal gammopathy, and a longer course, persisting for years. Beers, et al. describe a case of scleredema adultorum of Buschke in association with hypergammaglobulinemia and B-cell lymphoma. The patient was diagnosed with B-Cell lymphoma prior to the diagnosis of scleredema. The third type occurs primarily in obese middle-aged men with insulin-dependent diabetes mellitus, scleredema diabeticorum. The onset is subtle and involvement persists. Erythema, induration, and peau d'orange appearance of the skin is seen.

Systemic manifestations in scleredema include serositis, dysarthria, dysphagia, myositis, parotitis, and ocular and cardiac abnormalities. Lack of acral involvement, absence of Raynaud's phenomenon and absence of cuticular and mat telangiectasia helps differentiate scleredema from scleroderma.

Histologically, early lesions of scleredema are characterized by a thickened reticular dermis, with large collagen bundles separated from each other by mucin. Late lesions predominantly consist of fibrosis.

Treatment is unnecessary for scleredema associated with streptococcal infections because it is self-limited. Regression of scleredema associated with diabetes and monoclonal gammopathy is more uncommon and no specific treatment is available. Therapeutic benefit from PUVA, cyclophosphamide pulse therapy plus corticosteroids, cyclosporine, factor XIII infusion and electron beam therapy have been reported. Eberlein-Konig, et al reported a case of scleredema adultorum with striking clinical improvement with medium-dose UVA1 phototherapy (single dose, 50 J/cm2, 35 treatments). Bowen, et al. reported 3 cases of successful treatment, based on the improved angle of shoulder abduction, with radiation therapy after other treatments had failed. There was significant reduction in the degree of skin thickness, as measured by ultrasound, a softening of the skin, and a marked improvement in range of motion during the course of therapy. Control of hyperglycemia does not appear to affect the skin disease. This case presents an opportunity for discussion of therapeutic options regarding scleredema.

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Case 27
Mixed Cryoglobulinemia

Resident Physician
Josh Wharton, M.D.

Attending Physician
Jack L. Lesher Jr., M.D.

History
A 64-year-old male presented with a five year history of a mildly pruritic rash on his lower extremities that had progressively worsened. Within the previous three to four weeks, the patient developed skin breakdown and black-colored sores on his bilateral lower extremities that were painful. He reported similar sores that occurred on his ears the previous year that resolved without treatment. The patient also reported a "protein problem" that was previously diagnosed at an outside hospital.

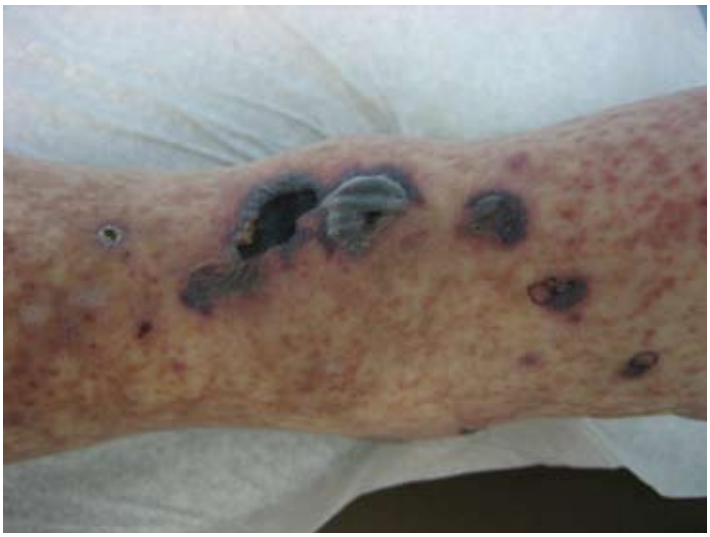
Clinical Findings
Black-colored, necrotic ulcerations are present on the right ankle more than the left ankle with a background of reticulated erythema and nonblanchable, erythematous and brown macules. Palpable purpuric papules are present diffusely on the bilateral lower extremities ranging in diameter from 0.2 cm to 3.4 cm. The trunk, abdomen, and bilateral upper extremities manifest a reticulated erythema as well.

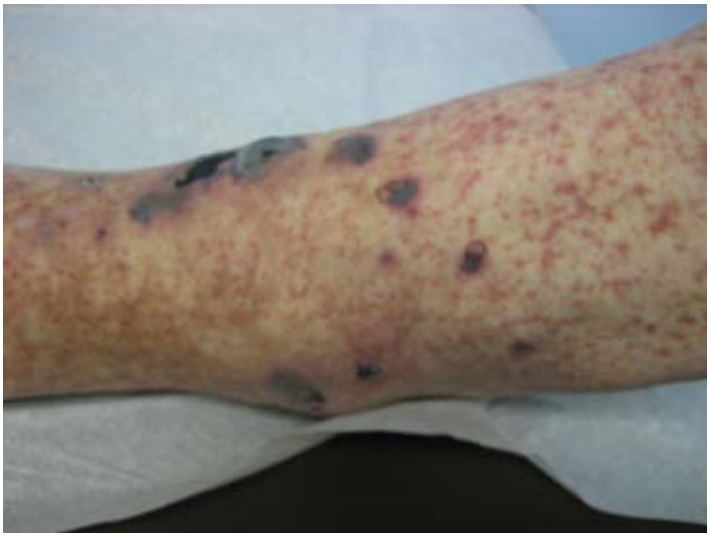
Laboratory/Studies
Serum cryoglobulins were positive and SPEP revealed a prominent monoclonal globulin spike. Reflex IFE revealed a prominent monoclonal IgG-kappa band migrating in cathodic gamma. ANA, ANCA, RF, and hepatitis panel were all negative. CBC, BMP, and U/A were within normal reference range.

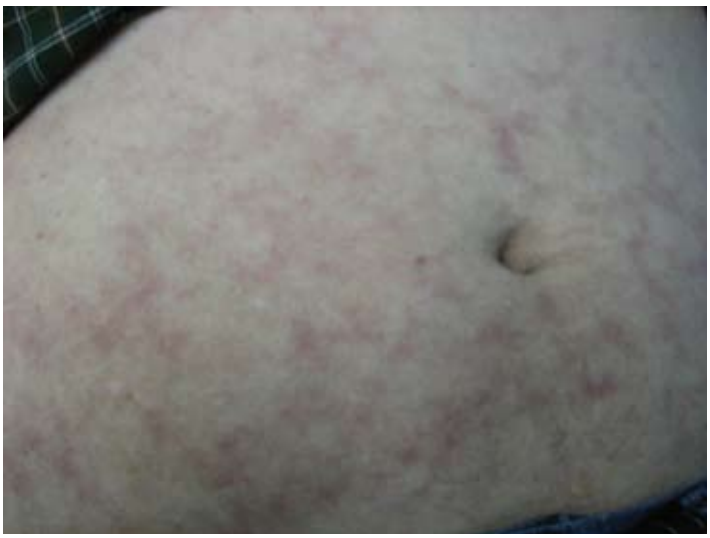
Histopathology
Two punch biopsies taken from the necrotic ulcerations of the right ankle revealed a combination of PAS-positive material in the vessels and small vessel vasculitis.

Clinical Course
The patient was initially begun on a prednisone taper, but the ulcerations and vasculitis continued to progress. The patient had extensive wound care for the ulcerations, and dapsone was eventually added, which resulted in clinical improvement. He has also been followed by heme/onc with plans to begin rituxan and perform a bone marrow and biopsy aspirate.

Discussion
Cryoglobulins are immunoglobulins that undergo reversible precipitation at low temperatures. Multiple forms of cryoglobulins have been identified, and each form determines the clinical manifestations. The cryoglobulins are present in the serum and may cause a clinical syndrome of systemic inflammation caused by immune complexes that contain the cryoglobulins.





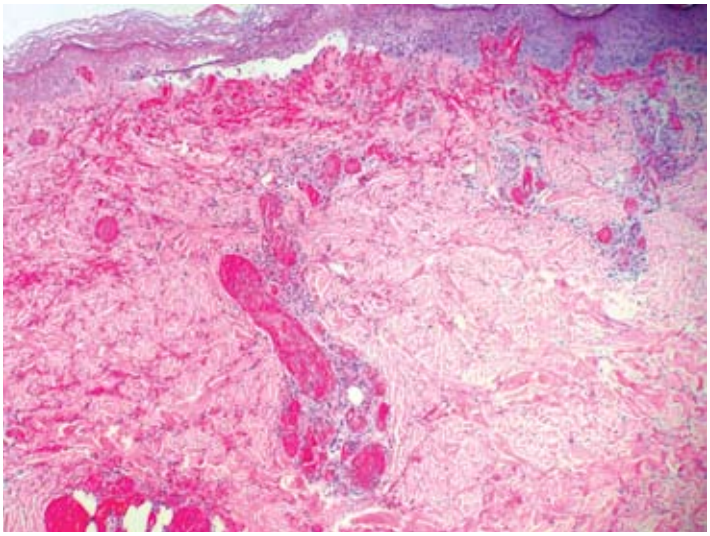


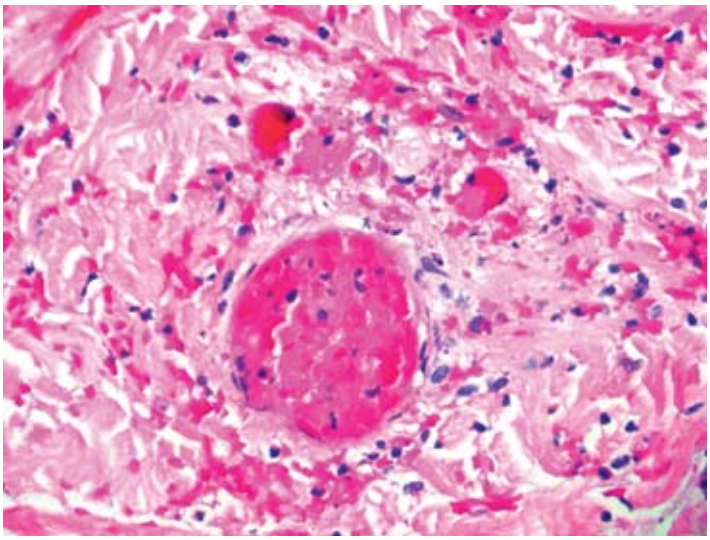
The Brouet classification of cryoglobulinemia is based upon the cryoglobulin composition. Type I cryoglobulinemia, simple cryoglobulinemia, is composed of a monoclonal immunoglobulin. Normally IgM is the immunoglobulin; however, IgG and IgA, or light chain varieties can also occur. Type II and III are the mixed cryoglobulinemias. Each contains rheumatoid factors (RFs), IgM being the most common. The RF may be monoclonal (Type II) or polyclonal (Type III). These RFs complex with the crystallizable Fc portion of polyclonal IgG. Types II and III cryoglobulinemias compose nearly 80% of all cryoglobulins.

