Chicago Dermatological Society

May 2008
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, May 21, 2008

Conference Host:
Department of Dermatology
Rush University Medical Center
Chicago, Illinois

Chicago Dermatological Society

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CDS Monthly Conference Program
May 2008 -- Rush University Medical Center

May 21, 2008

8:30 a.m.	**REGISTRATION & CONTINENTAL BREAKFAST** *Searle Conference Center, Professional Bldg., 5th Floor; Elevator II*
9:00 a.m. - 10:00 a.m.	**RESIDENT LECTURE** *Brainard; Searle Conference Center*
9:30 a.m. - 11:00 a.m.	**CLINICAL ROUNDS** Patient Viewing *Dermatology Clinic - Room 264 Professional Building (Elevator III)* Slide Viewing Herrick; *Searle Conference Center*
11:00 a.m. - 12:00 p.m.	**GENERAL SESSION** *Brainard; Searle Conference Center*
11:00 a.m.	CDS Business Meeting
11:15 a.m.	FREDERICK MALKINSON LECTURE -- "Vaccines for the Prevention of Infectious Diseases with Mucocutaneous Manifestations" *Stephen K. Tyring, MD, PhD*
12:15 p.m. - 1:15 p.m.	**AWARDS LUNCHEON** *Garden Room - 5th Floor Professional Building*
1:15 p.m. - 3:00 p.m.	**AFTERNOON GENERAL SESSION** *Brainard; Searle Conference Center* RESEARCH GRANT PRESENTATIONS -- "Evaluation and Manipulation of Cellular Molecular Determinants of ALA-induced PpIx Forumation" *Bernhard Ortel, MD; University of Chicago* "Topical Therapuetic Options for Keratosis Pilaris" *Sarah Kasprowicz, MD; Rush University* Discussion of cases observed during morning clinical rounds *Joan Guitart, MD, moderator* *Stephen K. Tyring, MD, PhD*

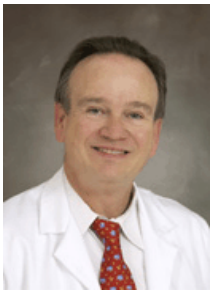
CME Information

This activity is jointly sponsored by the Chicago Medical Society and the Chicago Dermatological Society.

This activity has been planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Chicago Medical Society and the Chicago Dermatological Society. The Chicago Medical Society is accredited by the ACCME to provide continuing medical education for physicians. The Chicago Medical Society designates this educational activity for a maximum of four (4) *AMA PRA category 1 credits*™. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Commercial Support: There are no educational grants associated with this meeting. One or more companies may pay a fee to be present as exhibitors. The program content is free from any commercial or corporate influence.

Guest Speaker



Stephen K. Tyring, MD, PhD, MBA is a professor in the Departments of Dermatology, Microbiology/Molecular Genetics and Internal Medicine at the University of Texas Health Science Center at Houston. He is board certified by the American Academy of Dermatology, and he is a member of the Infectious Disease Society of America, the American Federation for Clinical research, and chairs the AAD Committee on Sexually Transmitted Diseases. Dr. Tyring sits on several editorial boards and serves as a reviewer for a number of journals, including the New England Journal of Medicine and the Journal of the American Academy of Dermatology. His research interests include the therapy and prevention of various mucocutaneous diseases. Dr. Tyring received his undergraduate degree from Indiana State University, his Master's Degree from Abilene Christian University, his medical degree from the University of Texas Medical Branch, a PhD from Texas Tech University and an MBA from Rice University.

Speaker CME Disclosure of Financial Interests

Dr. Tyring has the following disclosure: consultant, investigator, researcher – Abbott Labs; Amgen; Astellas; Merck; Epiphany; GSK; Novartis; LGO; Warner Chillcott; Galderma; Pfizer.

CME Credit Documentation

Following the meeting, the Chicago Medical Society will send you a certificate documenting your attendance at this conference and the number of Category 1 CME credits you earned. It is essential that you complete and return the CME sign-in sheet provided with your meeting materials. Do so before you leave the conference! If you have any questions about your credits, please contact the Chicago Dermatological Society at 847/680-1666, or by email: RichardPaul@DLS.net

Evaluation Forms

Please complete and return your meeting evaluation form. This feedback is an important part of the CME process and helps us to design programs in the future that better meet the needs of our members. Note that the form will be scanned by computer; keep your responses within the spaces provided, and avoid making any extraneous marks on the sheet. Thank you!

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Case #1

CASE PRESENTED BY: Michael D. Tharp, M.D. and Melanie Palm, M.D.

History: The patient is a 29-year-old white male, referred to Rush Dermatology by a community allergist for the treatment of recalcitrant verrucae. The patient had a history of therapy-resistant, progressive, extensive warts since childhood affecting the hands, penis, and perianal area. In addition, the patient had a history of frequent pneumonia and "flu-like" illnesses as well as unexplained anemia and leukopenia. He denied a history of sinusitis or cellulitis, but he was diagnosed with otitis during childhood. All of his infections responded promptly to antimicrobial therapy.

Past Medical History: Recurrent pneumonia and "flu-like illnesses"
"Fibromyalgia"

Medications: Oxycodone, diazepam, amitriptyline, Percocet

Family History: 14-month-old daughter with history of multiple hospitalizations for recurrent pneumonia. 10-year-old daughter with multiple verrucae involving both hands and a history of otitis media.

Review of Systems: General: marked fatigue; Musculoskeletal: diffuse myalgias and arthralgias

Physical Examination: Bilaterateral hands, dorsal and acral: numerous, well-circumscribed verrucous papules
Left 5^{th} lateral toe: one verrucous papule
Penile shaft, corona, prepuce, and scrotum: greater than 15 exophytic skin-colored to brown verrucous papules, some coalescing into plaques

Laboratory Data: Complete blood count (4/9/2008): WBC 3.15 (4-11 x 10^3/mL), Hemoglobin 10.2 (13.5-17.5 g/dL), Hematocrit 33.4 (42-54%), platelets 139 (150-399 x 10^3/mL); Differential: 47% neutrophils, 51% lymphocytes, 0.3% monocytes, 0.3% eosinophils

The following labs were negative, within normal limits, or non-reactive: HIV-1/2 antibodies, RPR, TSH, Rheumatoid factor, sedimentation rate, C-reactive protein, IgG, IgA, IgM, IgE levels, IgG anti-diphtheria, IgG anti-tetanus, IgG anti-Streptococcus pneumoniae, IgM/IgG anti-influenza A

Studies: Bone marrow biopsy (8/31/2004): normocellular bone marrow with decreased granulopoiesis and granulocytic left shift. Focal, very mildly disordered erythropoiesis and unremarkable megakaryopoiesis.
CT scan of chest (3/11/2007): reticular nodular infiltrates; mediastinal/hilar lymphadenopathy; splenomegaly
Molecular genetic testing (1/17/08): R334X mutation on one CXCR4 gene

Diagnosis: **WHIM syndrome**

Course and Treatment: An anergy panel consisting of *Candida*, mumps, and tuberculin antigens was placed on the patient. The patient mounted a positive reaction to *Candida* and tetanus, indicating an intact TH1 delayed-type hypersensitivity response to these antigens. Initiation of immunotherapy for his verrucae utilizing intralesional injection of *Candida* antigen is anticipated in May 2008.

Discussion: WHIM is an acronym representing a constellation of findings within a syndrome characterized by **W**arts, **H**ypogammaglobulinema, **I**nfections, and **M**yelokathexis. This rare immunodeficiency syndrome was first described in a 10-year-old girl in 1964 and to date, fewer than 40 cases have been described in the medical literature.[1] It displays both variable phenotypic expression and genetic heterogeneity, but neutropenia is a constant feature of the syndrome.[2]

Individuals affected by WHIM syndrome have a specific susceptibility to human papilloma virus-induced warts, usually manifesting in the second decade.[3] The verrucae are particularly recalcitrant to treatment and may occasionally remit in childhood, only to recur during adulthood.[1] Hypogammaglobulinemia is an inconstant finding in patients with WHIM syndrome.[4] Opportunistic infections are not reported in association with WHIM syndrome, and patients respond appropriately to childhood vaccinations. However, patients do characteristically develop recurrent bacterial sinus and pulmonary infections responsive to antimicrobial therapy. Patients may also experience recurrent cellulitis, periodontitis, or meningitis.[1] All infections cause an appropriate leukocytosis, making the diagnosis more difficult. Myelokathexis is the cardinal feature of WHIM syndrome. It describes marrow hypercellularity, premature apoptosis, and retention of mature bone marrow neutrophils, resulting in peripheral neutropenia.[5] Two cases of complex congenital cardiac disease have been described in WHIM patients, and the mutated WHIM gene plays a role in cardiac ventricular septum formation, raising the possibility of a causal relationship of cardiac defects in WHIM patients.[6]

Many, but not all cases of WHIM syndrome are inherited in an autosomal dominant fashion, producing a gain-of-function mutation in the CXC chemokine receptor 4 (CXCR4).[2] This chemokine receptor and its ligand, stromal cell-derived factor-1 (SDF-1, also known as CXCL12), play an integral role in cellular development and trafficking. The interactions of these molecules are important to bone marrow homing, movement of hematopoietic progenitor cells, mobilization of lymphocytes, and the release of neutrophils from the bone marrow.[5] The most common WHIM mutation involves premature truncation of the carboxy-terminus of CXCR4. This results in defective internalization of this G-coupled transmembrane protein, allowing prolonged or increased activation by its ligand, SDF-1.[3,5]

The differential diagnosis of WHIM syndrome includes other primary immunodeficiencies such as inherited neutropenias, common variable immune deficiency, as well as epidermodysplasia verruciformis for its prominent verrucoid phenotype.[6] Diagnosis of WHIM syndrome is based on cell blood counts and bone marrow examination. Absolute neutrophil counts are usually less than 300/μL. Bone marrow aspirates demonstrate pathognomonic features of myeloid hyperplasia with a rightward shift in granulopoiesis and abnormal mature neutrophils displaying hypersegmentation and vacuolization.[1,6]

Treatment is supportive. Monthly IVIg injections reduce the frequency of bacterial infections while daily injections of G-CSF normalize neutrophil counts and marrow cytology.[6] Warts are particularly difficult to treat and require aggressive management. Premature death in WHIM patients is usually secondary to overwhelming sepsis, although two cases of lymphoma have been described raising the possibility of a unique susceptibility in the WHIM patient population.[6, 7]

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Case #2

CASE PRESENTED BY: Arthur Rhodes MD, and Lauren Campbell MD

History: A three-year-old Mexican-American female presented with red-brown lesions on her neck, anterior and posterior trunk, arms, and legs for one month. Asymptomatic lesions start as red macules that gradually faded over a period of two to three weeks, while new lesions appear in crops. No treatment was attempted. The family denies fevers, chills, weight changes, headaches, diarrhea, nausea, vomiting, or other systemic symptoms. She traveled to Mexico three months prior to presentation, where she had a mild non-productive cough and runny nose for one week.

Past Medical History: Non-contributory

Medications: Daily multivitamin

Allergies: No known allergies to medications

Family History: No history of similar lesions in family members

Social History: Patient lives at home with her mother and father. There are no siblings or pets. The family moved from Mexico ten years ago. She has lived in the Chicago area her whole life.

Review of Systems: No fevers, chills, sweats, weight loss or rapid gain, headaches, seizures, diarrhea, vomiting, loss of appetite, genitourinary complaints, joint pains, or shortness of breath.

Physical Examination: Well-developed, well-nourished female child who appears alert and well. On the neck, anterior and posterior trunk, upper and lower extremities are dozens of oval-shaped non-blanchable red to brown speckled patches, ranging in size from approximately five to fifteen millimeters, and blotchy macular brown-grey hyperpigmentation. There was no involvement of mucous membranes, palms, or soles. There was no lymphadenopathy or hepatosplenomegaly.

Laboratory: Laboratory tests were performed by the patient's pediatrician two days prior to presentation. Rapid strep test: negative, throat culture: no growth. Complete blood count white blood cells 6,000/mm^3, hemoglobin 13.1 g/dl, hematocrit 37.9%, mean corpuscular volume 78.8 cu μm. platelet count 287,000/mm^3, erythrocyte sedimentation rate 4 mm/hr.

Studies: None

Histo-pathology: Focal interface dermatitis with occasional dyskeratosis and underlying perivascular infiltrate and extravasated erythrocytes.

Diagnosis: **Pigmented purpuric dermatosis**

Course and Treatment: During the ensuing nine to ten months, the patient continued to develop more lesions, while old lesions faded to hyperpigmented macules and patches. Three months ago, the patient was begun on three times weekly narrow-band UVB therapy, at an initial dose of 200 mJ/cm². There appears to be slight improvement with fewer crops of lesions. Over the past one month, she has not developed new lesions. We plan to continue phototherapy.