Type I is typically related to an underlying lymphoproliferative disease and, as such, may be clinically indistinguishable from Waldenström macroglobulinemia, multiple myeloma, or chronic lymphocytic leukemia. Type I cryoglobulinemia often results in hyperviscosity due to high levels of circulating monoclonal cryoglobulin, leading to physical obstruction of vessels. Also, nonobstructive damage may be mediated by immune complex deposition and subsequent inflammatory vasculitis.

Types II and III, also known as the mixed cryoglobulinemias, are associated with chronic inflammatory states such as systemic lupus erythematosus, Sjögren syndrome, and viral infections, particularly HCV. It has been associated with HCV in as high as 90% of cases.

Common skin manifestations include ischemic necrosis (40% in type I, 0-20% in mixed types), palpable purpura (15% in type I, 80% in mixed types), livedoid vasculitis (1% in type I, 14% in type III), cold-induced urticaria (15% in type I, 10% in type III), hyperkeratotic spicules in areas exposed to cold, scarring of tip of nose, pinnae, fingertips, and toes, acrocyanosis, and nailfold capillary abnormalities.





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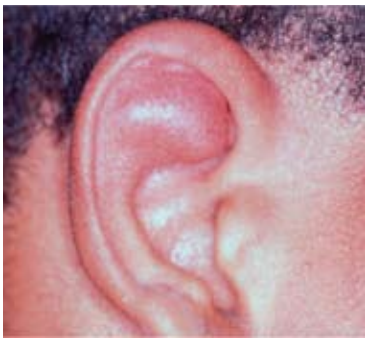
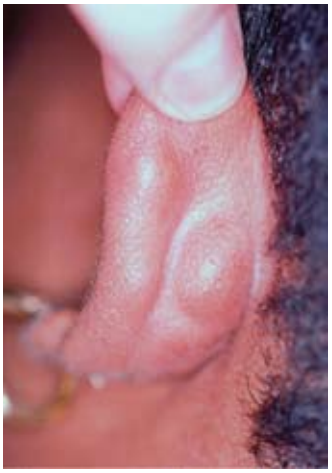
Case 28
Normolipemic Xanthomas

Resident Physician
Josh Wharton, M.D.

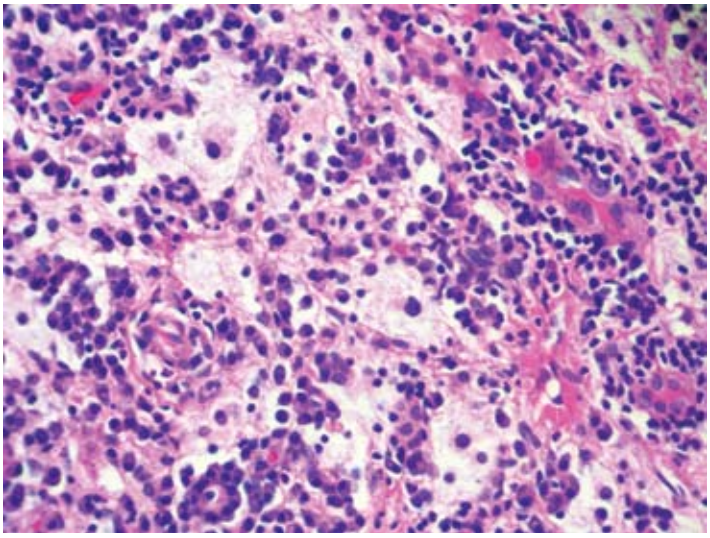
Attending Physician
Lorreta S. Davis, M.D.





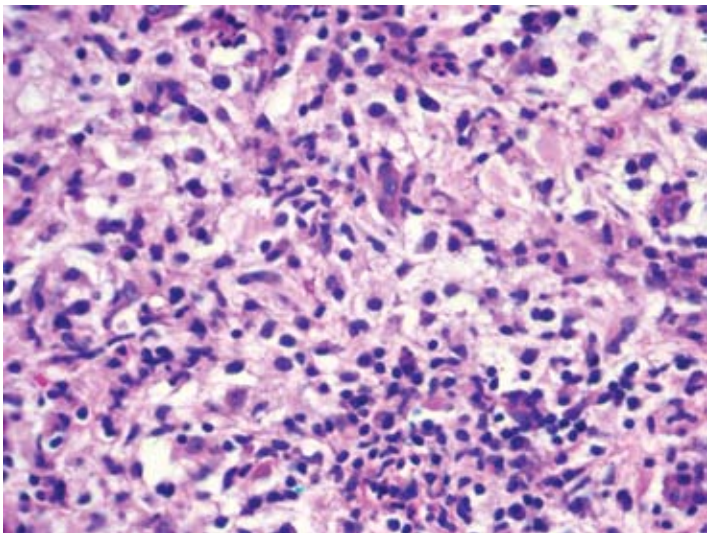
History
A 21 year-old female initially presented at the age of 14 with a complaint of occasionally painful ear nodules. She denied antecedent trauma. Over the past several years, multiple lesions have been surgically removed as new lesions continue to develop. Hearing has been compromised in the left ear due to obstruction of the left auditory canal. Family history was significant for keloids, but no personal or family history of similar ear nodules, lipid abnormalities, or premature cardiovascular disease was obtained.

Clinical Findings
Examination reveals multiple flesh-colored papules and nodules on the bilateral helices ranging in size from 0.5 to 2.7 cm. Confluent nodules obstruct the left auditory canal.



Laboratory/Studies
Fasting lipid panel, complete blood cell count, rapid plasma reagin, serum protein electrophoresis, and thyroid studies were normal.

Histopathology
Excisional biopsies were obtained. Intraoperatively, these firm nodules were well-circumscribed, with a glistening yellowish surface. Many lesions were adherent to underlying cartilage. Histologic examination showed multiple dermal nodules composed of foamy histiocytes and multinucleate giant cells surrounded by a mixed inflammatory infiltrate. Special stains for organisms were negative.



Clinical Course
The majority of the patient's xanthomas have been removed with serial excisions. One nodule was injected with triamcinolone 40 mg/ml with some decrease in size. However, she continues to have a hearing deficit in the left ear due to obstruction, and additional nodules have developed. The patient has been referred to otolaryngology for further evaluation and treatment of the obstructed left ear canal.

Discussion
Histologically, xanthomas appear as dermal aggregates of foamy histiocytes often attached to underlying tissue. Xanthomas typically result from a primary aberration in lipid metabolism. However, several clinical varieties of xanthomas can occur in the absence of hyperlipoproteinemia. Parker classified these normocholesterolemic xanthomatoses into three principal types based on their etiology. The first group (type I) includes xanthomas associated with altered lipoprotein content or structure. Type IA refers to abnormal accumulation of cholestanol and plant sterols found in cerebrotendinous xanthomatosis and betasitosterolemia,

respectively. Type IB includes patients in whom alterations in the protein portion of various lipoproteins result in xanthelasmas and tuberous xanthomas.

Type II normocholesterolemic xanthomatoses includes diffuse planar lesions that arise on the face and trunk because of underlying lymphoproliferative diseases. Paraprotein interaction in lipoprotein metabolism may be responsible for this xanthoma formation.

For the third group, local dermal tissue abnormalities may trigger xanthoma formation. Erythroderma, epidermolysis bullosa dystrophica, and febrile episodes associated with bright-red erythema of the skin incite inflammation altering vascular permeability so that lipoproteins may leak and be phagocytized by dermal histiocytes. Such a mechanism is responsible for the eruptive xanthoma formation described by Eeckhout et al in capillary leak syndrome, a well-known complication of sepsis.

The occurrence of auricular xanthomas in our healthy normolipemic patient is intriguing. She denied any antecedent inflammation of the auricles as a triggering event. Her lipid status remains normal, but will be monitored as xanthomas can present before the development of a documented lipid abnormality. We believe this is the first and only reported case of this unique entity.

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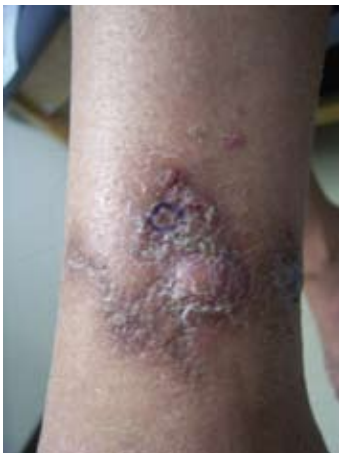
Case 29
Acquired Perforating Dermatosis

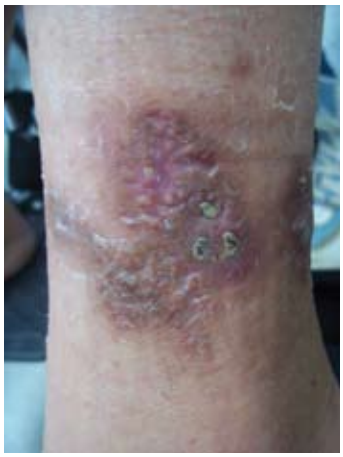
Resident Physician
Betsy R. Cooke, M.D.

Attending Physician
Daniel J. Sheehan, M.D.

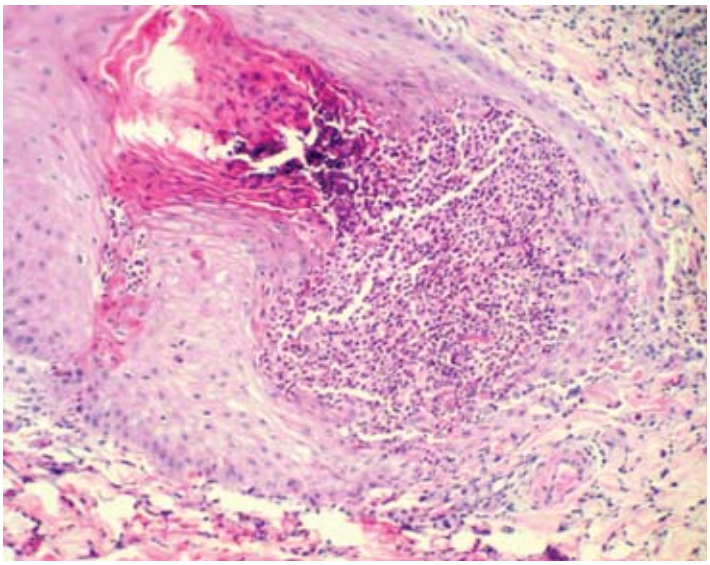
History
A thirty-five year old female presented for evaluation of tender skin lesions that arose on her extremities two years ago. She stated the areas had gotten larger. She used unknown topicals in the past without improvement. Her past medical history is significant for juvenile diabetes which has resulted in end stage renal disease and blindness. The patient does daily peritoneal dialysis.

Clinical Findings
Hyperkeratotic, crusted papules, nodules, and plaques are scattered on her bilateral lower legs. There are a few pink papules on her elbows.



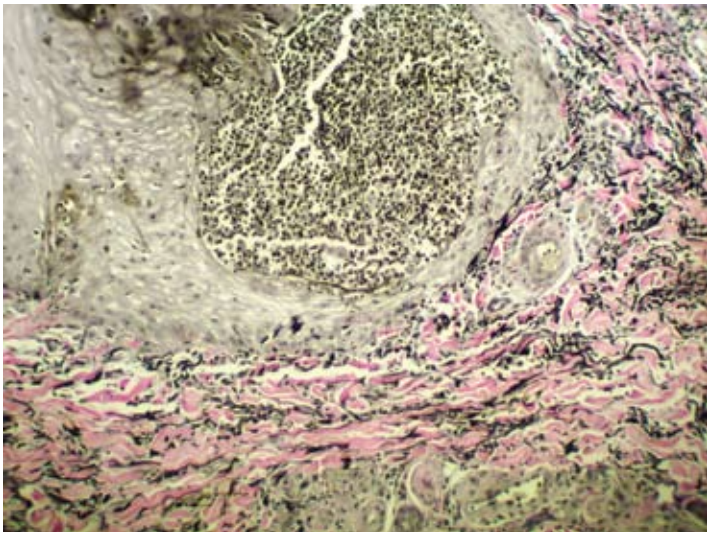


Histopathology
Biopsies from the right and left lower legs showed epidermal hyperplasia and downgrowths into the dermis creating perforating channels filled with degraded collagen fibers, elastic fibers, and basophilic debris.



Clinical Course
The patient was started on topical urea 40% as well as tretinoin 0.025% cream daily to the distinct lesions. A discussion regarding oral retinoids was initiated with the patient, but she was not inclined to use a systemic medication. The patient experienced improvement in the lesions with use of the topical retinoids. The strength of her tretinoin cream was increased, and she continues to see slow but steady results.

Discussion
Acquired perforating dematosis (APD) is now regarded as a general term for those perforating diseases previously referred to as perforating folliculitis, Kyrle's disease, and acquired perforating collagenosis. The lesions are hyperkeratotic papules and nodules usually found on the lower extremities but can be seen on the trunk or upper extremities. A central hyperkeratotic core can sometimes be seen in the lesions.



This skin condition is usually associated with diabetes mellitus or chronic renal failure or both. Diabetes is the most frequent cause of chronic renal failure in acquired perforating dermatosis patients. Approximately 10% of dialysis patients have APD. Others systemic conditions such as liver disease, hypothyroidism, hyperparathyroidism, and HIV infection have been noted in APD patients.

Histologically, there is transepidermal elimination of some components of the dermis. Collagen, elastic fibers, and inflammatory cells may be extruded. There are various theories as to the pathogenesis of APD. Some feel it is due to

trauma like scratching in response to pruritus from chronic renal failure. Others feel that the disease is predisposed by deposits of substances in the dermis such as calcium salts, a by-product of renal failure.

Treatment of acquired perforating dermatosis can be difficult. Narrowband UVB has been shown to be successful in both resolving skin lesions as well as treating pruritus. Topical retinoids, allopurinol, doxycycline, and isotretinoin have all been successful in flattening the lesions.

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Case 30
Folliculotropic Mycosis Fungoides

Presenting Physician
Allison R. Metzinger, M.D.

Attending Physician
Loretta S. Davis, M.D.

History
A 55 year old male of Cherokee descent presented with an eighteen year history of a progressive pruritic eruption. Biopsy ten years earlier was non-specific. Treatment with super-potent topical corticosteroids had been unsuccessful.

Clinical Findings
On exam, the patient has thin, erythematous scaly plaques and patches with superimposed follicular papules on the trunk. Thick well-defined erythematous plaques with silver scale are present on the scalp. Violaceous nodules are noted on both forearms with several well-defined violaceous papules in the right periocular area. No alopecia or nail abnormalities are noted. No cervical, supraclavicular, axillary or inguinal lymphadenopathy is appreciated.

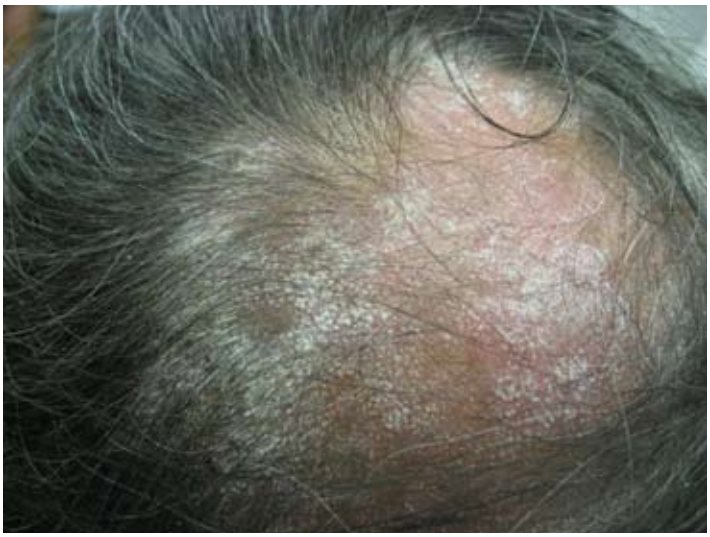
Laboratory/Studies
Complete blood count, metabolic profile, liver function studies and lipid profile were within normal limits. Potassium hydroxide prep was negative for hyphae and yeast.

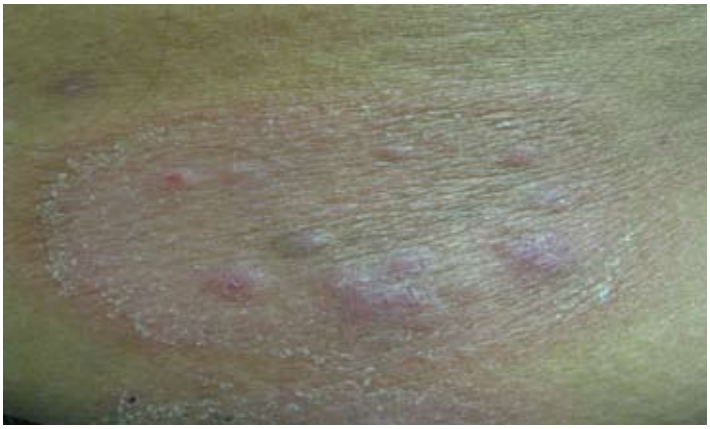
Histopathology
Microscopic examination revealed a follicular and perifollicular atypical lymphocytic infiltrate. Immunohistochemistry studies revealed a CD3 positive, CD4 positive, CD7 negative and CD8 negative lymphocytic phenotype.

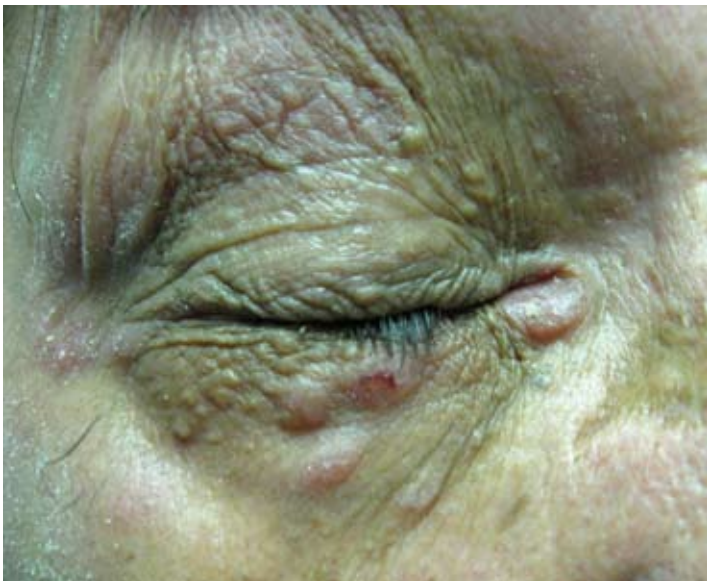
Clinical Course
The patient is currently undergoing treatment with PUVA. He is also applying Bexarotene 1% gel and Clobetasol ointment. After two months of treatment, some lesions have improved.

Discussion
Folliculotropic, or follicular, mycosis fungoides is rare, occurring in only 10% of patients with mycosis fungoides. This distinct variant of mycosis fungoides is characterized clinically by grouped papules, plaques or tumors which have a predilection for the head and neck. Lesions are typically intensely pruritic and can be associated with alopecia. Microscopically, atypical lymphocytes infiltrate the follicular epithelium with sparing of the epidermis. The atypical lymphocytes are phenotypically similar to those of typical mycosis fungoides with a CD3 positive, CD4 positive and CD8 negative phenotype.