Discussion: The term pigmented purpuric dermatoses (PPD) refers to a group of chronic purpuric variably pruritic eruptions of unclear etiology. PPD represents petechial hemorrhage thought to be caused by capillaritis. It is proposed that this process arises by minimal inflammation of the superficial papillary dermal vessels. PPD is uncommon. All races and both genders are affected, though it is more common in males. PPD can occur at any age but is more common in older adults.

Traditionally, PPD is divided into five main clinical entities: Schamberg's disease, purpura annularis telangiectoides of Majocchi, lichen aureus, pigmented purpuric lichenoid dermatosis of Gougerot and Blum, and eczematoid-like purpura of Doucas and Kapetanakis. The most common type is Schamberg's disease (also known as progressive pigmented purpuric dermatosis). This may uncommonly occur during childhood but occurs most frequently in men middle-aged and older. There has been one reported case of a three year old child with Schamberg's disease. Lesions appear as asymptomatic oval to irregular orange or yellow-brown colored patches with overlying pinpoint "cayenne pepper" macules which represent non-blanching petechiae. Schamberg's most commonly occurs on the lower legs but can be seen anywhere. Purpura annularis telangiectoides of Majocchi is seen most often in adolescents or young adults, more commonly in females, characterized by annular plaques with telangiectasias and cayenne pepper petechiae occurring in the borders. Lesions are usually asymptomatic and may continue to extend over a period of several years.

Lichen aureus occurs more commonly in children and young adults and usually consists of a single asymptomatic lesion most often on a lower extremity, although it may also be segmental or linear. The patch in lichen aureus is usually rust or purple-brown or may have a golden hue. Rarely, lesions may be painful. Pigmented purpuric lichenoid dermatosis of Gougerot and Blum is rare, usually occurring in men between the ages of 40 and 60 years. Lesions are similar to those in Schamberg's disease and usually occur with purpuric red to brown lichenoid papules that tend to fuse into plaques. These lesions are chronic and may be asymptomatic or pruritic. Eczematoid-like purpura of Doucas and Kapetanakis is most often seen in middle-aged or older males who present with scaly petechial or purpuric macules or patches. Lesions occur on the lower extremities and are often severely pruritic.

Histopathologically, characteristic features of pigmented purpuric dermatoses include red cell extravasation, endothelial cell swelling with luminal narrowing, and a perivascular lymphocytic infiltrate with hemosiderin-containing macrophages. In the superficial papillary dermis, this infiltrate is composed predominantly of CD4+ lymphocytes and occasional CD1a+ dendritic cells and macrophages. In pigmented purpuric lichenoid dermatosis of Gougerot and Blum and lichen aureus, a lichenoid infiltrate of lymphocytes may be seen along with epidermal spongiosis.

Pigmented purpuric dermatoses tend to be chronic and may persist for many years. PPD generally occurs in the absence of systemic disease. A number of co-morbidities have been associated with PPD, including diabetes mellitus, rheumatoid arthritis, lupus erythematosus, thyroid dysfunction, liver disease, hyperlipidemia, and others. The relationship between PPD and cutaneous T-cell lymphoma is controversial. Some authors have suggested that some variants of PPD may be biologically related to CTCL, with similar histological findings and with polymerase chain reaction (PCR) assay for γ-chain rearrangement revealing clonal populations of lymphocytes. Two cases of pediatric PPD associated with mycosis fungoides has been reported.

The clinical findings of PPD are often sufficient for diagnosis, but biopsy may aid in distinguishing the lichenoid variant from small vessel vasculitis. Pigmented purpuric eruptions on the legs must be differentiated from dermal hemorrhage secondary to venous hypertension and stasis, which presents as petechiae superimposed on diffuse hemosiderosis. Laboratory investigations are unremarkable in PPD. Follow-up is important in cases where the initial diagnosis is unclear, particularly in cases with widespread lesions, to exclude evolution to CTCL.

Treatment for PPD is difficult, as no medical intervention has proven consistently beneficial in controlled studies. Pruritus may be alleviated with topical steroids or and/or anti-histamines. Phototherapy with psoralen and UVA has been reported to be successful in Schamberg's disease, lichen aureus, and pigmented purpuric dermatosis of Gougerot and Blum. Other successful therapies that have been reported in small case studies include oral griseofulvin, pentoxifylline, cyclosporine, rutoside, and ascorbic acid.

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Case #3

CASE PRESENTED BY: Mark Hoffman, M.D. and Melinda Simon, M.D.

History: The patient is a 58-year-old Polish female who with presented with a two month history of "bumps" initially appearing within the left axilla and spread to other areas of the trunk, genitalia, an arm and the tongue. New lesions continued to appear. She stated that recently she had some difficulty with air exchange--"not enough air goes in"—but denies shortness of breath or wheezing. She also reported the need to urinate every 30 minutes for the past month, up to twelve times daily, whereas voiding 2-3 times per day was typical for her in the past. She was denied consuming an excess of fluids.

Past medical history is notable for hyperlipidemia with records indicating triglycerides as high as 1300 and cholesterol of 353 in 2002. She also has low-density, hypoechoic lesions in the liver first identified in 2004 during evaluation for abdominal pain that have been unclassifiable.

Past Medical / Surgical History: Transient ischemic attacks x 2; gastritis; fibromyalgia; migraines; hypertension; renal cyst vs angiomyolipoma.

Medications: ASA, clonidine, esomeprazole, losartan potassium-hydrochlorothiazide, metoprolol, optive, Osteobiflex, Premarin, Sucralfate, Zolpidem.

Physical Examination: 2mm-4mm smooth yellow papules, many with pink rims: inframammary and inguinal folds; left axilla; abdomen, flanks, and lower back; left palm; chin; right lateral tongue.

Laboratory Data: Triglycerides 423 (< 150); cholesterol 304 (< 200); HDL 38 (> 40). AST 52 (10-35); ALT 104 (6-40). Urine osmolality 786 (50-1200 mOsm/kg).

CBC with differential; comprehensive metabolic profile; serum protein electrophoresis; thyroid function studies all normal except as noted above.

Histo-pathology: Punch biopsy (abdomen) showed superficial to mid-dermal histiocytic infiltrate with numerous Touton giant cells containing foamy cytoplasm with surrounding lymphocytic infiltrate, consistent with xanthoma disseminatum.

Diagnosis: **Xanthoma Disseminatum**

Course and Treatment: The patient consulted with ENT for upper aerodigestive tract exam with laryngoscopy showing an 8 mm lesion on the left soft palate above tonsil and 3-4 mm lesions on the nasal vestibules. Ophthalmologic exam was unremarkable. Multi-agent anti-hyperlipidemic therapy has been proposed.

Discussion: Originally described by Montgomery and Osterberg in 1938, xanthoma disseminatum, (XD), is a rare non-langerhans cell histocytosis disorder of histiocytic proliferation

affecting the skin and mucous membranes as well as the central nervous system, gastrointestinal, respiratory, and ocular systems. Rarely the skeletal system is affected. Roughly 100 cases have been reported. Pathogenesis is unknown, but given that many patients are normolipemic, it has been speculated that this is a reactive histiocytic proliferation with secondary lipid amassing.

Patients with XD may have the classic triad of cutaneous xanthomas, mucous membrane xanthomas, and diabetes insipidus. XD affects males more than females, typically in childhood or young adulthood. The cutaneous xanthomas are red, yellow or brown papules and are symmetrical often on the flexural and intertriginous areas. Lesions may be grouped, atrophied, and even disfiguring. Forty to sixty percent of patients will have mucous membrane findings. Patients have abnormal lipid levels in twenty percent of cases. Forty percent of patients have hypothalamus and pituitary lesions, which can result in diabetes insipidus. Vision can be impaired with ocular lesions involving the cornea and conjunctivae. Thyroid disorders, plasma cell disorders and monoclonal gammopathy are found rarely in patients.

On histopathology, early lesions show a dense histiocytic infiltrate in the dermis with few inflammatory or foamy cells. Later lesions will show many foam cells and histiocytes, lymphocytes, plasma cells, neutrophils, and the characteristic Touton cells. The histiocytes are CD68, CD11b, CD11c, CD14, Factor XIIIa positive and stain for α1-antitrypsin and lysozyme. The cells are S-100 and CD1a negative and do not have Birbeck granules.

There is no standard therapy for XD. Cyclophoshamide has been shown to be useful for mucosal lesions. Other therapy for cutaneous lesions include CO2 therapy, intralesional corticosteroid, cryotherapy, excision, radiotherapy, electrocoagulation, and dermabrasion. Clofibrate's success in treating the cutaneous lesions has been varied. Oral and topical corticosteroids have not proven useful. Klaus et al. described a therapeutic combination of 3 lipid lowering agents of rosiglitazone 4mg daily, acipimox 250mg BID, and simvastatin 10mg daily. This combination caused partial remission with regression of lesions and stability for 2 years. Radiotherapy is typically used for upper airway obtstruction. Diabetes insipidus responds well to DDAVP (Vasopressin).

Caputo et al. described three forms of XD distinguished by their prognosis. The forms include a self healing form, a persistent form, and a progressive form which may go on to extensive gastrointestinal and pulmonary involvement, the latter of which can be fatal as described by Hisanaga et al. in 2004. This highlights the need for close follow up in these patients.

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Case #4

CASE PRESENTED BY: Michael Tharp, M.D. and Melinda Simon, M.D.

History: The patient is a 2-year-old African American female with a history of precocious puberty, diagnosed at age 6 months when the patient began developing breast tissue and pubic hair. She presented to our clinic with hyperpigmented macules on her bilateral upper and lower extremities, left groin and abdomen since 2 months of age. The lesions are asymptomatic. At presentation, the patient's bone age study showed a bone age 12 months greater than her chronological age indicating the presence of precocious puberty.

Past Medical History: The patient was born full term without complications.

Medications: Leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, injections monthly.

Allergies: NKDA

Family History: No family history of similar lesions.

Review of Systems: The patient has no bone pain, signs of fractures, visual or auditory impairment or headaches.

Physical Examination: Normal appearing, well developed female. No obvious gynecomastia, no pubic or axillary hair since beginning leuprolide therapy. No signs of acromegaly. Left lower abdomen to left mons pubis and labia with a two palm area of medium brown macule, light brown at inferior and lateral edges, with irregular borders. Right abdomen with 1.5 palm of light brown macule. Right extensor forearm, left thigh, left leg with medium brown macules. Right anterior thigh with quarter size hypopigmented macule. Back with multiple gray brown macules consistent with dermal melanosis. No LAD noted.

Laboratory Data: A recent TSH was 0.41, low. CBC, BMP, T4, T3, prolactin, cortisol, IGF all within normal limits.

Studies: At 22 months of age, a bone age study showed that the patient's bone age was 36 months above the normal range. Ultrasound initially indicated ovarian follicles, which subsequently decreased in number after the initiation of leuprolide therapy. Radiographic films of her skull and extremities showed no lytic lesions. MRI showed a normal sized pituitary gland. Chromosome analysis revealed 46, XX karyotype, but could not rule out low level of mosaicism.

Diagnosis: **McCune Albright Syndrome**

Course and Treatment: The patient is being followed by dermatology with full skin examinations. She follows closely with her pediatrician and endocrinologist. Leuprolide injections given monthly allowed resolution of patient's signs of precocious puberty (pubic hair and gynecomastia).

Discussion: McCune Albright Syndrome, (MAS), first described in 1937 by Donovan James McCune and Fuller Albright, is a rare, sporadic disorder with the classic triad of café-au-lait macules, (CALMs), polyostotic fibrous dysplasia and hyperfunction of endocrine glands. Patients may not exhibit all of these clinical findings. This disorder occurs equally in males and females. MAS is caused by defects in the GNAS1 gene that encodes Gsα, a protein that stimulates adenylate cyclase, resulting in an overexpression of cAMP, and subsequent increase in stimulation of tyrosinase and eumelanin production. The latter accounts for the CALMs. MAS is presumed to be lethal unless in a mosaic state.

The café-au-lait macules typically appear at birth or during infancy, end at the midline, and may have the "coast of Maine" appearance, with irregular borders. This is in contrast to the "coast of California" CALMs, with smooth borders, which are found in neurofibromatosis. Approximately 50% of patients will have CALMs. Common sites for CALMs include the head, neck, trunk, and buttocks. These lesions may follow Blaschko's lines and overlie bony changes.

Polyostotic fibrous dysplasia occurs when fibrous tissue from the medullary cavity invades the cortical bone. These changes affect long bones and facial bones most commonly. Patients may have limb length discrepancies, deformities, recurrent fractures, limb bowing, as well as skull sclerosis. Patients may have a shepherd's hook deformity, which consists of a leg length discrepancy, a limp, and pain. Two-thirds of patients will have these changes by age 10 years. Malignant transformation into osteosarcoma or fibrosarcoma is rare.