Follicular mycosis fungoides is an aggressive variant of cutaneous T-cell lymphoma which is difficult to treat and does not typically respond to skin-directed therapies. PUVA has led to improvement in these patients. Combination of PUVA with retinoids or interferon alpha produces increased response. More advanced disease requires aggressive therapy, however many patients do not respond to chemotherapeutic agents.







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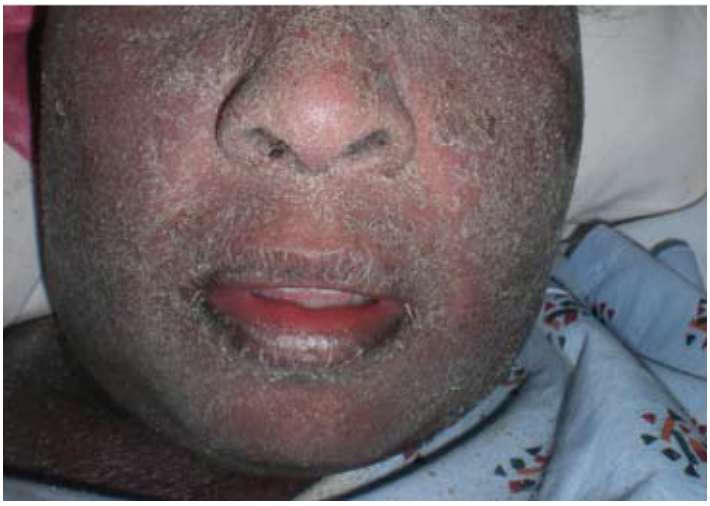
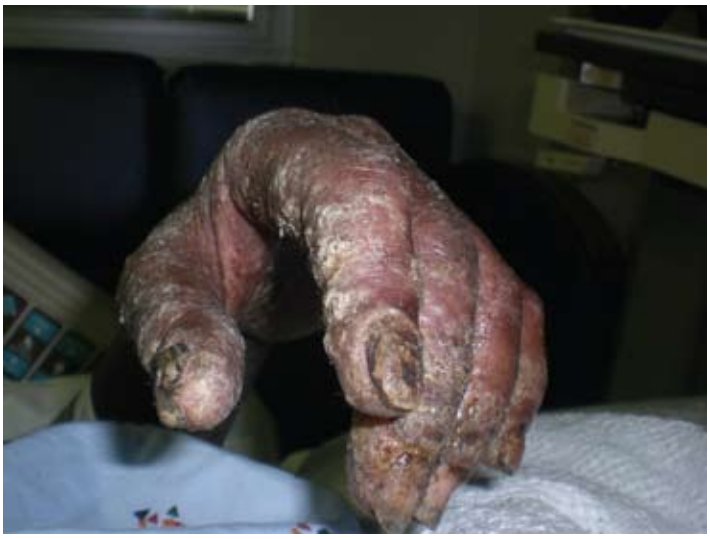
Case 31
Cutaneous T Cell Lymphoma

Resident Physician
Susan Corey, M.D.

Attending Physicians
Daniel Sheehan, M.D.
Loretta S. Davis, M.D.
Jack L. Lesher, M.D.
Cheryl Barnes, M.D.

History
This 32-year old female was first seen in our dermatology clinic in 2004 and diagnosed with mycosis fungoides by biopsy. At this time, the patient was treated with PUVA for over a year with moderate improvement of her disease. She also used topical corticosteroids and carmustine, but this was stopped secondary to skin irritation. In 2005, the patient was transferred to Emory University where she underwent Total Skin Electron Beam Therapy (TSEBT). She then returned to our clinic in 2008, and at this point the extent of her skin disease had significantly worsened. A repeat skin biopsy was performed and she underwent an extensive evaluation by hematology oncology including imaging and a lymph node biopsy. Her disease was staged as IIIB with sezary syndrome, and after discussion of multiple treatment options the patient was started on vorinostat.





Clinical Findings
The patient has diffuse scaling and xerosis, scattered weeping fissures, and hyperkeratosis of palms and fingers.

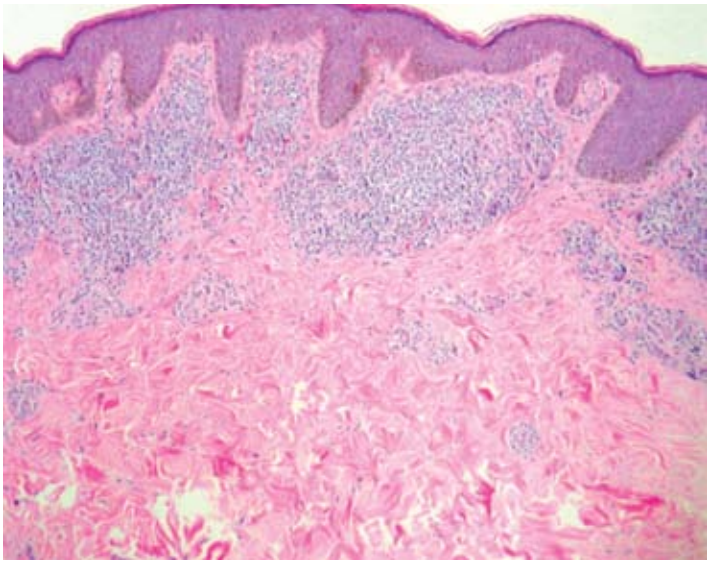
Laboratory/Studies
Complete blood count revealed an elevated white blood cell count(11.6thou/mm^3) and anemia(Hgb 9.1 d/L). Chest X Ray was within normal limits. CT scan of the abdomen, thorax, and pelvis revealed bilateral axillary and groin lymphadenopathy. In the left axilla, excisional biopsy revealed a population of CTCL cells with a positive T cell gene rearrangement study. Flow cytometry done on peripheral blood revealed a population of lymphoid cells positive for CD2,3,4, and 5 with loss of expression of CD7.

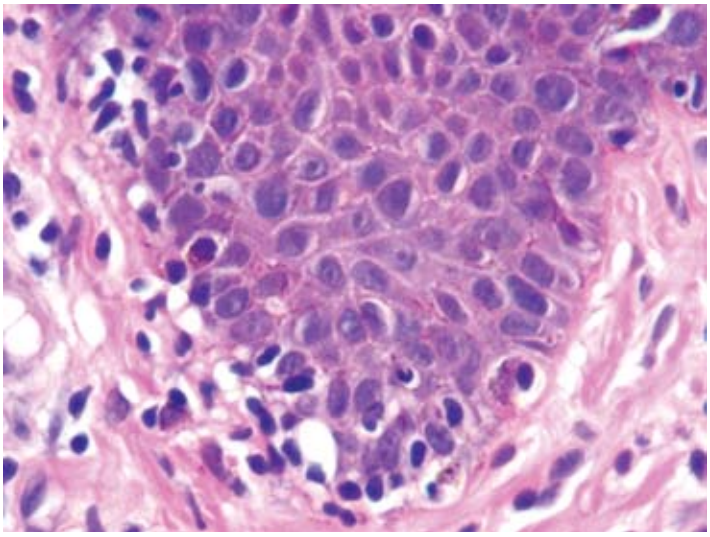
Histopathology
Atypical lymphoid infiltrate consistent with mycosis fungoides, PCR for T cells showed the presence of a clonal population

Clinical Course
As of the time of this publication, the patient was still on vorinostat. She has been offered many other treatment options by hematology and oncology, but declined as she is caring for young children and has difficulty with transportation. She continues to have significant skin pain, which has been debilitating to her at times. Her course has also been complicated over the last few months with several admissions to the hospital with staphylococcal sepsis and renal failure presumed secondary to dehydration.

Discussion

Primary cutaneous T cell lymphoma or mycosis fungoides is a malignancy of T-lymphocytes, most often T memory cells. It is most common in middle-aged African American males, but it can occur in all races and in all ages. Patients often have several biopsies done before diagnosis is made. In most cases, it is a chronic disease that slowly progresses and rarely causes patient mortality. Treatment for patients is based on the extent of their disease and the patients overall health. Often in stage I disease topical steroids, nitrogen mustard, bexarotene gel, and phototherapy are used. Total skin electron bean phototherapy may be added in stage II disease. Chemotherapy and photophoresis are often employed in patients with more advanced disease. Vorinostat is a chemotherapeutic agent that has been used in our patient. It is a histone deacetylase (HDAC) inhibitor that was recently approved in 2006 for advanced cutaneous t-cell lymphoma





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Case 32
Langerhans Cell Histiocytosis

Resident Physician
Betsy R. Cooke, M.D.

Attending Physician
Jack L. Lesher, Jr., M.D.

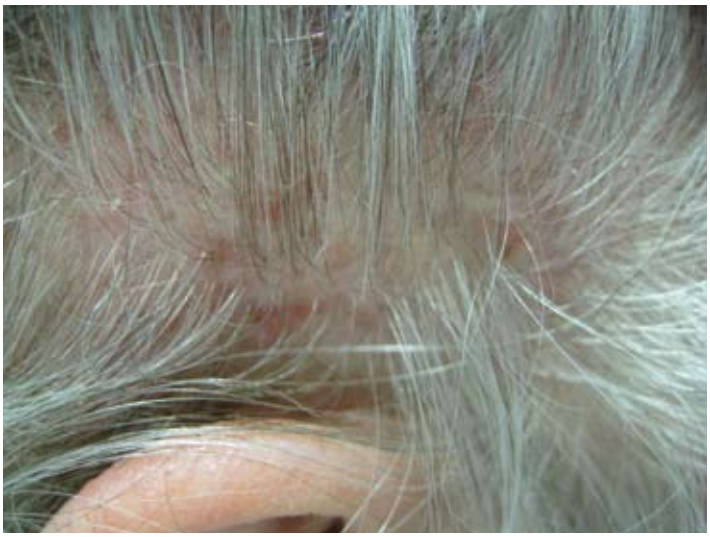
History
A forty-six year old female presented with the complaint of a pruritic scalp rash which she described as flaky. The area she felt was most affected was the temporoparietal scalp. Past medical history is significant for hearing loss in the right ear which was found to be due to a temporal bone tumor. This tumor was resected, but six months later hearing loss occurred in the left ear. Another temporal bone tumor was found on the left side, and the patient underwent surgical removal. She does have residual hearing loss and has received a cochlear implant. The patient has also developed diabetes insipidus and continues to follow with endocrinology for this problem.

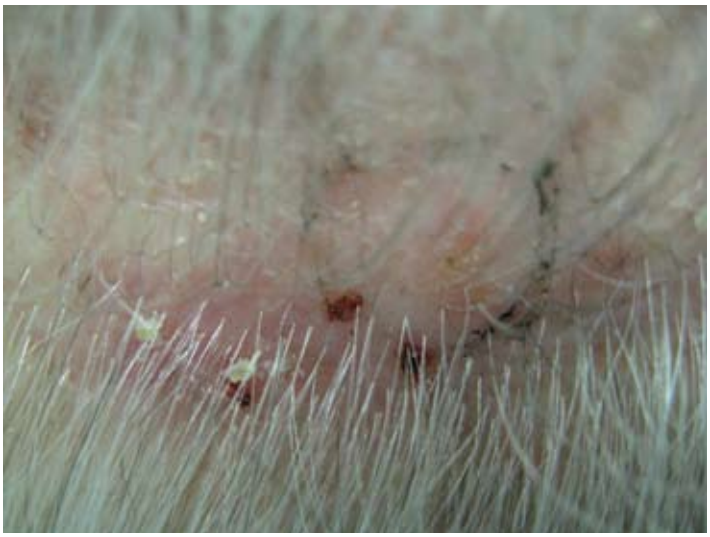
Clinical Findings
The patient has difficulty communicating due to hearing loss. There are erythematous and purpuric patches with scale in the temporal region of the scalp bilaterally. Some areas are friable, and the skin can be easily broken.

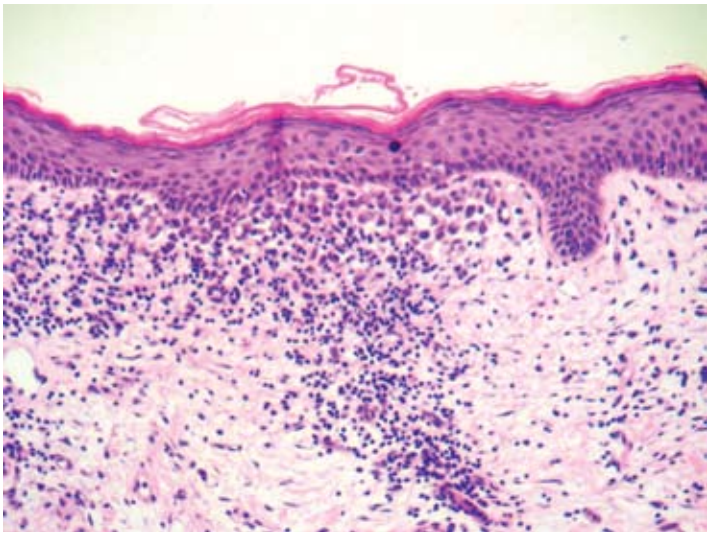
Histopathology
Two punch biopsies were performed of the left temporoparietal scalp. A diffuse, dense, predominantly histiocytic infiltrate was seen within the papillary and superficial reticular dermis. The deep reticular dermis and subcutis were unremarkable. Immunohistochemistry performed for S-100 and CD1a was diffusely positive in the infiltrating histiocytic cells. Immunohistochemistry for CD68 showed scattered background staining.

Clinical Course
The patient was started on imiquimod cream to affected areas of the scalp. After five months of treatment, the patient noted improvement in the chronic scaling of the scalp and resolution of the pruritus. Her physicians had her stop the application of imiquimod to the scalp prior to the placement of her cochlear implant in May, 2008. She has not re-started the topical imiquimod but is currently receiving chemotherapy with vinblastine and mercaptopurine.

Discussion
Langerhans cell histiocytosis (LCH) is characterized by clonal proliferation of Langerhans cells that are CD1a and S100 positive and which contain Birbeck granules. The term Langerhans cell histiocytosis includes a spectrum of diseases that can be separated into individual entities for historical interest. Many organ systems including skin, lymph nodes, lungs, liver, spleen, endocrine glands, and the nervous system can be affected. The disease can be classified by single organ involvement or multisystem disease.







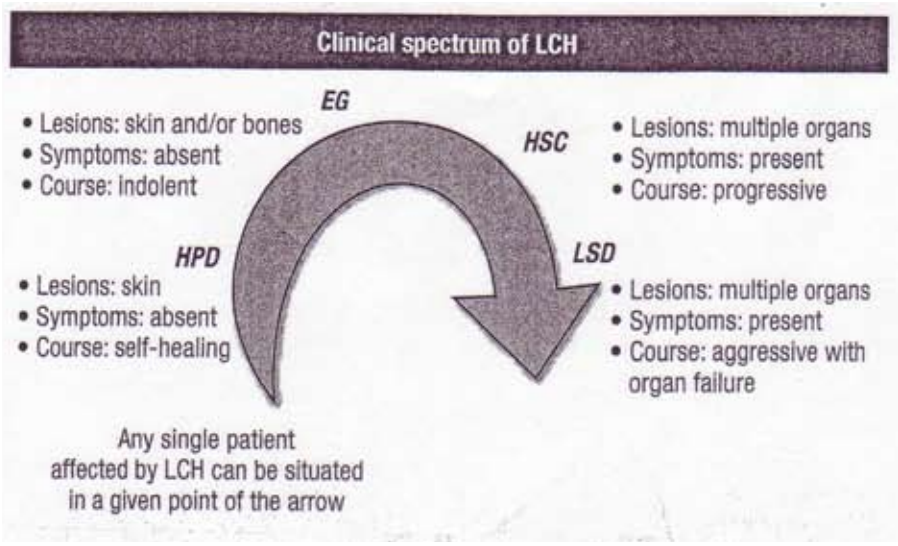


TABLE 148-3
Classification of Langerhans Cell Histiocytosis (LCH) According to Extent of Disease

- Single-system disease or restricted LCH
  - Skin lesions without any other site of involvement
  - Monostotic lesion with or without diabetes insipidus, adjacent lymph node involvement, or rash
  - Polyostotic lesions involving several bones or more than two lesions in one bone, with or without diabetes insipidus, adjacent lymph node involvement, or rash
- Multisystem disease or extensive LCH
  - Visceral organ involvement with or without bone lesions, diabetes insipidus, adjacent lymph node involvement, and/or rash but without signs of organ dysfunction of the lungs, liver, or hematopoietic system
  - Visceral organ involvement with or without bone lesions, diabetes insipidus, adjacent lymph node involvement, and/or rash but with signs of organ dysfunction of the lungs, liver, or hematopoietic system

LCH may be diagnosed at any age from birth to those over 80 years of age. It is rare in adults, and when it does occur, the sites most commonly involved include skin, lung, and bone. When bony involvement of the skull is present, diabetes insipidus can develop. Our patient had bilateral temporal bone involvement, skin involvement, and diabetes insipidus.

In regards to treatment of LCH in the skin, past agents used in literature reports include topical or systemic steroids, topical nitrogen mustard, methotrexate, vinblastine, and systemic interferon. In skin LCH refractory to multiple therapies, systemic interferon has been effective. Imiquimod is a topical immunomodulator that causes release of interferon-alpha, interferon-gamma, and interleukin-2. It was postulated in the literature that topical imiquimod could be effectively used so that patients did not have to experience the systemic side effects of interferon treatment. The investigators saw resolution of both pruritus and the lesions with five consecutive day use per week for two months. Temporary remission was seen for 6 months. Our patient used imiquimod to the scalp for approximately five months. Both a reduction in scaling and pruritus was experienced. She has now begun chemotherapy, and imiquimod was discontinued prior to its initiation.

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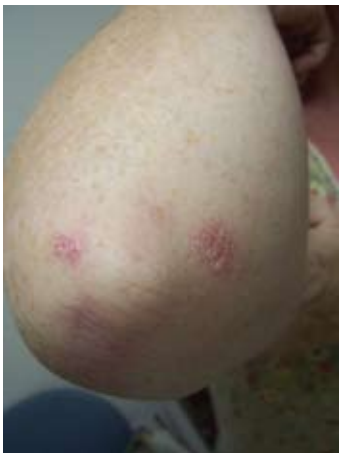
*Associated charts are from this source. Additionally, the key for the figure is EG - eosinophilic granuloma; HPD - Hashimoto-Pritzker disease; HSC - Hand-Schuller-Christian disease; LSD - Letterer-Siwe disease

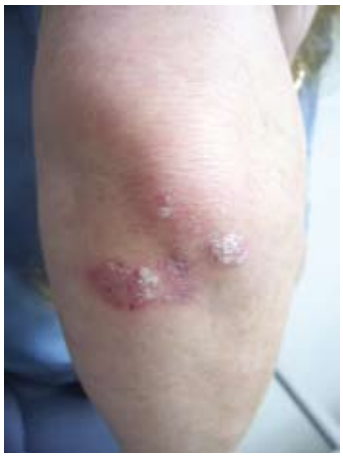
Case 33
Psoriasis and Hepatitis C

Resident Physician
Josh Wharton, M.D.

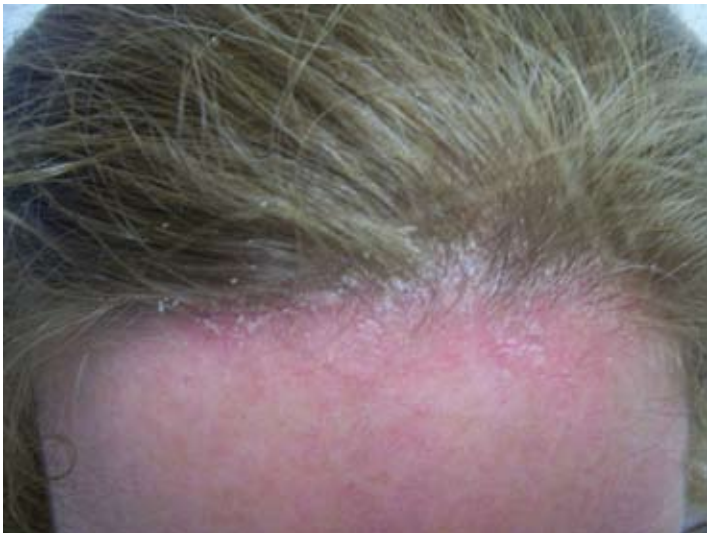
Attending Physician
Daniel J. Sheehan, M.D.