Endocrine findings include precocious puberty, pituitary gigantism or acromegaly, Cushing's syndrome, and hyperthyroidism. Pituitary tumors may demonstrate growth hormone or prolactin producing hyperplasia. Diagnostic workup includes skeletal X-rays, thyroid function tests, alkaline phosphatase, LH, estrogen, and cortisol levels. Our patient had an abnormal TSH, a history of precocious puberty with ovarian follicles that decreased in number after initiation of leuprolide therapy, and advanced bone age.

Cosmetic treatment for the CALMs includes cryotherapy, dermabrasion, and laser therapy. The former two may lead to pigmentary changes that are unsatisfactory to the patient. The latter offers the best cosmetic outcome. However, even with these modalities, the lesions are hard to treat. Lasers that have been reported with variable success in the treatment of café-ai-laits include the Q-switched Nd:YAG lasers (532nm or 1064nm), the Q-switched alexandrite (755nm), and the Q-switched ruby laser (694nm). Q-switched alexandrite lasers were less promising. Multiple treatment sessions are needed and postoperative purpura and pigmentary changes are common. For this reason, use of lasers in skin types IV-VI should generally not be performed.

Gonadotropin releasing hormone agonists such as leuprolide, somatostatin analogs, such as octreotide, growth hormone antagonists, and dopamine receptor agonists are used to treat the endocrine abnormalities. Surgical intervention for pituitary tumors is difficult

secondary to skull base bone dysplasia. Radiotherapy for pituitary tumors is controversial with its risk of inducing bone sarcomas. Galland et al. suggested that pegvisomant, a GH antagonist may be used and beneficial for patients with acromegaly if surgery is not an option and when somatostatin and radiotherapy have failed. Close monitoring needs to be done for bone changes with X-rays and orthopedic evaluation for new bony symptoms.

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Case #5

CASE PRESENTED BY: Vassilios Dimitropoulos, M.D. and Melanie Palm, M.D.

History: The patient is a 32-year-old Hispanic male transferred to Rush University Medical Center in March 2008 from an outside hospital for a 2 month history of progressive cough, hemoptysis, fever, and sweats. The patient had previously undergone a bronchoscopy a month prior to admission at the outside hospital. Based on a lung biopsy at that time, the patient was diagnosed with bronchiolitis obliterans organizing pneumonia and was discharged to home on a high-dose, slow taper course of prednisone, beginning at 100mg po daily. The dermatology service was consulted for two skin lesions of approximately 2 weeks duration. Both lesions on his nasal tip and upper back had begun as pustules and evolved into a necrotic papule and ulceration, respectively.

Past Medical History: None

Medications: Prednisone 40 mg po BID

Social History: Truck driver for construction materials. Driving route includes the Midwest region. The patient reports recent travel to Mexico in December 2007.

Review of Systems: General: persistent fever, night sweats. Respiratory: persistent cough and slight dyspnea since December 2007.

Physical Examination: Nasal tip: 1 cm diameter necrotic violaceous plaque with peripheral rim of erythema

Upper back: 20 x 13 mm ulceration with slightly hyperemic border; no frank purulent discharge

Right shoulder: 6 mm diameter heme-crusted slightly necrotic papule with surrounding erythema

Laboratory Data: Complete blood count with differential: within normal limits except White Blood Cell count: 15.37 $x10^3$/mL

Tissue culture of skin (3/18/08): DNA probe assay confirmation, growth of *Coccidioides immitis* on 3 of 3 media. Aerobic, atypical mycobacterial cultures (3/18/08): no growth

Whole blood, Coccidioides antibody complement fixation test (3/20/08): 1:4 (Reference: normal less than 1:2) HIV-1/HIV-2 Antibody (3/18/08): none detected

Studies: CT of chest (3/19/08): Diffuse miliary noncalcified micronodular pattern throughout the lungs, concerning for miliary tuberculosis or fungal infection. Large area of consolidation

with air bronchograms within the right upper lobe. Multiple enlarged mediastinal lymph nodes, which may be inflammatory or reactive in nature.

Histo-pathology: Punch biopsy, upper back (3/18/08): suppurative and granulomatous inflammation with innumberable spherules, some containing endospores. Periodic-acid Schiff and Gomori methenamine silver stain identify numerous collections of spherules within areas of inflammation.

Diagnosis: **Disseminated coccidioidomycosis**

Course and Treatment: The patient was begun on an accelerated taper of oral prednisone and the infectious disease service was consulted for further management of coccidioidomycosis. The patient was placed on intravenous lipophilic amphotericin B (Ambisome) therapy, but experienced acute nephrotoxicity three days after initiation of therapy with a rise in his creatinine from 1.1 to 1.7. Amphotericin B was discontinued at this time, the patient was placed on IV fluids, and fluconazole was begun at an appropriate renal dose of 200mg per day. He was discharged two days later. The patient experienced a skin biopsy-proven drug eruption secondary to fluconazole approximately 10 days after discharge and was readmitted to the Rush University medical intensive care unit for voriconazole densensitization. The patient was discharged three days later on oral voriconazole. The patient's course and duration of antifungal treatment is to be determined by infectious disease on an outpatient basis.

Discussion: Coccidioidomycosis, also known as "Valley Fever," is caused by dimorphic fungi disrupted from the soil in semi-arid climates of the southwestern U.S., Mexico, and occasionally Central and South America.[1] Two species have been identified, *Coccidioides immitis*, native to the San Joaquin Valley of California, and *C. posadasii,* found outside the Valley region. In endemic areas, infection rates rise after duststorms, earthquakes, or droughts, or in areas of soil disturbance such as construction sites or archeological excavations.[2] Coccidioides exists as a saphrophyte in the soil, but disturbance causes release of infectious arthroconidia, which are inhaled, initiating the parasitic phase of spherule production in human tissues.[2]

Approximately 150,000 new cases are diagnosed in the U.S. annually. Sixty percent of cases comprise an asymptomatic infection.[3] The remaining 40% of cases have a variable clinical course. Most symptomatic patients experience a flu-like illness with fever, cough, night sweats, or pleuritic chest pain with resolution within a month.[2] Lungs are overwhelmingly the primary site of infection and most patients, even asymptomatic, show abnormalities on chest radiograph. Less than 1% of patients suffer from a disseminated infection. The skin is the organ most often affected by hematogenous dissemination,[4] but the meninges, bones, joints, peritoneum, and thoracic cavity may also be involved.[2,3] Primary cutaneous infection is extraordinary, with approximately 20 cases reported in the medical literature.[5]

Because of its protean clinical features, coccidioidomycosis has been described as the "other great imitator."[1] Disseminated cutaneous lesions localize preferentially to the head and neck and may appear as papules, pustules, nodules, verrucous plaques, abscesses, or ulcerations.[2,4] Possibly due to ethnic genetic variation in cell-mediated immunity, Filipino and African American individuals are 175 and 10 times more likely than Caucasian patients

to develop disseminated infection, respectively.[1] Other high risk populations include HIV-positive patients, organ transplant recipients, those on immunosuppressive medications, pregnant women, young children, the elderly, and more recently, patients on anti-TNFα biologic agents in endemic areas.[2]

Diagnosis of coccidioidomycosis is made by culture or microscopic examination. *Coccidioides* grows quickly as a white colony, usually in 2-5 days, on various bacterial and fungal culture media.[4] Laboratory workers should be alerted if this diagnosis is entertained, as the arthroconidia are highly virulent and *Coccidioides* is classified as an agent of bioterrorism.[6] Microscopic examination reveals spherules, 10-80 μm in diameter, sometimes containing endospores, predominately in the upper dermis. Organisms are visible with hematoxylin & eosin preparation, but specials stains such as Gomori methenamine silver, periodic acid-Schiff, or Papinacoulau may facilitate identification of spores.[4]

Serologic tests are useful ancillary tests for diagnosing infection, but culture is considered the "gold standard." IgG complement-fixing antibodies are highly specific and titers are used to follow disease activity and response to therapy.[2]

Amphotericin B has been used since the 1950s to treat cocccidiodomycosis.[7] Newer lipid preparations have reduced the renal toxicity of amphotericin B, but patients may experience systemic symptoms during intravenous administration and potassium and magnesium levels should be monitored.[4] In 2000, the Infectious Disease Society of American set forth new recommendations for treatment of coccidiodomycosis.[1] Amphotericin B is reserved for cases of severe pulmonary, rapidly progressive, recurrent infections while azoles such as fluconazole and itraconazole are efficacious for uncomplicated cases of coccidioidomycosis.[7] Treatment duration with either azoles or amphotericin is typically 3-12 months.[2,7] Cases of recurrent infection or chronic disseminated disease may require lifelong azole suppression and require close monitoring for an infectious disease specialist.

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Case #6

CASE PRESENTED BY: Arthur Rhodes MD and Lauren Campbell MD

History: A nine year-old Latin American girl has had plaque-type psoriasis since the age of four years, managed with topical therapy. She presented with a one week history of redness covering most of her scalp, face, torso, upper extremities, palms and soles. She also complained of new joint pains for ten days in her bilateral shoulders, left knee, and bilateral hips. She had been applying tar baths and 10% LCD in Aquaphor twice daily alternating with triamcinolone ointment 0.1 % for approximately three months. For the two weeks prior to presentation, she had been applying the triamcinolone to greater than 50% of her body surface area twice daily.

Past Medical History: Psoriasis without joint involvement for the past five years. She takes no medications. Otherwise, non-contributory.

Medications: No oral medications

Allergies: None

Family History: Father has psoriasis

Social History: Lives at home with mother, father, and grandparents, all of whom are Spanish-speaking only. Mother and father both work full-time jobs, and transportation for follow-up has been difficult.

Review of Systems: Subjective fever (not measured) one week prior to presentation. No chills, weight changes, joint pains, seizures, headaches, genitourinary complaints, chest pain, or shortness of breath.

Physical Examination: The patient was afebrile. There were erythematous scaling confluent plaques involving approximately ninety percent of the total body surface area. There was onycholysis and pitting of the finger nails. The oral mucosa, conjunctiva, and genitalia were clear. There were no blisters, erosions, pustules, or crusting. Lungs were clear to auscultation, and the cardiac examination was normal. There was lymphadenopathy in the neck, axillae, and groin bilaterally. There was no hepatosplenomegaly.

Laboratory Data: **Within normal limits**: Serum chemistries, blood urea nitrogen and creatinine, fasting lipids, liver function tests, magnesium, hemoglobin and hematocrit, rheumatoid factor, serum ACTH, and urinalysis were all within normal limits. Anti-nuclear antibody < 1:40.

Abnormal: 8 am plasma cortisol level 2.0 mcg/dL (normal 4.5-23 mcg/dL). Erythrocyte sedimentation rate 45 mm/hr, Complete blood count: MCV 77.2 cu μm, white blood cells 18,000/mm³, platelets 718,000/mm³, neutrophils 72%, lymphocytes 17.9%.

Studies: Plain chest radiograph revealed no signs of cardiopulmonary disease. Intradermal PPD was negative at 72 hours.

Histo-pathology: None

Diagnosis: **Exfoliative erythroderma secondary to psoriasis, and hypothalamic-pituitary suppression secondary to use of medium potency topical corticosteroids to large areas of body surface**.

Course and Treatment: The patient was admitted to the hospital and treated with intensive topical therapies including triamcinolone ointment under occlusion, tar baths, and petrolatum U.S.P. Within one week her total body surface area involved had decreased to approximately 55%. When she returned to clinic one week after discharge, she again had greater than ninety percent body surface area involvement. The patient was started on cyclosporine 3 mg/kg/day divided twice daily and etanercept 0.4 mg/kg/day (total dose 12.5 mg) twice weekly two weeks later. She was continued on topical steroids including betamethasone valerate to the scalp and hydrocortisone 2.5% ointment to the face. After adrenal-pituitary suppression was suspected with a low plasma 8 am cortisol level, she was referred to pediatric endocrinology for adrenal-pituitary evaluation. She was placed on maintenance oral hydrocortisone. The patient returned to clinic two weeks after initiating systemic therapies and continued to have exfoliative erythroderma involving 99% body surface area. She was unable to ambulate well due to contractures of her extremities and was confined to a wheelchair. She was unable to attend school. Her cyclosporine was increased to 5 mg/kg daily divided twice daily (total dose 150 mg daily). Approximately eight weeks after initiation of systemic therapy, large areas of surface area began to clear. By twelve weeks, there was minimal disease remaining . The cyclosporine was tapered and eventually discontinued over a period of four weeks. The patient was continued on etanercept 0.4mg/kg/day twice weekly and was able to be tapered off of oral hydrocortisone. We plan to initiate narrow-band UVB therapy.

Discussion: This child is presented because of her multiple complications of disease and treatments. The prevalence of psoriasis in children is not known. Approximately one-third of adult patients with psoriasis first develop their symptoms during adolescence, and it is not known what percentage manifests their disease before puberty. The most common presentation in children and adolescents is generalized plaque-type psoriasis, followed by guttate psoriasis and juvenile psoriatic arthritis. Though rare in infants, flexural disease is a common presentation. Children and adolescents with psoriasis often suffer as much or more from psychological and psychosocial implications of disease than their physical ailments. In this case, our nine year-old patient experienced mobility impairment associated with exfoliative erythroderma, and was unable to attend school for several months.