History
A 40-year-old female presented with a seven year history of a pruritic, scaly rash that affected her scalp, hands, feet, and thighs. Previous treatments with tar products were unsatisfactory. She recently began to experience arthralgias and stiffness in multiple joints, especially elbows, wrists, hands, and knees. The joint aches were impairing her quality of life. The patient also had a history of hepatitis C and smoking.





Clinical Findings
Erythematous scaly plaques are present over the occipital scalp, extensor elbows and knees, and left anterior thigh. Fingernails and toenails have onycholysis and pitting. She hobbles when walking secondary to joint pain.



Laboratory/Studies
Baseline labs, including CBC and CMP revealed slightly elevated ALT of 61. Purified protein derivative and HBV were negative. Quantitative HCV PCR= 6.4 log10 (2,340,000) IU/mL and HCV genotype 1.

Clinical Course
The patient was begun on etanercept 50 mg SQ twice weekly, in addition to a topical regimen consisting of clobetasol solution and calcipotriene cream and solution. Her treatment course on etanercept has been complicated by injection site reactions, leading to a decreased dosing regimen and pretreatment of injections with oral antihistamines and topically with ice and mid-potency steroids. She is currently taking 50 mg SQ/weekly, with evidence of clinical improvement and subjective improvement in joint pain. She is also followed by rheumatology and gastroenterology. Results of a recent ultrasound-guided liver biopsy are pending. The patient has declined the option of switching to an alternative biologic such as adaluminab.

Discussion
Many studies report an association between hepatitis C, psoriasis, and psoriatic arthritis. The treatment of psoriasis in the setting of HCV infection is difficult because several anti-psoriatic drugs are contraindicated owing to their liver toxicity. In addition, treatment of HCV with IFN- has been shown to trigger or worsen psoriasis. The recent introduction of biologic agents in the treatment of psoriasis and psoriatic arthritis offers an alternative for these complicated patients.

Of the available biologics, etanercept (Enbrel) has been the most extensively used and studied in the treatment of concomitant psoriasis and HCV. Elevated TNF-α levels have been documented in HCV-positive patients and are associated with a poorer prognosis and increased resistance to treatment. TNF-α appears to be involved in the pathogenesis of liver fibrosis through the stimulation of apoptotic pathways. Etanercept effectively neutralizes this proinflammatory effect of TNF-α. Etanercept has even been used as adjuvant therapy to IFN/ribavirin in the treatment of HCV in patients without psoriasis. Significant improvement in virologic response and decreased incidence of adverse reactions associated with interferon and ribavirin were seen with adjuvant therapy.

Recent observations in the literature suggest that etanercept is a safe and effective therapeutic choice in the setting of HCV and psoriasis. Multiple reports support the notion that etanercept does not increase hepatitis C viral load, affect liver function tests, or increase the risk of infections. The long-term safety or efficacy of anti-TNFα agents in chronic hepatitis C patients is unknown. However, at this time, they appear to be a relatively safe alternative for these challenging patients.

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Case 34
Familial Pityriasis Rubra Pilaris

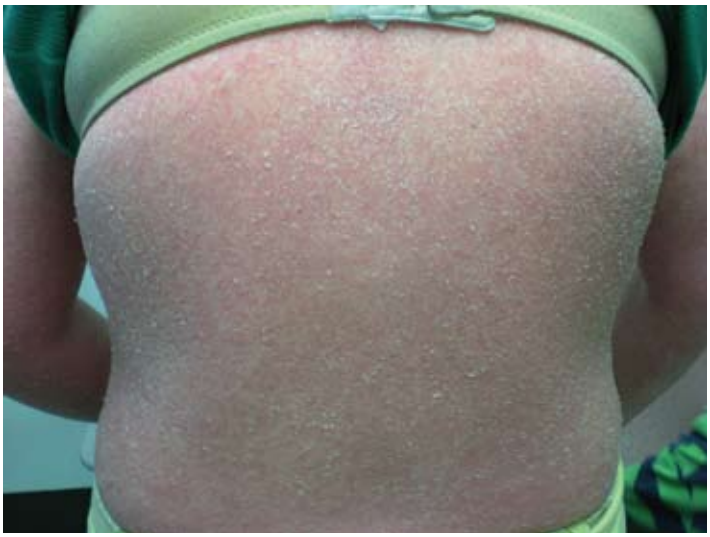
Resident Physician
Susan Corey, M.D.

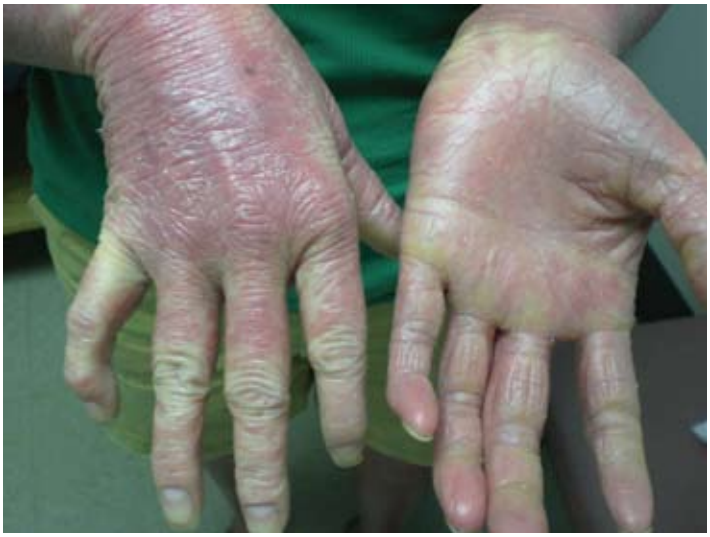
Attending Physician
Loretta S. Davis, M.D.

History
This 32 year-old female with pityriasis rubra pilaris, atypical juvenile type, was first diagnosed at Vanderbilt University at the age of four by clinical appearance and skin biopsy. Her first symptom of palmoplantar hyperkeratosis began around two months of age. The patient has twin boys with pityriasis rubra pilaris. One child has a more significant phenotype than his brother. The patient has a cousin with some palmoplantar hyperkeratosis, but he has not been formally diagnosed with the disease.

Clinical Findings
During skin flares, the patient has erythematous scaly plaques with "islands of sparing" and waxy keratoderma.

Clinical Course
Throughout her life, the patient has developed intermittent disease flare-ups with secondary infection and severe pain that required hospitalization. The first occurred at the age of twelve after an ear infection, and then again in 1995 after a stillbirth. In 1995, the patient was started on methotrexate and her skin remained well controlled for the following years. After having her twin boys in 2005, the patient's disease again flared. She was given etanercept and methotrexate with mild improvement. Narrowband UVB was tried with mild to moderate improvement. Isotretinoin and acitretin were discussed as possible therapeutic agents at this time, but were not used secondary to the patient's childbearing potential. More recently the patient has been on the combination of infliximab and methotrexate with good control of her disease.





Discussion
Pityriasis rubra pilaris (PRP) is an uncommon papulosquamous disorder that affects women and men equally. Patients present with coalescing erythematous papules and plaques with follicular hyperkeratosis. Lesions often start in the head and neck area and progress caudally. Often "islands of sparing" are noted on the trunk, but the patient may otherwise appear erythrodermic. Waxy, orange keratoderma is often present on the palms and soles, and nail dystrophy may occur. Skin biopsy shows acanthosis, hyperkeratosis, and alternating parakeratosis in a 'checkerboard' pattern.

Pityriasis rubra pilaris is most frequently classified into six types. The classic adult form accounts for the majority of diagnosed patients and these patients often have resolution of their eruption within 3 years. A minority of adults diagnosed with PRP fall into another type with a more chronic course. Children may also present with PRP. The classical juvenile form has a similar clinical presentation and outcome as the classical adult form. These patients usually present in the first two years of life. More frequently, children present in pre-adolescence with the circumscribed juvenile form. Lesions are more localized that in the classical juvenile type and are most frequently found on elbows and knees. The outcome in these patients is more variable than in the classical type. A third type of PRP in children is the atypical juvenile type, which is often familial. Like the classical juvenile and adult types, lesions are often generalized. These patients tend to have a more chronic and unpredictable course as compared to the other types of juvenile PRP. The last category of PRP is found in patients with HIV.

Multiple agents have been used for treatment of PRP, but not many large-scale randomized trials have been done with these medications. Methotrexate, PUVA, UVB, azathioprine, corticosteroids, cyclosporine, TNF-alpha receptors/ antibodies have all shown some success in limited studies and case reports.

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Case 35
Wells' Syndrome (Eosinophilic Cellulitis)

Resident Physician
Jeannette Hudgens, M.D.

Attending Physicians
Frances Florentino, M.D.
Jack L. Lesher, Jr., M.D.

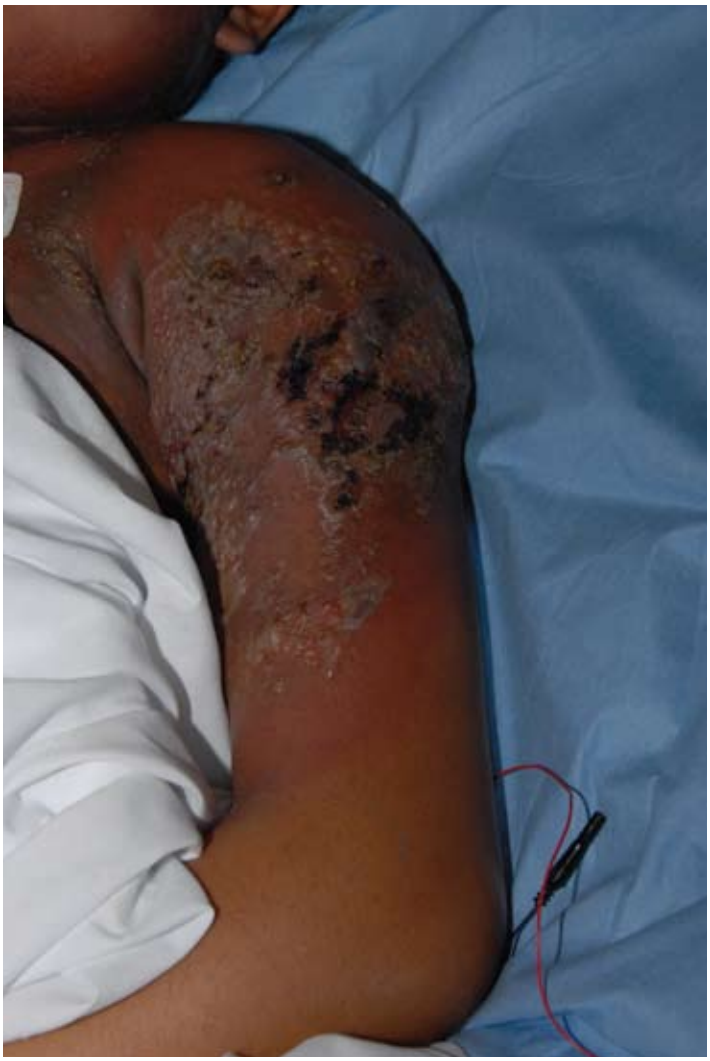
History
An 11 year-old previously healthy female presented with an erythematous plaque on her left arm, thought due to an insect bite. The local urgent care center started Bactrim for presumed cellulitis, despite her mother's allergy to sulfa. Two days later rash progressed, developing bullae. Bactrim was discontinued and pt was started on topical and oral steroids with concern for possible drug eruption. She was later admitted to a local hospital for fever, facial edema, and worsening bullous rash that covered approximately 40-50% of her body surface area. She was given multiple antibiotics without improvement. Due to the large amount of denuded skin, the patient was transferred to a burn center where she received IVIG and high dose IV steroids and debridement. Skin biopsy was read as Sweet's Syndrome due to presumed neutrophilia and negative DIF.

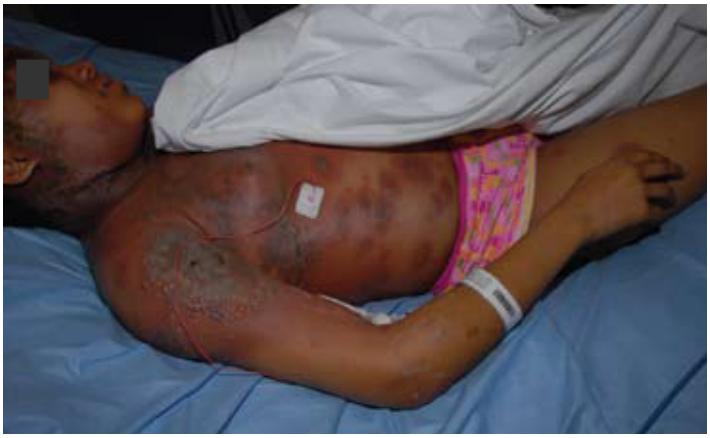
Clinical Findings
The original lesion developed into erythematous edematous plaque with dusky center and bulla formation. Additional lesions developed on the right arm, trunk, lateral areas of her face and neck, and finally her proximal lower extremities.

Laboratory/Studies
WBC count was elevated with peripheral eosinophilia. Blood cultures remained negative throughout the course of her disease.

Histopathology
A second biopsy showed a diffuse infiltrate of eosinophils with lymphocytes and histiocytes in the deep dermis. Subepidermal bullae formed with immense papillary edema. Epidermal spongiosis and intraepidermal vesicles were also seen. Free eosinophilic granules were deposited on collagen bundles forming flame figures. There was no vasculitis and the direct immunofluorescence was negative.

Clinical Course
After the second biopsy was done, the diagnosis of Wells' Syndrome was made. The patient was transferred to our facility where IV methylprednisolone was continued. The patient no longer developed bullae and her existing skin lesions continued to improve. Upon follow-up, she developed extensive post-inflammatory hyperpigmentation with minimal scarring of the more serious lesions. A few months later, she experienced a slight recurrence that was controlled with another tapering dose of systemic corticosteroids.





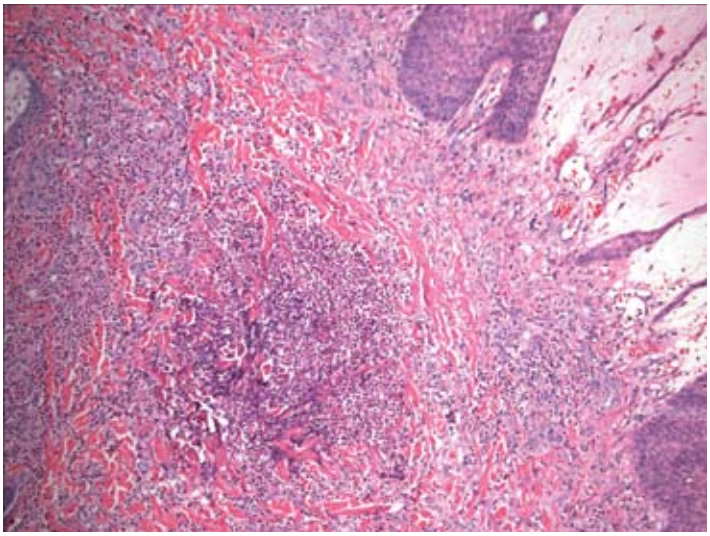
Discussion

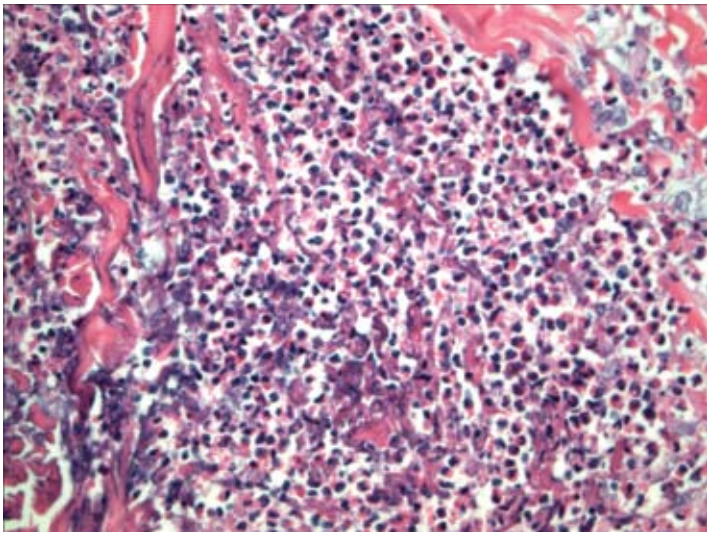
Wells' Syndrome is uncommon in childhood with only 27 reported cases. Classically patients present with recurrent episodes of itching and burning followed by erythematous annular or arcuate plaques or edematous nodules that can resemble cellulitis or urticaria. The lesions evolve rapidly over 2-3 days and are sometimes associated with bullae. They initially appear bright red, but then fade to green, brown, or slate-gray. In one case series by Caputo et al., of 19 patients, the classic plaque-type presentation was the most common variant found in children, while the annular granuloma–like presentation was the most common variant in adults. None of the children in this study had a bullous presentation. The extremities are most commonly involved, but the trunk can also be affected. Fever, lymphadenopathy, arthralgias, and other systemic symptoms are rare, but have been reported. Lesions usually resolve spontaneously over 2-8 wks leaving residual skin atrophy and hyperpigmentation, resembling morphea. The disease can be recurrent over several years.

The characteristic histopathology of Wells' syndrome is eosinophils with flame figures. These represent eosinophil major basic protein that deposits on collagen bundles. Other diseases can form flame figures, including arthropod assault, parasitic and dermatophyte infections, eczema, prurigos, and mastocytomas. There is no vasculitis and the direct immunofluorescence is negative, which is helpful in distinguishing Wells' syndrome from other diseases. Patients usually develop an elevated WBC count with peripheral eosinophilia, which is found in 50% of cases with active disease. The erythrocyte sedimentation rate and IgE levels can also be elevated.

The pathogenesis is unknown. Currently the accepted theory is a local hypersensitivity reaction. There have been reports of associated precipitants, including insect bites, medication reactions, recent immunization, myeloproliferative disorders, malignancies, infections, and infestations including tinea and Toxocara canis. However approximately half of patients present without a precipitating factor.

Topical steroids can be used for limited disease without systemic symptoms. However, extensive disease requires systemic steroid therapy. Typically oral prednisone at 10-80mg per day, is tapered over one month. If the disease is recurrent, alternative treatments have been used to avoid the adverse effects of long term steroid use. These include minocycline, colchicine, dapsone, antimalarial drugs, cyclosporine, azathioprine, interferon, and PUVA. When the disease course is chronic, lasting >6months, referral to hematology is warranted.





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Case 36
Vohwinkel Syndrome

Resident Physician
Sarah Josephson, M.D.

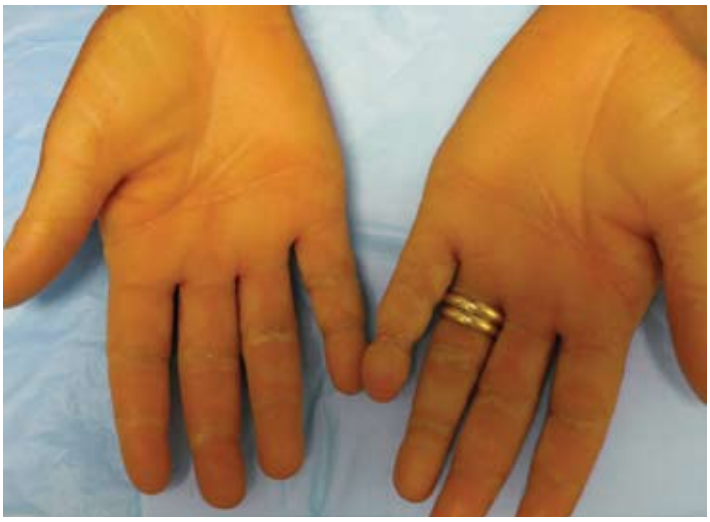
Referring Physician
Sanders R. Callaway, M.D.