The primary goal of psoriasis treatment in children is to improve the physical and psychological symptoms, while at the same time maximizing the benefit to risk ratio. Limited forms of disease are generally treated with topical therapies, as was the case with this patient for the first 3-4 years of her disease. Topical therapies include corticosteroids, tacrolimus, calcipotriol, tazarotene, coal tar, and anthralin.

Therapy for psoriasis in both children and adults often starts with topical corticosteroids. The most severe systemic side-effect of topical steroids, as we saw in our patient, is the development of hypothalamic-adrenal-pituitary axis suppression. This risk is increased in children and in patients applying steroids under occlusion, applying potent steroids, or application to large body surface areas. As little as 14g/wk of clobetasol propionate ointment may induce suppression in children, while 49g/wk of betamethasone diproprionate is required to suppress cortisol levels. Allenby et al reported adrenal suppression in as many as 64% of adult patients using 50 grams or more of potent topical steroids for more than two weeks. Kwinter et al reported abnormal cortisol levels in 29 % of subjects in a retrospective study of vitiligo patients using moderate-to-potent topical steroids for a mean of two weeks. Some authors recommend routine screening with a morning cortisol level at baseline and four weeks post treatment. All patients who have abnormal cortisol levels should be referred to endocrinology for further evaluation.

More severe forms of psoriasis, including exfoliative erythroderma, often require systemic therapies. The efficacy of cyclosporine in children with severe psoriasis is well established. Cyclosporine (an oral calcineurin inhibitor) may lead to renal insufficiency and hypertension, although these effects are usually reversible upon discontinuation of the drug. The drug is usually well-tolerated in children. The doses employed for children are based upon doses used in adults for treating psoriasis, but there is a shortage of controlled studies.

Etanercept is a soluble fusion protein that binds to tumor necrosis factor (TNF) and blocks binding to TNF receptors. The compound is FDA-approved for the treatment of psoriasis in adults. Until recently, there was very little information to support the use of etanercept in the pediatric psoriasis population because of a lack of randomized, placebo-controlled clinical trials. There have been a few preliminary reports demonstrating the efficacy and safety in pediatric psoriasis. Paller et al published a placebo controlled, double-blinded randomized clinical trial evaluating the clinical efficacy and safety of the use of etanercept in children with psoriasis. In this study, 211 children ages 4-17 were enrolled and were given 12 once-weekly subcutaneous injections of placebo or 0.8 mg of etanercept per kilogram of body weight (maximum 50 mg) per week. An open-label arm of the study was continued for 24 weeks to investigate the effects of withdrawal and retreatment. The primary endpoint of PASI 75 at twelve weeks for etanercept was achieved by 57% of patients, compared with 11% for placebo. Only four serious adverse events occurred, including three infections developing in three patients during treatment with open-label etanercept. All infections resolved without sequelae. This study demonstrated significantly reduced disease severity in children and adolescents with moderate-to-severe plaque psoriasis. The long term course of etanercept and possible complications later in life are unknown. Discontinuation of etanercept may be associated with recurrent psoriasis that may be more difficult to manage, but this issue requires further study.

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Case #7

CASE PRESENTED BY: Michael Tharp, MD, Marianne O'Donoghue, MD and Reshma Nair Haugen, MD

History: The patient is a 15-year-old Hispanic female who presented with a six month history of an asymptomatic rash localized primarily to her face, but also involving her trunk and upper extremities. She had been previously treated with topical fluticasone, mupirocin, clotrimazole, oral cephalexin and griseofulvin without improvement. A review of symptoms was negative for oral ulcers, arthralgias, discoid lesions, serositis, renal, neurologic or rheumatologic disorders.

Past Medical History: Noncontributory

Medications: None

Allergies: No known drug allergies

Family History: Noncontributory

Social History: The patient was born in the United States and has never traveled to South America.

Physical Examination: Numerous brown crusted papules and plaques with underlying erythema on the malar cheeks, nose, forehead, upper chest, abdomen, back and arms. The conjunctiva and oral mucosa are clear.

Laboratory Data: The following laboratory values are within normal limits:
CBC, CMP, TSH, T3, T4, CRP, G6PD, ANA (<1:40)

The following laboratory values were abnormal:
Intercellular Skin Autoantibodies > 1:160

Histo-pathology: The epidermis has a subcorneal split with acantholytic cells and an underlying superficial perivascular infiltrate with eosinophils and neutrophils.

Direct immunofluorescence demonstrates C3 and IgG deposition in the intercellular space of the epidermis. There is no immunoglobulin or complement deposition along the basement membrane.

Diagnosis: **Pemphigus Foliaceus**

Course and Treatment: Treatment was initiated with prednisone 50 mg daily and doxycycline 100 mg twice daily, as well as hydrocortisone 2.5% ointment to the face and triamcinolone 0.1% ointment to

the body. The patient responded well initially, and was able to discontinue the prednisone within 6 weeks. She remained lesion free on doxycycline for four months. A subsequent flare required prednisone 60 mg daily. Sun protection and supplementation with calcium and Vitamin D was emphasized. After obtaining a normal G6PD, the patient was started on dapsone 50 mg daily as a steroid-sparing agent. The dose was steadily increased to 125 mg daily which allowed the prednisone to be tapered to 15 mg daily. In addition, the topical steroids were discontinued and replaced with topical tacrolimus 0.1% ointment.

Discussion: Pemphigus Foliaceus (PF) is a cutaneous, autoimmune bullous disease in which the recognized target is desmoglein 1[1]. The two major categories of PF are endemic and sporadic. The endemic form, also know as fogo selvagem (FS), occurs in the rural areas of Brazil and is thought to be transmitted by the black fly, *Simulium nigrimanum*. Unlike FS which mainly affects children and young adults, the sporadic form of PF is a disease of the middle-aged and elderly. Nonendemic PF is exceedingly rare in children; there are less than thirty reported pediatric cases. Pemphigus erythematosus (PE), or Senear-Usher syndrome, is considered a variant of PF where lesions are localized to the malar and seborrheic areas of the face. Direct immunofluorescence of perilesional skin demonstrates immunoglobulin and/or complement deposition at the dermal-epidermal junction. In addition, many patients with PE have serologic features of lupus erythematosus, including a positive ANA[2,3].

The histologic changes of PF, PE, and FS are very similar: a subcorneal blister with acantholytic cells detaching from the roof of the blister. These superficial blisters are histologically indistinguishable from those seen in staphylococcal scalded skin syndrome or bullous impetigo, where desmoglein 1 is also targeted. Eosinophilic spongiosis can also be seen in very early lesions. In the superficial dermis a perivascular mononuclear infiltrate with a few eosinophils is seen. Direct immunofluorescence shows intercellular deposition of IgG and C3.

The differential diagnosis of PF includes other forms of pemphigus, bacterial and fungal infections especially bullous impetigo, subcorneal pustular dermatosis, linear IgA bullous dermatosis and seborrheic dermatitis.

Because the sporadic form of PF rarely affects children, information on treatment guidelines and course of disease is lacking[1,4]. In contrast to childhood pemphigus vulgaris, the clinical course of sporadic PF is milder[1,4,5,6]. A retrospective review of 29 cases of PF showed that 88% of children were clear of disease within one year regardless of the type of therapeutic intervention[1].

The mainstays of therapy include systemic and topical corticosteroids as well as steroid-sparing immunosuppressive agents. Dapsone has been reported to be a helpful adjuvant[1,4,5,6,7,8]. A possible mechanism that may account for its effectiveness may be the inhibition of eosinophilic spongiosis observed in pemphigus lesions[7]. The use of dapsone in our patient allowed us to decrease the dose of prednisone significantly. Finally, the use of topical tacrolimus has allowed us to discontinue topical steroids in our patient. To our knowledge, there are only 2 other reports of the efficacy of topical tacrolimus in PF[8,9].

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Case # 8

CASE PRESENTED BY: Lady C. Dy, M.D. and Reshma Nair Haugen, M.D.

"Unknown"

Case # 9

CASE PRESENTED BY: Michael D. Tharp, MD and Reshma Nair Haugen, MD

History: The patient is a 27-year-old African American male with congenital deafness who presented with diffuse alopecia areata affecting his scalp, groin, and extremities for three years. He reported a sister and cousin with alopecia areata. He denied a personal or family history of diabetes mellitus, thyroid disease, vitiligo, pernicious anemia or myasthenia gravis. During his examination the patient was noted to have heterochromia irides. Upon questioning, he revealed a strong family history of congenital deafness and heterochromia. He also described a patch of grey hair in his frontal scalp prior to the onset of his alopecia areata. The patient denied a personal or family history of depigmented patches, limb abnormalities or Hirschsprung's disease.

Past Medical History: Congenital sensorineural deafness, Heterochromia irides

Medications: None

Allergies: No known drug allergies

Family History: See pedigree

Physical Examination: Bilateral pale blue eyes with partial heterochromia and lateral displacement of the medial canthi. Patches of alopecia on the scalp, trunk and extremities with no evidence of a white forelock. No depigmented patches.

Laboratory Data: The following laboratory values were within normal limits: CBC, Iron, TIBC, Ferritin, TSH
The following laboratory value was abnormal: *W index* = 2.176

Diagnosis: **Alopecia areata in a patient with Waardenburg Syndrome**

Course and Treatment: A consultation with the geneticist for pedigree analysis confirmed the diagnosis of Waardenburg syndrome. The patient declined additional molecular genetic testing. For the patient's diffuse alopecia areata, he was given an oral prednisone taper as well as clobetasol solution. Within a few months, there was significant evidence of hair regrowth and the presence of a white forelock. The patient was tapered off prednisone and continued topical clobetasol with no additional hair loss.

Discussion: Waardenburg syndrome (WS) is a rare, autosomal dominant disorder characterized by congenital hearing loss, pigmentary abnormalities of the eyes, skin and hair, and craniofacial abnormalities[1,2,3]. Originally described in 1951, the condition is caused by the physical absence of melanocytes in the eyes, skin, hair and the stria vascularis of the cochlea[2]. The estimated prevalence of WS is 1 in 42,000 in The Netherlands and 1 in

20,000 in Kenya[2,3,4]. There is no reported prevalence in the United States. Waardenburg syndrome accounts for more than 2% of congenital deafness cases[1,2].

The diagnosis of WS is a clinical one, where an individual must have 2 major or 1 major plus 2 minor criteria. The major criteria are congenital sensorineural hearing loss, heterochromia irides, white forelock, dystopia canthorum and an affected first degree relative. The minor criteria include leukoderma, confluent eyebrows or synophyrys, broad nasal root, hypoplasia of the alae nasi and premature graying of hair.

WS has been classified into four distinct subtypes. WS type 1, caused by a mutation in the PAX3 gene on chromosome 2, is characterized by the presence of a white forelock, deafness, heterochromia irides and dystopia canthorum. WS type 2 is similar to WS type 1 but without the dystopia canthorum. It is caused by a mutation in microphthalmia-associated transcription factor, or MITF. WS type 3, or Klein-Waardenburg syndrome, has associated upper limb deformities[2,3]. It is also linked to a mutation in the PAX3 gene. WS type 4, or Shah-Waardenburg syndrome, is associated with Hirschsprung's disease and is linked to a mutation in EDN3 gene, its receptor EDNRB or the SOX10 gene.

Cutaneous pigmentary defects, consisting of both hypo- and hyperpigmented patches occur in 8.3 to 50% of patients[1]. The most common hair abnormality is the white forelock; however, cases of red, brown and black patches have been reported[2,4]. Additionally, some patients demonstrate premature graying of scalp and body hair. Dystopia canthorum is found in 41.2 to 99% of the reported cases. Avias and Mota developed the *W index* for the diagnosis of dystopia canthorum: $W = X + Y + a/b$, where $X = [a - \{0.21119c + 3.909\}]/c$ and $Y = [2a - \{0.2479b + 3.909]/b$; a is the inner canthal distance, b is the interpupillary distance and c is the outer canthal distance[1,4].
A $W > 1.95$ is indicative of dystopia canthorum.

No treatment is available for patients with WS, but prompt diagnosis and referral to a hearing specialist are crucial for the normal development of patients affected with this condition[2] Genetic counseling is also recommended.

Although our patient did not want to undergo molecular genetic counseling, we hypothesize that he had WS type 1 based on the presence of dystopia canthorum, lack of limb abnormalities and Hirschsprung's disease.

Finally, to our knowledge, this is the first report of a case of WS with diffuse alopecia areata. Two other members of the patient's family have alopecia areata, one of whom also has WS. It is possible that alopecia areata should be considered in the wide spectrum of WS clinical features.