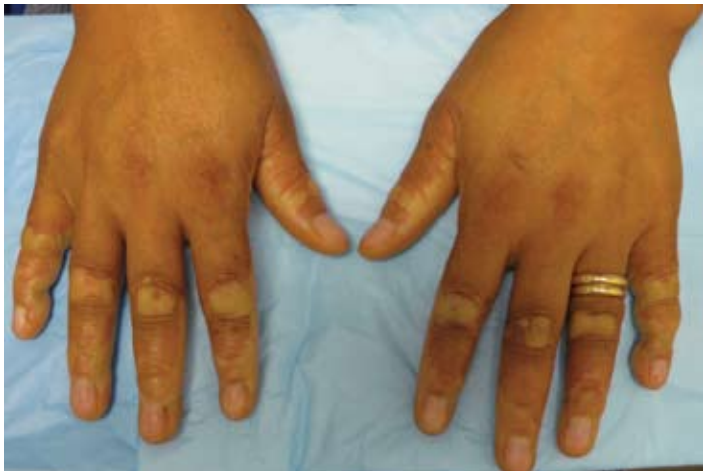
History
A thirty-eight year old female with complete hearing loss since birth presented with thickened skin on her palms and soles, plaques on the knuckle pads, and constriction bands of the fingers (most prominent on the fifth fingers). She developed these skin findings at the age of eight. She has similar skin findings and hearing loss within her family tree (mother and sisters). One of her sisters had constriction bands that ended in surgical amputation of her finger. The patient has two brothers and a half-sister who are unaffected and two nieces with hearing loss. She has two biological children, a three-year-old son who is unaffected and an eleven-year-old daughter who recently began to develop light plaques on her finger and toe knuckle pads.

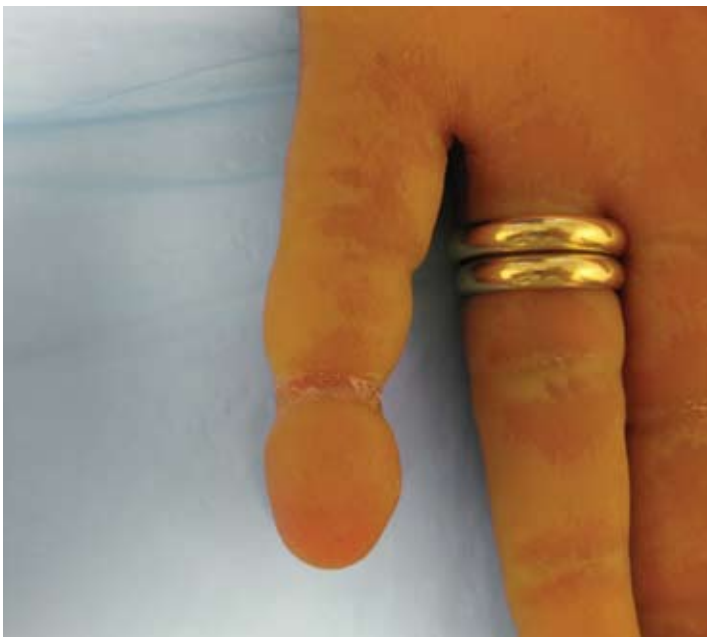
Clinical Findings
She presents with diffuse, honeycombed hyperkeratosis of the palms and soles, starfish-shaped keratoses over the knuckles of the fingers and toes, and constricting keratotic rings around her fingers, most prominent on her bilateral fifth digits, the left greater than the right. She also has sensorineural hearing loss and associated mutism. She does not have evidence of alopecia or ichthyosis. Her eleven-year-old daughter has recently developed multiple keratotic papules on the knuckles of the fingers and toes, and she has been deaf since birth.

Clinical Course
She presented with a working diagnosis of scleroderma. Given the characteristic neuroectodermal findings and significant family history as described above, Dr Callaway diagnosed her with a hereditary palmoplantar keratoderma, Keratoderma Hereditaria Mutilans, or Vohwinkel Syndrome. She has been evaluated by a hand surgeon for possible surgical correction of the constriction band on her left fifth digit. Genetic testing for a connexin 26 (Cx26) missense mutation is pending.

Discussion
Hereditary palmoplantar keratodermas (PPKs) are a diverse group of hereditary and acquired disorders. They can be inherited in both an autosomal dominant and recessive fashion. They are classified by genetic transmission, morphology and distribution of affected skin, and the presence of skin lesions on areas other than the palms and soles. Simple keratodermas only manifest on the palms and soles and can further be classified as diffuse, focal and puntate PPKs. Complex keratodermas are associated with lesions of non-volar skin, hair, teeth, nails, or sweat glands. Syndromic keratodermas are associated with abnormalities of other organs.

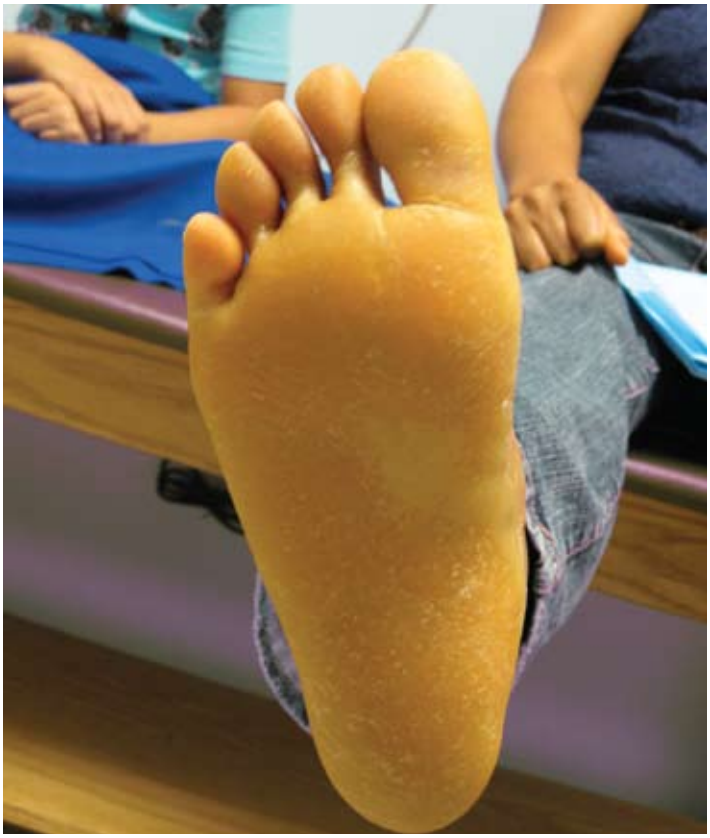


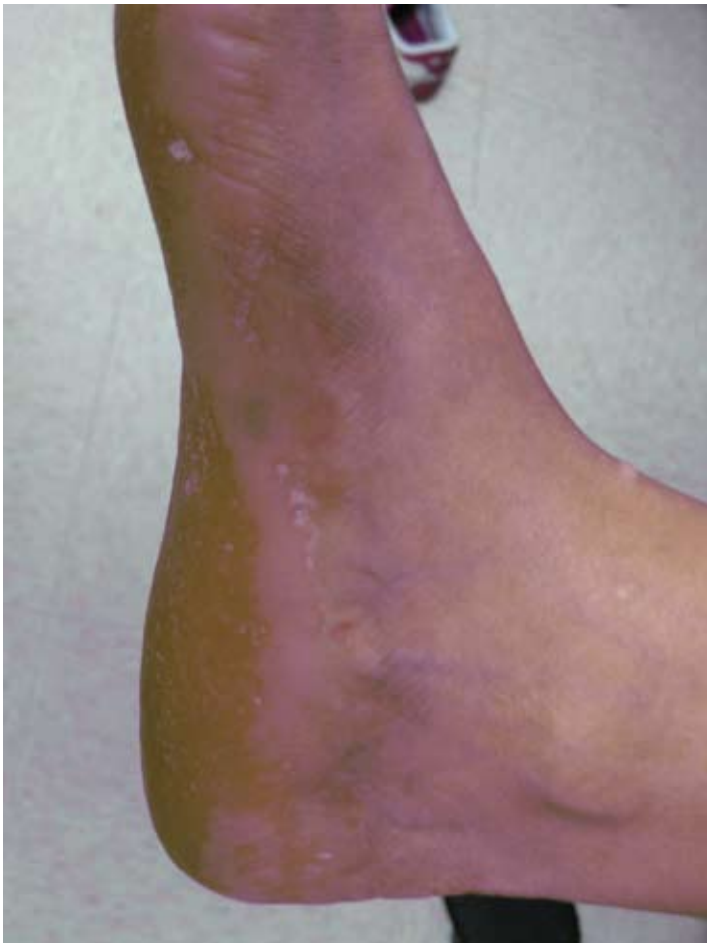




Vohwinkel first described this disorder in 1929. It is a rare, autosomal dominant, genodermatosis characterized by diffuse palmoplantar keratoderma. Typically the honeycomb, hyperkeratotic palms and soles appear in infancy. In early childhood, the constriction bands of the digits appear, which may lead to autoamputation, i.e. pseudoainhum. Starfish-shaped keratoses, a characteristic feature of this disorder, occur on the knuckles of the fingers and toes. Some associated features include hearing loss, alopecia, and ichthyosis. Hyperkeratosis with parakeratosis, acanthosis, and hypergranulosis are seen histopathologically. Vohwinkel keratoderma maps to chromosome 1q21. Recent molecular studies indicate that there are two variants of Vohwinkel syndrome. A variant associated with a mutation in the gene that encodes loricrin, a major cornified envelope protein. It manifests with ichthyosis and normal hearing. The second variant, as described in this case, is associated with a missense mutation of the connexin-26 gene.

The treatment of all hereditary keratodermas is difficult, and tends to be symptomatic. Topical keratolytics, topical or systemic retinoids, soaks and paring, and surgical debridement or excision are all reported in the literature.





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