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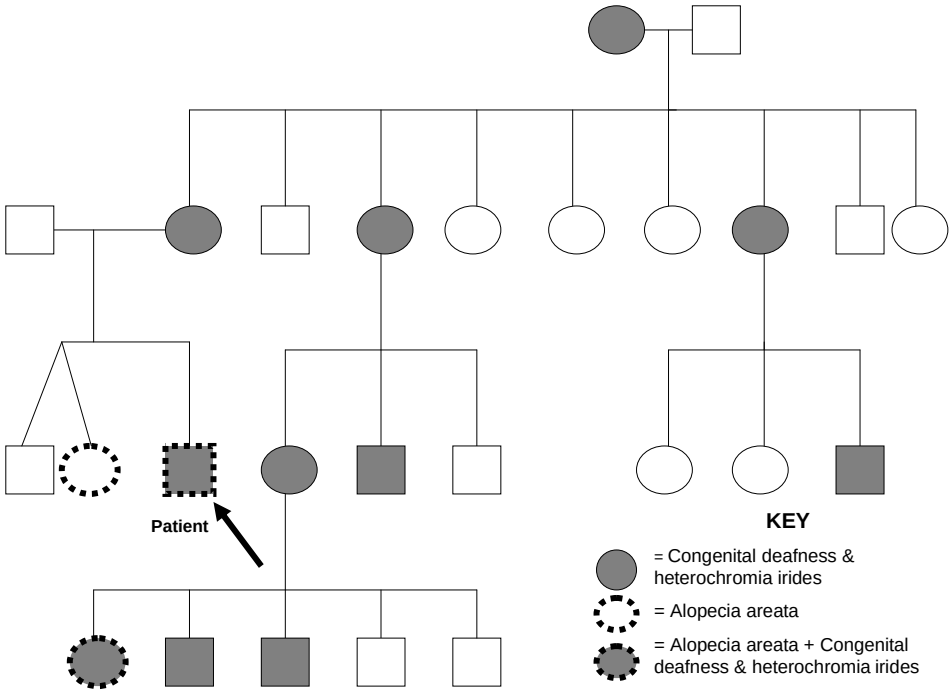
Pedigree Analysis



Case #10

CASE PRESENTED BY: Michael D. Tharp, M.D. and Melanie D. Palm, M.D.

History: The patient is a 59-year-old male with a 43 year history of type I diabetes mellitus who presented to clinic in 2007 with a 17 year history of skin "tautness." He first noted hardening of his posterior neck and upper back in 1990 while performing exercises that involved shoulder abduction during his routine workout. From the time of initial symptoms, the patient has experienced a progressive hardening of the skin over the posterior neck, shoulders, upper back, and arms. He denies any preceding or concurrent erythema, preceding upper respiratory illness, or streptococcal infection. The patient has no history of paraproteinemia or history of a myeloproliferative disorder. His diabetes is well-controlled under the supervision of a diabetologist.

Past Medical History: Diabetes Mellitus, type I, diagnosed in 1964
Hypertension
Dyslipidemia
L2-L5 laminectomy following back injury in October 2007

Medications: Insulin, pioglitazone, lisinopril, simvastatin, venlafaxine, zolpidem tartrate, diclofenac

Allergies: No known drug allergies

Social History: Disabled engineer following back injury in September 2007. Patient denies tobacco or alcohol use.

Review of Systems: Mild decrease in bilateral shoulder abduction. Otherwise, noncontributory.

Physical Examination: Posterior neck, upper one-half of back, shoulders, and arms: hardened, "woody" nonpitting induration of skin with overlying peau d'orange changes. No underlying erythema. Skin is slightly shiny in appearance.

Laboratory Data:

Abnormal results: Hemoglobin A1C (3/10/08): 6.3% (ref range:3.9-6.2%)
Hemoglobin (12/19/07): 10.4 g/dL (13.5-17.5 g/dL)

Normal laboratory results:
Quantitative serum protein electrophoresis and immunotyping electrophoresis (4/21/08): normal electrophoresis pattern, no monoclonal antibodies or paraprotein detected.
Recent basic metabolic panel and lipid panel were within the normal limits.

Histo-pathology: Punch biopsy, right upper arm (3/10/08): Dermal thickening with large thickened collagen bundles and widely-spaced fenestrations. No dermal inflammatory infiltrate present. Colloidal iron stain shows minimal dermal mucin deposition.

Diagnosis: **Scleredema adultorum (diabeticorum), type III**

Course and Treatment: The patient was offered PUVA treatment but has declined at this time due to his back injury.

Discussion: The name scleredema adultorum of Buschke references Abraham Buschke's 1902 description of a middle-aged, carriage varnisher who suffered from progressive skin hardening of the neck, trunk and extremities.[1] An earlier description is credited to Curzio in 1752 and Tourane *et al.* in their 1936 review of the condition. Scleredema adultorum shows no ethnic predilection and approximately 50% of patients are older than 20 years, although cases occur in the pediatric population.[2]

Scleredema adultorum is characterizes by a progressive, symmetric "woody" induration, usually beginning on the neck or upper back and spreading centrifugally to involve the face, scalp, shoulders, and trunk.[1] The distal extremities are classically spared from skin hardening. The condition is classified into three subtypes. Type I disease (55% of total cases) occurs after a febrile illness and is characterized by complete resolution within months to 2 years. Type II scleredema (25%) has no preceding illness, has an insidious onset, and follows a slowly progressive course. Patients with type II scleredema adultorum are at risk for developing paraproteinemias and multiple myeloma. Type III disease (20%) is associated with long-standing insulin-dependent diabetes mellitus, does not have a preceding febrile illness, and follows a progressive, non-remitting course.[3] Type I and II disease have a female predominance, whereas type III affects males more frequently. Extracutaneous involvement may occur in the heart, lungs, muscles, esophagus, or eyes.[3]

The pathogenesis of sclerema adultorum is unknown. No laboratory values are characteristic for this disorder, although ASO titers may be elevated in type I, indicating a preceding streptococcal infection. Poorly controlled glucose control in DM as indicated by elevated serum glucose levels and hemoglobin A1C have been reported in patients with type III scleredema.[1] The diagnosis is based on clinical and histopathologic findings. A skin biopsy classically reveals a normal epidermis with a thickened dermis, up to four times normal.[4] The collagen is swollen and separated by widened spaces containing mucin visible by colloidal iron or Alcian blue stains.

Therapies are inconsistently effective but have included corticosteroids, immunosuppressants, various forms of PUVA, antibiotics, pituitary extract, thyroid hormone, electron beam radiation, extracorporeal photopheresis, NB-UVB and physiotherapy. [1,3-5] Case reports and small case series have demonstrated improvement of scleredema, including scleredema diabeticorum, with UVA1 phototherapy. [6-8]

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Case #11

CASE PRESENTED BY: Julie Moore M.D. and Tracy Campbell M.D.

History: A 45-year-old female with a history of multiple dysplastic nevi and lentigines presented in 2001 for a full skin exam, and has been followed every six months for dysplastic nevi. Photographic surveillance was recommended considering the patient's multiple dysplastic nevi, and was initiated in 2002. The patient was diagnosed in November of 2005 with a gastrointestinal stromal tumor (GIST) after removal of a 6.2 cm mass from her colon. After surgery in November 2005, she underwent an endoscopic ultrasound and endoscopy in January of 2006 which revealed three small gastric tumors which were found to be consistent with GIST. The patient was treated with imatinib mesylate (Gleevec) in February of 2006 in an attempt to decrease her tumor load. Three months later the patient noticed a decrease in the number of pigmented lesions on bilateral palms, a lightening of her genital area, and a graying of her pubic hair, eyebrows, and scalp hair. She has continued to notice disappearance of her pigmented macules since starting her treatment.

Past Medical History: Over 10 moderately atypical dysplastic nevi removed

Medications: Imatinib mesylate (Gleevec) 400 mg daily, hydrochlorothiazide, sertraline 100 mg daily

Allergies: Intravenous contrast dye

Family History: Mother with a GIST tumor
Maternal Grandmother: Deceased at age 83 in 1987, history of multiple intestinal "sarcomas" diagnosed 20 years earlier after bowel obstruction surgery

Social History: The patient is a nonsmoker who rarely drinks alcohol. The patient denies any elicit drug use.

Review of Systems: Significant for slight weight loss, nausea, periorbital edema secondary to imatinib mesylate therapy.

Physical Examination: Pre February 2006 (original photographs taken 2002): Too numerous to count medium brown flat macules generalized to entire the cutaneous surface with involvement of palms and soles. Diffuse darkening of her mucosa labia minora. No oral or anal pigmentation.
October 2006 (repeat photographs taken): Decreased number brown macules on the trunk. Palms, soles and face have very few pigmented lesions. Lightening of her labia minora.

Laboratory Data: Exon 11 mutation of the c-kit gene, confirmed by gene studies.

Studies: 11/05 Regional lymph node biopsies were negative for malignancy in the right colon and hepatic flexure.
1/06 Endoscopy revealed three tumors in stomach lining that were biopsy proven GIST

2/08: Computed Tomography (CT) Scan – no metastatic disease, no evidence of malignancy
3/08: Endoscopic ultrasound – no metastatic disease, no evidence of GIST tumors, stomach lining tumors have regressed
5/08: Positron Emission Tomography (PET) Scan - pending

Histo-pathology: 5/08 Right deltoid and Right lower back. Both biopsies of disappearing lentigines show an increased number of melanocytes at the basal layer seen with the hematoxylin and eosin and Melan-A immunohistochemical stains. However the Fontana-Masson stains revealed only subtle focal melanin pigmentation.

Diagnosis: **Familial GIST syndrome with the c-kit exon 11 mutation presenting with disappearance in pigmented lesions and pigmented terminal hair secondary to imatinib mesylate.**

Course and Treatment: Since her diagnosis, the patient has undergone computed tomography (CT) scans every 3 months, endoscopic ultrasounds every 4 months, colonoscopies every 8 months, and Positron Emission Tomography (PET) scans every 6 months for the first 2 years after her diagnosis. The patient continues her treatment at the Dana-Farber/Brigham and Women's Cancer Center where she receives counseling, monitoring, treatment, and is involved in clinical trials for familial GIST syndrome. The patient continues to do very well on imatinib mesylate and states that the graying of her terminal hair, the lightening of her genital area, and the decrease in her pigmented lesions has stabilized. The patient remains healthy with no evidence of new GIST foci or metastasis.

Discussion: Gastrointestinal stromal tumors (GISTs) are very rare tumors of the GI tract that originate from the interstitial cells of Cajal (ICCs). ICCs are part of the autonomic nervous system and the "pacemakers" of the human digestive tract. These cells are found in the wall of the GI tract between the connective tissue and muscles layers. Symptoms of GISTs include abdominal discomfort, pain and bleeding into the intestinal tract resulting in melena, metastatic, and anemia. Currently Neurofibromatosis Type 1 and familial gastrointestinal stromal tumor syndrome are the only two known risk factors.

Familial gastrointestinal stromal tumor syndrome is even more rare despite being an autosomal dominant condition. Only 24 families with familial GIST syndrome have been reported. Approximately 80% to 85% of GISTs harbor activating mutations of the KIT tyrosine kinase. The remaining are a mutated PDGF receptor alpha (PDGFRA), or unknown mutation. C-kit and its ligand stem-cell factor regulate melanocyte development and survival. These patients have a lifetime risk of >90% of developing GIST or multiple GISTs. Both KIT and PDGFRA proteins are receptors for growth factors that are activated in normal tissues, have a similar structure, and are tyrosine kinases receptors. The majority of KIT mutant GISTs have mutations in exon 11 (66.1%) since exon 11 is the most common mutation for GISTs in all anatomical locations. Several papers have found that patients with deletions within exon 11 (in contrast to substitutions or duplications) have a poorer prognosis (greater probability of recurrence or metastasis) than other GIST patients. Our patient's family has a KIT exon 11 mutation that resulted in the deletion of codon 579.

Mutations in C-kit and PDGFRA occur in both familial and sporadic GIST patients. Since KIT mutations are found in every cell of the body in familial GIST, the disease tends to have a different natural course than sporadic GIST. Despite the tendency for multiple tumors to develop in the GI tract, familial GIST patients may have less of a tendency for metastasis. The clinical course has been described as relatively indolent. In some cases diagnosis of GIST exhibit anticipation, or manifests earlier with each younger generation. Individuals in some families may show areas of hyperpigmentation on the face, neck, hands, feet, or other areas. Complications include gastrointestinal bleeding, obstructive complications, severe anemia secondary to bleeding, and death.

Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that inhibits bcr-abl tyrosine kinase (the constitutive abnormal tyrosine kinases encoded by the Philadelphia chromosome abnormality in CML). It also is an inhibitor of the receptor tyrosine kinases for the platelet-derived growth factor (PDGF) and C-kit, and it inhibits PDGF and SCF mediated cellular events. Imatinib mesylate induces apoptosis in GIST. It is indicated for the treatment of Philadelphia chromosome positive CML and Kit (CD117)-positive gastrointestinal stromal tumors (GIST) that cannot be surgically removed and/or have spread to other parts of the body. The effectiveness of imatinib mesylate in Kit+ GIST is based on objective response rate (measurements of tumor shrinkage). There are no studies showing that symptoms caused by the disease improve or that patients live longer. The role of this medication as a therapeutic or preventive intervention in GISTs remains to be defined; however, there are several anecdotal cases of familial GIST patients in remission. Recent data indicate that the response of GIST patients to tyrosine kinase inhibitors varies by the specific mutation displayed by their tumors. This data indicates a stronger and longer-duration response to imatinib mesylate for patients with KIT mutations in exon 11, as in our patient, than for those with mutations in exon 9 or for patients with c-kit GIST.

Side effects of imatinib include hair repigmentation, hypopigmentation, photosensitization, pruritus, edema, ocular toxicity, xerosis, and various exanthums. Reports of pigmentary abnormalities secondary to imatinib therapy are described in the literature as localized, patchy or diffuse pigment dilution that is generally reversible. The pathology of hypopigmented areas in the literature showed a decrease in melanocytes with the Fontana-Masson stains showing a decrease in the amount of melanin. However, as stated above, these biopsies were taken from diffuse or focal areas of hypo or depigmented patches, not lightened lentigines. Our patient is unique in that she does not have patches of hypopigmentation, but a hypopigmentation of her lentigines. Because very little is known about familial GIST syndrome and imatinib mesylate's actual role in this disease, the molecular basis for the disappearance of pigmented remains elusive. One theory is imatinib mesylate interferes with the production of melanin, resulting in decreased pigmentation of the skin via the KIT-MITF pathway. We present this rare familial syndrome and rare cutaneous side effects secondary to treatment with a tyrosine kinase inhibitor for interest and suggestions on potential mechanisms of pigmented inhibition.

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CASE #12

CASE PRESENTED BY: Michael Tharp, M.D. and Sarah Kasprowicz, M.D.

History: This patient is a 53-year-old female with chronic urticaria for 11 years, unresponsive to multiple treatments. The patient has experienced urticarial lesions some of which itch while others burn and sting. Some lesions last longer than 24 hours and have left a residual purpura at the site of expression. Over the years she has had seven skin biopsies of both early and late lesions. Most biopsies have shown urticaria with a neutrophil predominant infiltrate. However, two of the biopsies have shown leukocytoclastic vasculitis. Over the years, the patient has been treated with prednisone, doxepin, cetirizine, dapsone, fexofenadine, cyproheptadine, zileuton, colchicine, plaquenil, cyclosporine, azathioprine, IVIg (three infusions) mycophenolate mofetil, and etanercept, all with variable response. In 2006 the patient was started on a trial of methotrexate (maximal dose of 17.5 mg/wk) in conjunction with dapsone, low-dose prednisone, and doxepin, with eventual clearing of her lesions. She is currently controlled on 2.5mg/week of methotrexate. In the last few months she has been tapered off of the prednisone and the dapsone. Currently she reports complete clearing of her lesions with the occasional, transient flare resulting from pressure.

Past Medical History: Patient has a past medical history of fibromyalgia, depression and osteopenia. Patient was hospitalized in 2004 for pancreatitis and a hysterectomy.

Medications: methotrexate, folic acid, doxepin, pregabalin

Family History: No family history of allergic diseases

Physical Examination: No active urticarial lesions

Laboratory: Work-ups for malignancy, endocrine abnormalities and infectious causes have all been negative.
CH50: 198 (70-290 U/mL); C1q: 13(11-21 U/mL); C3: 130 (77-179 mg/dL); C4: 35 (13-49 mg/dL); ESR 6 (0-27 mm/hr)
ANA, RF, CRP, Serum IgG, IgA, IgM: all within normal limits

Histo-pathology: Consistent with urticarial vasculitis: many neutrophils and eosinophils around necrotic blood vessels

Diagnosis: **Urticarial vasculitis responsive to methotrexate**

Discussion: Urticarial vasculitis is a clinicopathological condition comprised of urticarial lesions with histologic features of leukocytoclastic vasculitis. It presents as an eruption of erythematous wheals that clinically resembles urticaria but, in contrast to typical urticaria lesions, the lesions of urticarial vasculitis typically persist longer, may or may not be pruritic, and often typically leave residual hyperpigmentation.

The incidence of urticarial vasculitis is unknown. It is thought that 5%-10% of individuals with urticarial lesions may have urticarial vasculits on histologic examination. Most patients with urticarial vasculitis are normocomplementemic and their lesions last an

average of three years. Urticarial vasculitis can be associated with systemic lupus erythematosus and other connective tissues diseases. It may also be associated with infections, medications, and malignancies.

Clinical and laboratory findings in urticarial vasculitis are highly variable. Patients with normal complement levels tend to have skin-limited disease, whereas up to 50% of patents with the hypocomplementemic form of the disease have arthritis, pulmonary, or gastrointestinal symptoms. Our patient's laboratory evaluation has shown normal ANA, RF, C3, C4, ESR, CH50, C1q. No underlying cause for her urticarial vasculitis could be identified.

Antihistamines and NSAIDs may be helpful in reducing inflammation of the lesions. Corticosteroids, dapsone, colchicine, hydroxychloroquine, and mycophenolate mofetil have all been shown anecdotally to have some effect. This patient was initially responsive to high doses of dapsone but over approximately two years became refractory to this medication and numerous other therapies including colchicine, azathioprine, dapsone, zileuton, plaquenil, IVIg (three infusions), mycophenolate mofetil, and etanercept. She cleared completely on cyclosporine but had severe myalgias necessitating discontinutation. Subsequently, she began methotrexate which has proven to provide the most relief for her urticaria. Methotrexate was initiated in November of 2006. The patient's dose was increased to 17.5 mg/week before her lesions resolved and she has been slowly tapered and controlled with 2.5 mg/wk.

Methotrexate therapy has previously been reported to be effective in two patients with chronic idiopathic urticaria, although these patients showed no evidence of vasculitis. The mechanism of action of methotrexate is the inhibition of dihydrofolate reductase, decreasing the supply of reduced folate cofactors for RNA and DNA synthesis. The mechanism of action in urticarial vasculitis is not known but may be related to its effects on lymphocytes and cytokine production.

The adverse effects of methotrexate include bone marrow suppression, teratogenicity, hepatic toxicity, gastrointestinal intolerance, interstitial pneumonitis, pulmonary fibrosis and small vessel vasculitis. Monitoring guidelines include a baseline complete blood count (CBC), liver function tests (LFTs), and hepatitis panel. Follow-up monitoring includes CBC and LFTs every two weeks initially and then every 3-4 months, thereafter. At the present time it is recommended that a liver biopsy be obtained after a cumulative total dose of 1.5-2.0 grams.

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Case #13

CASE PRESENTED BY: Victoria Barbosa, M.D. and Melinda Simon, M.D.

History: The patient is a 15-year-old African American female presenting with a congenital lesion on her right trunk and buttock. The lesion was initially 2cm in size and has gradually increased in width and in height. The lesion is mildly pruritic and is also tender with trauma. No therapy for this lesion had been attempted.

Past Medical History: Developmental delay, asthma, benign ventricular septal defect, scoliosis s/p surgical repair, history of gastroesophogeal reflux s/p Nissen fundoplication

Medications: Fluticasone propionate (Advair), montelukast (Singulair)

Allergies: NKDA

Family History: Neurofibromatosis 1 in the patient's mother and brother

Social History: 9th grade student with special learning needs, now in mainstream education

Physical Examination: The patient had macrocephaly, low set ears, short stature, and scoliosis. Her right lower abdomen, right torso, right lower back, and right buttock had a large hyperpigmented, wormlike, lobulated plaque, consistent with a plexiform neurofibroma. Bilateral axillary freckling was noted. The patient's chest, abdomen, back, bilateral upper and lower extremities had multiple hyperpigmented macules and patches, consistent with café au lait macules, as well as multiple skin colored to hyperpigmented soft papules, some pedunculated, consistent with neurofibromas.

Studies: The patient's MRI demonstrated a large heterogeneous plexiform neurofibroma, up to 5 cm in thickness from the level of the iliac crest extending 22 cm in length. A 2.2 cm area of decreased enhancement likely represents subcutaneous fat but cannot exclude malignant degeneration, which is much less likely.

Diagnosis: **Neurofibromatosis 1**

Course and Treatment: The patient is being followed by pediatrics, ophthalmology, orthopedic surgery, and dermatology. She was recently referred to plastic surgery for excision of the plexiform neurofibroma, and has required no other interventions.

Discussion: Neurofibromatosis 1, (NF1), or von Recklinghausen's Disease, is a genodermatosis with an autosomal dominant inheritance pattern with spontaneous mutation in 50% of cases. NF1 has a prevalence of 1 in 3000. First described thoroughly by von Recklinghausen in 1882, it has subsequently been found that mutations in the NF1 gene lead to neurofibromatosis type 1. The NF1 gene encodes neurofibromin, which is likely involved in the negative regulation of the protoncogene Ras.

Diagnostic criteria include the following; at least two of the six conditions must be present: six or more café au lait macules > 5mm for prepubertal patients and >15mm for postpubertal patients, axillary or inguinal freckling (Crowe's sign), two or more Lisch nodules (iris hamartomas), optic gliomas, bone lesions such as long bone thinning or sphenoid wing dysplasia, and a first degree relative with such criteria.

Additional cutaneous features may include cutaneous or subcutaneous neurofibromas, which may appear at age 4-5 years, but typically appear around puberty, plexiform neurofibromas, and juvenile xanthogranulomas. Plexiform neurofibromas, (PNFs), are likely congenital and occur in 10% of patients with NF1. They can not only invade the skin but also fascia, muscle and bone. The PNFs may progress into a malignant peripheral nerve sheath tumor, or MPNSTs. This occurs in 1-5% of patients with NF1, with an overall lifetime risk of 8-13% in NF1 patients. Pain and rapid increase in size are worrisome for the transformation as this tumor may be fatal. Patients have 15 year decrease in life expectancy, with MPNSTs accounting as the leading cause of death in young adults.

Skeletal conditions that occur include macrocephaly, scoliosis, pseudoarthrosis, spina bifida, and absent patella. Ocular findings include hypertelorism and glaucoma. Patients may have neoplasms such as malignant peripheral nerve sheath tumors, pheochromocytoma, juvenile chronic myelogenous leukemia, rhabdomyosarcoma, somatostatinoma, and parathyroid adenoma. Unidentified bright objects of unknown significance can appear on MRI, and mental retardation, learning difficulties, precocious puberty and hydrocephalus may occur. And finally, cardiac conditions that may manifest in patients include hypertension, pulmonic stenosis, and renal artery stenosis.

A differential diagnosis of the PNFs includes a congenital nevus as both are "congenital," may begin as flat lesions and may increase in size or height, and may become hypertrichotic. As such, it is important to not confuse PNF as a congenital nevus as it is imperative to monitor the patient for previously discussed findings if the lesion is a PNF. Conversely, it is important to evaluate a congenital nevus for malignant melanoma potential.

Histopathologically, cutaneous neurofibromas are well circumscribed dermal compilations of spindle cells, nerve fibers, fibroblasts, and Schwann cells with possible mucin and mast cells. Plexiform neurofibromas have Schwann cells, fibroblasts, and hypertrophied nerves, all in a myxoid surrounding. Malignant peripheral nerve sheath tumors may have hyperchromatic and pleomorphic nuclei, cellular as well as myxoid regions, increased mitoses and may stain with S-100.

Therapy for patients with NF1 is multidisciplinary. Physicians caring for a patient may include a pediatrician, dermatologist, endocrinologist, orthopaedic surgeon, ophthalmologist, neurologist, geneticist, cardiologist, and hematologist-oncologist. Neurofibromas can be excised for cosmetic reasons. Patients should have close follow up to evaluate for any new symptoms and plexiform neurofibromas should be monitor closely for possible malignant transformation. The National Neurofibromatosis Foundation that can assist families with this condition.

The patient presented today has impressive findings of neurofibromatosis as she has many of the criteria including the family history. Additionally, she has the large plexiform

neurofibroma with increasing size and tenderness, which raises the concern for malignant transformation and subsequent therapy.

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Case #14

CASE PRESENTED BY: Mark D. Hoffman, M.D., and Sarah Kasprowicz, M.D.

History: This 27-year-old man presented for the evaluation of a congential nevus on his leg. On physical exam he was noted to have clinical features suggestive of tuberous sclerosis, although he did not carry this diagnosis.

Past Medical History: At birth bilateral enlarged kidneys, a webbed neck and communicating hydrocephalus were noted. A diagnosis of Noonan syndrome has been entertained since birth.

There is a history of developmental delay (first walked at age 4), hearing loss, persistent sinus problems, osteoporosis, and mitral valve prolapse. According to the patient's mother, a childhood MRI was performed that was "basically normal." He was diagnosed with polycystic kidney disease at age 12 and subsequently underwent a bilateral nephrectomy. Pathological inspection of the kidneys showed multiple cysts. At age 15 he had a kidney transplant. At age 16, he was diagnosed with a seizure disorder, which is currently well-controlled.

Medications: Epoetin alfa, mycophenalate mofetil, diltiazem, phenytoin, ASA, simvastatin, nephrocaps

Family History: Both the patient's father and his paternal aunt were diagnosed with Huntington's disease and polycystic kidney disease (father deceased at age 53; aunt is living). Patient has five paternal uncles: three had polycystic kidney disease, one has Huntington's disease, and one died in infancy. He has one sister who has polycystic kidney disease. There are no other siblings**.**

Physical Examination: Numerous small pink papules are present on the nose and medial cheeks. A faint oval hypopigmented macule is found on the right dorsal foot. There are dysmorphic facial features including low-set ears with an ear pit, a high arched palate with dental crowding, and abnormal head shape.

Studies:
1. Shave biopsies x 2 (nose and right cheek, 9/12/2007): consistent with angiofibromas.
2. Opthalmology examination: strabismus and amblyopia noted but negative for retinal findings of tuberous sclerosis.
3. MRI brain (2004): The bilateral lateral ventricles demonstrate non-enhancing irregularities of their lateral walls, consistent with heterotopia, or subependymal nodules of tuberous sclerosis.
4. MRI brain (2007): Small subependymal irregularities along the margin of the lateral ventricles, unchanged from the study of 2004.

Diagnosis: Probable tuberous sclerosis / polycystic kidney disease contiguous gene syndrome

Discussion: Tuberous Sclerosis (TS) is an autosomal dominant, multisystem neurocutaneous disease with an incidence that is estimated to be between 1 in 5800 and 1 in 10,000. It is characterized by the development of multiple hamartomas in various organ systems. The classic tuberous sclerosis triad consists of seizures, mental retardation and cutaneous

angiofibromas. Although, the presence of the complete triad is only evident in 29% of cases and 6% of tuberous sclerosis patients have none of these three findings. TS is transmitted in an autosomal dominant pattern and two-thirds of the cases are thought to be caused by sporadic mutations. Two gene defects have been identified in Tuberous Sclerosis: TSC1, on chromosome 9q34 which encodes for the protein hamartin and TSC2 on chromosome 16p13 which encodes for the protein tuberin. Interestingly, more than 1200 different allelic variants have been identified in both the TSC1 and TSC2 genes. It is thought that this is the cause for such diverse clinical presentation of the disease.

More recently the roles of TSC1 and TSC2 have been more clearly identified. Hamartin and tuberin are thought to be two proteins that regulate cell cycling, growth and tumorigenesis. The two proteins are thought to complex, forming a tumor suppressor heterodimer. The complex inhibits the mTOR pathway. The mTOR pathway is known to regulate cellular proliferation.

This patient has both a personal and family history of polycystic kidney disease. The major gene for autosomal dominant polycystic kidney disease (ADPKD) has been identified on chromosome 16p13. This gene is located immediately adjacent to the TSC2 gene. Large gene deletions disrupting both the TSC2 and PKD1 gene have been identified in some patients with both phenotypes. However, renal cysts have also been associated with TSC1 gene-affected patients and the TSC1 gene is located on chromosome 9.

Revised diagnostic criteria for tuberous sclerosis are based on a 1998 consensus meeting. A definite diagnosis includes two major or one major feature and two minor features. Probable TS includes one major plus one minor feature. There are 11 major features: facial angiofibromas or forehead plaque, nontraumatic ungula or periungual fibroma, hypomelanotic macule (3 or more), shagreen patch, multiple retinal nodular hamartomas, cortical tuber, subependymal nodule, subependymal giant cell astrocytoma, cardiac rhabdomyoma (single or multiple), lymphangiomyomatosis, and renal angiomyolipoma. There are nine minor features that include the following: multiple randomly distributed dental pits, hamartomatous rectal polyps, bone cysts, cerebral white matter radial migration lines, gingival fibromas, nonrenal hamartomas, retinal achromic patch, confetti skin lesions and multiple renal cysts.

Cutaneous findings in TS include hypomelanotic macules, confetti-like lesions, facial angiofibromas, ungual fibromas, forehead fibrous plaques and shagreen patches. Hypomelanotic macules are seen in over 90% of TS patients and they are usually present at birth. The “ash leaf” spot is characteristic of tuberous sclerosis but varies in geometric configuration. Facial angiofibromas are found in 75% of all patients with TS. They are found primarily on the nasolabial folds, cheeks and chin. Ungual fibromas (Koenen tumors) are present in 25% of affected patients; they tend to develop later in life. The shagreen patch is a connective tissue nevus found most commonly in the lumbosacral region.

Recently, molecular genetic testing has become available. PCR is used to identify mutations in the TSC1 and TSC2 genes.

The treatment of TS is geared towards the organ systems involved. A multidisciplinary approach is important to appropriately manage individuals diagnosed with tuberous sclerosis. Dermatologists, neurologists, urologists, pediatricians and geneticists should all be involved. Patients should undergo regular neuroimaging, renal ultrasound,

ophthalmologic examination, and neurodevelopmental and psychiatric evaluations should be performed.

Recently, sirolimus has been looked at for treating TS. Sirolimus, also known as Rapamycin, is an immunosuppressant used in organ transplantation. Rapamycin is an antibiotic derived from a bacterium (*Streptomyces hygroscopicus*) that is found in the soil on Easter Island. Rapamycin normalizes the dysregulated mammalian target of rapamycin (mTOR) pathway in cells lacking either wild-type TSC1 or TSC2, and seems to be an effective therapy for TSC. Rapamycin (sirolimus) is the first therapeutic advancement for this disease.

The Tuberous Sclerosis Alliance (www.tsalliance.org) and the Tuberous Sclerosis Association (www.tuberous-sclerosis.org) are two organizations that can serve as good resources for patients, friends and family.

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Case #15

CASE PRESENTED BY: Michael Tharp, M.D, and Sarah Kasprowicz, M.D.

History: This 62-year-old male presented with a solitary lesion on his right mid-back for approximately two years. He reported the lesion has remained stable in size and configuration. The lesion became apparent to the patient in 6/2006 with pruritus and slight redness. A biopsy was performed by a local dermatologist which showed a mild superficial perivascular lymphohistiocytic infiltrate. He was treated with a one month course of topical corticosteroids. Since 6/2006 the lesion has become more atrophic and red. The patient is no longer using any topical treatments. On further questioning of his medical history, the patient reported a number of prolonged cardiac catheterization procedures. He describes the fluoroscopy procedure being "2.5 hours long because they had difficulty placing the stent." The patient was lying on his right side during the procedure.

Past Medical History: Coronary Artery Disease, Myocardial Infarction at age 38.

Surgical History: 1999: Cardiac catheterization
5/2005: Cardiac catheterization. Patient was lying on R side and the procedure took 2.5 hours secondary to a difficult stent placement.
10/2005: Cardiac catheterization. Patient was lying flat on his back and the procedure took 6 hours, secondary to difficult stent placement.

Medications: atarvastatin, metroprolol, clopidogrel bisulfate, aspirin

Allergies: Morphine

Family History: No family members with similar lesions

Physical Examination: Right mid back, inferior border of scapular outline: 7.5 cm x 6 cm rectangular, hypopigmented, slightly atrophic patch with mild erythema and numerous telangectasias throughout the lesion.

Histo-pathology: Right back 8/2006: atrophic epidermis, mild superficial perivascular lymphohistiocytic infiltrate in the dermis. No evidence of collagen changes typical of morphea. Features possibly represent a fixed drug eruption.

Diagnosis: **Radiation induced skin injury from fluoroscopy**

Discussion: Cardiac catheterization procedures using fluoroscopy are known to expose patients to high doses of radiation, especially in cases of repeated procedures. A number of radiation-induced skin injuries have been reported in relation to the increased number of interventional procedures being performed. More than 700,000 fluoroscopy-guided procedures are performed each year in the United States. Typically these procedures do not result in perceptible radiation-induced skin injury, but the potential risk of skin

manifestations increases as indications for use, frequency and duration of these interventional procedures increases.

In addition to fluoroscopy, radiation-induced skin injury can result from a number of diagnostic and therapeutic radiological interventions such as MRI and radiotherapy. Radiation-induced skin injury may be acute in onset but also have a chronic course.

Acute cases often develop within a few hours or a few days after the procedure; the lesions may start with pruritus and pain, leading to erosion and ulceration. In chronic cases, the skin changes do not typically occur until months to years after radiation exposure and appear as erythema, poikiloderma, and ulceration. In chronic cases, the irradiated area may develop basal or squamous cell carcinomas, typically occurring after a few years. MRI procedures can cause first, second or third degree burns when metal contacts the skin creating a closed-loop conduction. The exact cause of MRI burns is not known but it is thought that both pulsed radiofrequency and pulsed magnetic gradient fields play a role. Radiation dermatitis may also occur in people undergoing radiotherapy. It is thought that in up to 87% of women undergoing radiotherapy some type of radiation dermatitis will develop.

Radiobiological knowledge has been increased by the understanding of the effects of cytokines. Ionizing radiation inhibits proliferation, primarily in stem cells but also activates a multitude of cytokine receptors and adhesion molecules. This cascade may also initiate angiogenesis and lead to skin sclerosis and atrophy.

A number of cases of radiodermatitis have been reported after repeated therapeutic interventional procedures using prolonged fluoroscopic imaging. Here we report a case of a patient who underwent a cardiac catheterization two years ago and developed his current lesion since the procedure. Normally such changes would be expected on the left posterior trunk. However the patient has skin changes on the right back, which we believe are the result of the patient undergoing prolonged fluoroscopy while lying on his right side. This case highlights the need to be aware of such reactions, as the number of these procedures being performed is increasing. Also, it is important to educate patients with similar lesions about the potential of developing skin cancers in the sites of radiation injury.

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Case #16

CASE PRESENTED BY: Clarence W. Brown Jr., M.D. and Tracy Campbell M.D.

History: A 47-year-old African American male presented with a six month history of painful, bleeding periungual lesions that were increasing in size and number. The patient complained of red, friable, beefy exophytic tissue nodules periungually and subungually on eight out of ten toes. The patient was unable to ambulate even a short distance because of the pain, bleeding, and oozing of the lesions and has been confined to a wheel chair for the last four months. The patient noted no new medications within the last year and denied trauma to the nails. There was no history of onychocryptosis or any previous similar lesions.

Past Medical History: The patient has a complicated medical history including a hospitalization one year prior for a blastomycosis epidural abscess complicated by necrotizing fasciitis of his left lower extremity, perineum, and right thigh. After undergoing multiple surgeries including a laminectomy, debridement of his lower extremities, and extensive skin grafting of his left extremity and perineum, the patient was released from his hospital stay to a rehabilitation facility. The patient underwent extensive physical rehabilitation due to skin grafting extending across his joints, and intermittent paralysis of his right leg secondary to the excised epidural blastomycosis infection.

Medications: Hydrocortisone, lisinopril, carvedilol, hydrocodone bitatrate / acetaminophen, noisacodyl sodium, magnesium hydroxide, famotidine, baclofen, vitamin E, and gabapentin.

Allergies: NKDA

Family History: Brother with ingrown onychocryptosis.

Social History: No smoking or alcohol use.

Review of Systems: Negative except for pain and lack of ambulation stated above.

Physical Examination: Red friable tissue subungually and periungually on bilateral feet

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Laboratory Data: Tissue culture was negative for fungal, acid-fast bacilli, and anaerobic bacteria. A light growth of tetracycline sensitive Staphlococcus aureus was grown from the broth of the tissue culture.

Histo-pathology: Histopathologic exam revealed ulcerated granulomatous inflammation consistent with granulation tissue. No features of a pyogenic granuloma or infection were found. Tissue culture and stains were negative for fungus, acid-fast bacilli and atypical mycobacteria.

Diagnosis: Exuberant idiopathic granulation tissue treated with silver nitrate

Course and Treatment: The patient was initially treated with tetracycline 500 mg BID for one month because of the light growth of Staphylococcus aureus. The patient returned to our clinic one month later without improvement. He was treated with an avulsion of the right 5th toenail, while 3 toenails on the left foot were treated with silver nitrate. The patient returned two weeks later and noted some improvement of the silver nitrate treated areas on the left foot but no change at the nail avulsion site on the right foot. The right 3rd toenail was avulsed at this visit and silver nitrate was applied to all other affected areas except the right great toe. Treatment was withheld on the right great toe in order to evaluate the efficacy of the silver nitrate. The patient returned three weeks later with new granulation tissue on the two avulsed nail bed surfaces. This physical finding made it clear that ingrown toenails were not the primary process of this granulation tissue response. Treatment was held at this time and wound care was discussed. The patient reported slightly decreased pain. He was still unable to ambulate and continued to travel via wheelchair.

The patient returned one month later with exuberant granulation tissue much improved on the silver nitrate treated sites. The patient had begun to ambulate again with a walker because of the decreased pain and continued healing of his toes. Silver nitrate was then applied to the right great toe, the only site not previously treated. The patient continues to improve and was last seen in March.

Discussion: Painful periungal lesions are documented in the literature as adverse effects of systemic retinoids, cyclosporine, chemotherapeutic agents, and protease inhibitors. Both isotretinoin and etretinate therapies may stimulate increased granulation tissue production at the sites of ingrown nails and healing acne lesions. Drug induced subungual and periungual pyogenic granulomas have been reported in patients taking indinavir and mitozantrone. Cyclosporine induced periungal granulation tissue has been noted in both psoriatic and renal transplant patients. In almost all the reports in the literature, the lesions resolved after lowering or cessation of the offending medication. Our patient was on numerous medications that were unchanged during the course of his presentation. The etiology is unclear in this case.

Treatment for excessive periungal and subungual granulation tissue of unknown etiology is not well reported. The offending agent or medication is usually discontinued, or the underlying anatomical defect is corrected (onychocryptosis). Our patient had no history of onychocryptosis (ingrown toenails). There are multiple treatments for onychocryptosis which include CO2 laser ablation, partial nail avulsion followed by CO2 matricectomy, segmental chemical ablation with phenol, and multiple other devices that are used to separate the nail plate from the lateral nail fold. These therapies were all considered; however, because of the extreme discomfort of these lesions we choose to go with the least invasive treatment modality was chosen.

The possibility of onychocryptosis was treated by avulsion which should decrease the patient's discomfort and stop the proliferation of granulation tissue. However, in this case, the granulation tissue continued to proliferate and the patient's discomfort continued even after two nail avulsions. Ingrown toenails results from compression of the lateral nail folds on the nail plate. Removing soft tissue surrounding the nail plate and decompressing the nail reduces the inflammation. The decompression can be done by avulsion, surgically removing the soft tissue, a matricectomy, or a combination of the aforementioned

treatments. Because of the patient's lack of response to the nail avulsion, the probability that these lesions stem from onychocryptosis is low.

In conclusion, because we do not have a clear understanding of the events that could have caused these lesions, the etiology remains idiopathic. This case is unusual because of the dramatic, simultaneous, eruption of granulation tissue without stimulus of onychocryptosis, medications, or trauma. We present this case for clinical interest due to successful treatment of granulation tissue with silver nitrate.

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Case #17

CASE PRESENTED BY: James Ertle, M.D., Mark D. Hoffman, M.D., and Sarah Kasprowicz, M.D.

History: This 86-year-old male presented in 2006 to an outside physician with an asymptomatic growth on the left buttock and left posterior leg. A punch biopsy of one of the lesions showed focal acantholytic dyskeratosis. The lesion remained stable until the same year when he had an adenocarcinoma of the stomach resected, followed by a subtotal gastrectomy. At this time the lesion began to extend down the left leg to the ankle. On presentation to the clinic in 2007, after another biopsy was consistent with Darier's disease, he was started on Tazorac 0.1% cream at bedtime. After two weeks, there appeared to be a good response with some flattening of the lesion and after a month he was alternating Tazorac 0.1% cream and Salex lotion with good results. Two months later the lesion became inflamed and topical steroids and Protopic ointment (0.1%)were applied, successfully reducing the inflammation. Patient is currently maintained on the Tazorac 0.1% cream.

Past Medical History: History of hypertension, osteoarthritis and a myocardial infarction. Basal cell carcinoma on left shoulder

Medications: pantoprazole, aspirin, metoprolol, atorvastatin, Tylenol

Allergies: Penicillin and diazepam

Family History: No family members with similar lesions

Physical Examination: There are yellow-brown papules coalescing into a rough, verrucous surface beginning in the left intergluteal fold and extending in a narrowing linear manner to the left posterior upper leg, calf and ankle.

Histo-pathology: 3/27/2006: left buttock: focal acantholytic dyskeratosis

5/11/07: left posterior upper leg: epidermis shows verrucoid hyperplasia. There is acantholysis, corps ronds and parakeratosis

Diagnosis: **Linear Darier's disease**

Discussion: Darier's disease (Darier-White disease, keratosis follicularis, dyskeratosis follicularis) is an autosomal dominant genodermatosis that produces abnormalities in keratinization of the epidermis, nails and mucous membranes. This disease results in chronic eruptions of hyperkeratotic papules in seborrheic areas, palmoplantar pits, V-shaped nicking or longitudinal ridging of nails and cobblestone papules in the oral mucosa. Histologically, acantholytic dyskeratosis is seen with suprabasilar clefting and corps ronds and grains are found. The cutaneous signs are known to be exacerbated by triggers such as heat, perspiring, and UV light. Lesions tend to be pruritic and associated with malodor, secondary to bacterial colonization.

The reported prevalence of Darier's disease has been estimated to be between 1:30,000-100,000. In approximately 70% of patients, the disease begins between the ages of 6 and 20 years, with peak onset during puberty. Darier's disease follows a chronic course without spontaneous remission. Darier's disease can fluctuate; some patients will improve over time and others will worsen.

Darier's disease is linked to mutations in the endoplasmic reticulum Ca2+ ATPase ATP2A (gene product SERCA2), most likely through haploinsufficiency. ATP2A mutation results in inadequate filling of the endoplasmic reticulum (ER) calcium stores. The sarcoplasmic endoplasmic reticulum Ca2+ isoform 2 (SERCA2) is an intracellular pump that replenishes endoplasmic reticulum calcium. Dysfunction of this pump is thought to impair the normal processing of the proteins necessary for efficient cell-to-cell adhesion.

In addition to generalized Darier's diseases, there is a subset that present with segmental expression. Several patients with unilateral, linear, localized, or Blaschkoid patterned lesions have been reported. Two types of distributions have been described in segmental Darier's. Type 1 follow Blaschko's lines unilaterally on a background of otherwise normal skin. Alternatively, Type 2 lesions represent focal areas of increased severity superimposed on a background of generalized Darier's.

This patient likely represents a case of Type 1 disease. There have been no reports of patients with mosaic Darier's disease giving rise to offspring with the generalized form of the disease. Caution must be exercised when counseling patients on the risk of transmission, as limited cutaneous involvement may or may not reflect the true extent of mosaicism.

Treatment of segmental Darier's is the same as the generalized form of the disorder. Milder cases are treated with emollients, sunscreens, and avoiding overheating. More severe disease requires oral and topical retinoids, calcipitriol and 5-fluorouracil.

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Case #18

CASE PRESENTED BY: Michael O'Donoghue M.D., Lady C. Dy M.D., and Lauren Campbell M.D.

History: A 48 year-old white man presented with a sudden extremely pruritic annular scaly eruption covering his trunk, extremities, and buttocks. Lesions first appeared on his abdomen and spread rapidly within two weeks, covering most of his body surface area, sparing the genitalia. He had a history of a similar cutaneous eruption 10 months ago where he was treated with fluocinonide for approximately two months with partial response. His severe pruritus was unresponsive to fexofenadine and hydroxyzine. He was using no topical therapies at the time of presentation.

Past Medical History: Adult-onset diabetes mellitus for twelve years, peripheral vascular disease. peripheral neuropathy, hypercholesterolemia, osteoarthritis

Past Surgical History: Right great toe amputation, left below the knee amputation, rotator cuff repair, cardiac catheterization, appendectomy

Medications: Aspirin, enalapril, simvastatin, lansoprazole, glipizide, cilostazol, metformin, insulin, amitriptyline

Allergies: Clopidogrel-skin eruption

Family History: Mother is deceased (lung and brain cancer). Father and all three siblings living. No family history of skin disease.

Social History: 30+ pack year history of cigarette smoking. Reports occasional alcohol use. He is currently living in an assisted-care rehabilitation facility.

Review of Systems: No fevers, chills, sweats, weight loss or rapid gain, headaches, seizures, diarrhea, vomiting, loss of appetite, genitourinary complaints, joint pains, or shortness of breath.

Physical Examination: The patient was afebrile. On the trunk, buttocks, and extremities there are erythematous band-like plaques arranged in a parallel fashion in concentric swirls involving about 65% of the total body surface area. The genitalia are spared. There is fine white scale arranged concentrically trailing the border of erythema in most of the plaques. There was no appreciable lymphadenopathy or hepatosplenomegaly.

Laboratory Data: **Abnormal:** Fasting blood glucose 165 mg/dl (65-110), sodium 132 mEq/L (135-148), chloride 97 mEq/L (98-108), hematocrit 44.3 % (38-44), mean corpuscular volume 31.1 fl (27-31).

Within normal limits: Blood urea nitrogen and creatinine, potassium, alkaline phosphatase, carbon dioxide, calcium, liver function tests, hemoglobin, white blood cell count and differential, platelets, erythrocyte sedimentation.

Studies: CT Chest abdomen and pelvis with and without contrast: Axillary, mediastinal, and groin adenopathy. Lymphoma is possible. Further work-up recommended for lymphoma.

Histo-pathology: Hyperkeratotic and acanthotic epidermis with parakeratosis with an underlying mild perivascular lymphocytic infiltrate. Although changes are minimal, given impressive clinical presentation they are consistent with erythema gyratum repens.

Diagnosis: **Erythema gyratum repens, associated with possible lymphoma**

Course and Treatment: The patient was started on mid-potency topical steroids twice daily and over the past month has experienced significant clearing of large body surface areas. His pruritus is significantly decreased. He was referred to hematology/oncology, who ordered an excisional lymph node biopsy to further evaluate him for lymphoma.

Discussion: The differential diagnosis for gyrate erythemas is broad, but one is virtually always associated with internal malignancy. Erythema gyratum repens (EGR) was first reported and described in the literature in 1952 by Gammel. Since that time numerous cases have been reported, and the vast majority are associated with an identifiable underlying malignancy. There is a male predominance of 2:1 with a mean age of onset of 63 years. EGR has only been reported in whites.

EGR is perhaps one of the most striking skin diseases in both clinical appearance and evolution. There are numerous serpiginous macular (or occasionally papular) bands of erythema arranged in a parallel configuration of concentric swirls usually covering most of the body. It is often referred to as having a "wood-grained" appearance. These lesions expand at an alarmingly fast rate, estimated at one centimeter per day. Slight scale is often seen along the trailing edge of erythema. Hands, feet and face are commonly spared. There may be bullae within the erythema. Patients almost universally experience severe pruritus that is difficult to control.

Several authors have theorized that EGR involves an immunologic mechanism. One salient theory is that antibodies to tumor antigens may cross-react with similar antigens in the skin. Another author pointed out that if EGR is caused by antigens producing an autoimmune response, then antigens other than just tumor must at times be involved, as not all cases of EGR have been associated with an underlying malignancy. Currently, the pathogenesis of erythema gyratum repens remains unknown.

The histopathology of EGR is non-specific, demonstrating hyperkeratosis, acanthosis, and spongiosis. There is a superficial and perivascular mononuclear infiltrate. One interesting pathologic finding that has been reported in EGR is the accumulation of active Langerhans cells in the upper layers of the epidermis. In some patients direct immunofluorescence (DIF) has demonstrated deposits of IgG and C3 in the basement membrane zone. In isolated cases similar deposits have been found within the identified underlying neoplasm.

Given the striking and unique clinical appearance, the diagnosis is usually rapidly made on physical examination alone. Laboratory abnormalities in EGR are often nonspecific. Peripheral eosinophilia is found in 59%. Complement studies have shown normal amounts of C3 and increased C4. Immunoglobulin levels may be normal or low.

In 82% of patients with EGR an underlying malignancy is found. The diagnosis of cancer is made an average of four to nine months after the appearance of the eruption. The most common malignancy found is bronchial cancer in 32% of patients; esophageal cancer in 8%, 6% with breast cancer and 6% with malignancy of unknown primary. Other cancers that have been reported include cervical, gastric, pharyngeal, uterine, prostate, bladder, tongue, rectal, small bowel and pancreatic cancer. Patients with EGR have also been reported to have non-malignant conditions including pulmonary tuberculosis, liner IgA disease, bullous pemphigoid, pemphigus vulgaris, and hypereosinophilic syndrome.

The definitive treatment of erythema gyratum repens consists of treating the underlying malignancy if one can be identified. After treatment of the primary tumor, the eruption will begin to rapidly resolve in most cases and the patient's pruritus will dissipate. In patients with a large tumor burden that cannot be significantly treated, the eruption will persist until shortly before the patient's death, when the lesions may suddenly remit. It has been theorized that this sudden clearance is secondary to the immunosuppression that may occur just before death. In patients without an underlying malignancy, topical and systemic corticosteroids have been used with varying success. Treatment failures have been reported with Vitamin A and azathioprine.

Erythema gyratum repens is a paraneoplastic skin disease with a dramatic presentation. The most frequent associated underlying malignancy is bronchial cancer. The diagnosis of erythema gyratum repens should precipitate an aggressive search for an underlying cancer.

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