Chicago Dermatological Society

November 2009
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, November 18, 2009

Conference Host:
Section of Dermatology
University of Chicago Hospitals
Chicago, Illinois

Program

Venue Information

See site map on following pages

Duchossois Center for Advanced Medicine (DCAM)
5758 S. Maryland Ave.
- Registration
- Board/committee meetings
- Patient viewing

Wyler Children's Hospital (WCH)
5841 S. Maryland Ave.
- Slide viewing
- Lectures, business meeting & case discussions
- Lunch

Committee Meetings

DCAM - Room 1402 (off main lobby near elevators)

8:00 a.m.	CDS Plans & Policies Committee
9:00 a.m.	IDS Board of Directors

Program Activities

8:00 a.m.	Registration Opens for All Attendees *DCAM - Main Lobby*
9:00 a.m. - 10:00 a.m.	*RESIDENT LECTURE – Billings Auditorium, P-117 (WCH)* "New insights on Neurophyisology of Itch and Scratch" *Gil Yosipovitch, MD*
9:30 a.m. - 11:00 a.m.	*CLINICAL ROUNDS* Patient viewing – *Dermatology Clinic 5D (DCAM)* Slide viewing – *Rm. L-107 (WCH)*
11:00 a.m. - 12:15 p.m.	*GENERAL SESSION - Billings Auditorium, P-117 (WCH)* *Allan Lorincz Lecture:* "Itch More Than Scratching the Surface" *Gil Yosipovitch, MD*
12:15 p.m. - 12:45 p.m.	Box Lunches
12:45 p.m. - 1:00 p.m.	CDS Business meeting – *Billings Auditorium, P-117 (WCH)*
1:00 p.m. - 2:30 p.m.	Case Discussions – *Billings Auditorium, P-117 (WCH)*
2:30 p.m.	Meeting adjourns

Future Meeting Schedule – check the CDS meeting calendar on our website: www.ChicagoDerm.org

Next meeting – Wednesday, December 9, 2009 at the University of Illinois – Chicago

Duchossois Center for Advanced Medicine (DCAM)
5758 S. Maryland Avenue

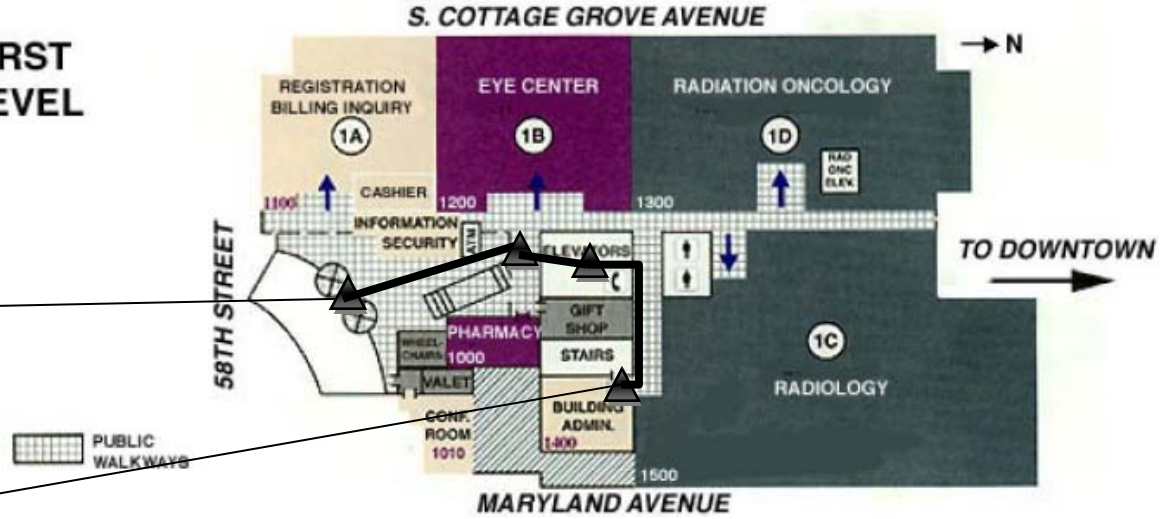
Registration:
Report Here First -- Enter through DCAM main entrance. Table will be in Lobby near Elevators on 1st Floor.

Rm. 1402: (board meetings) Go past elevators and turn right for IDS and Plans and Policies Meetings.

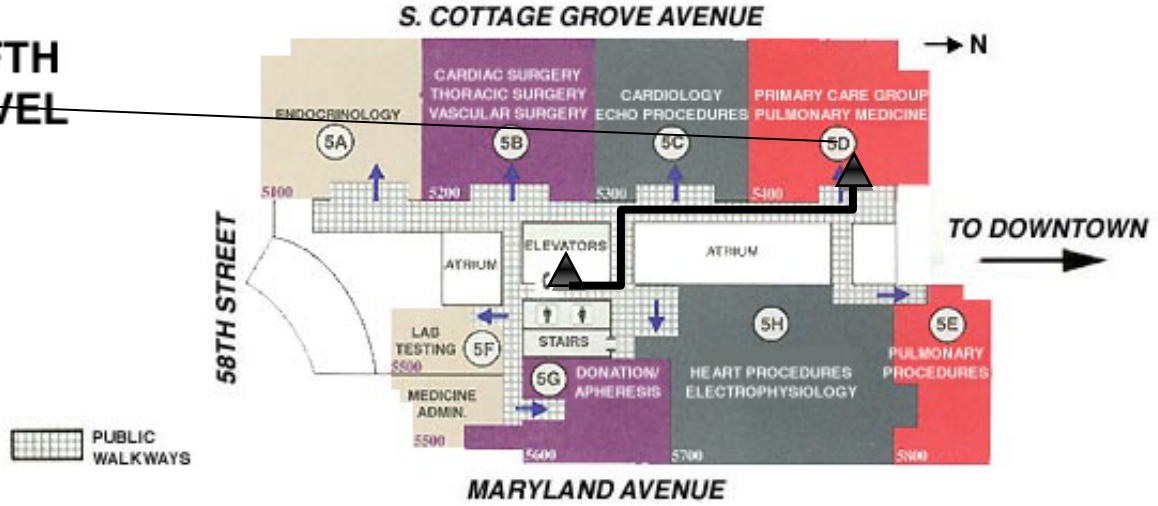
Derm Clinic 5D: Take elevators up to 5th floor for Patient Viewing.

Valet Parking is highly encouraged and is located on 58th St - just south of the DCAM and north of the parking garage. $10

FIRST LEVEL



FIFTH LEVEL



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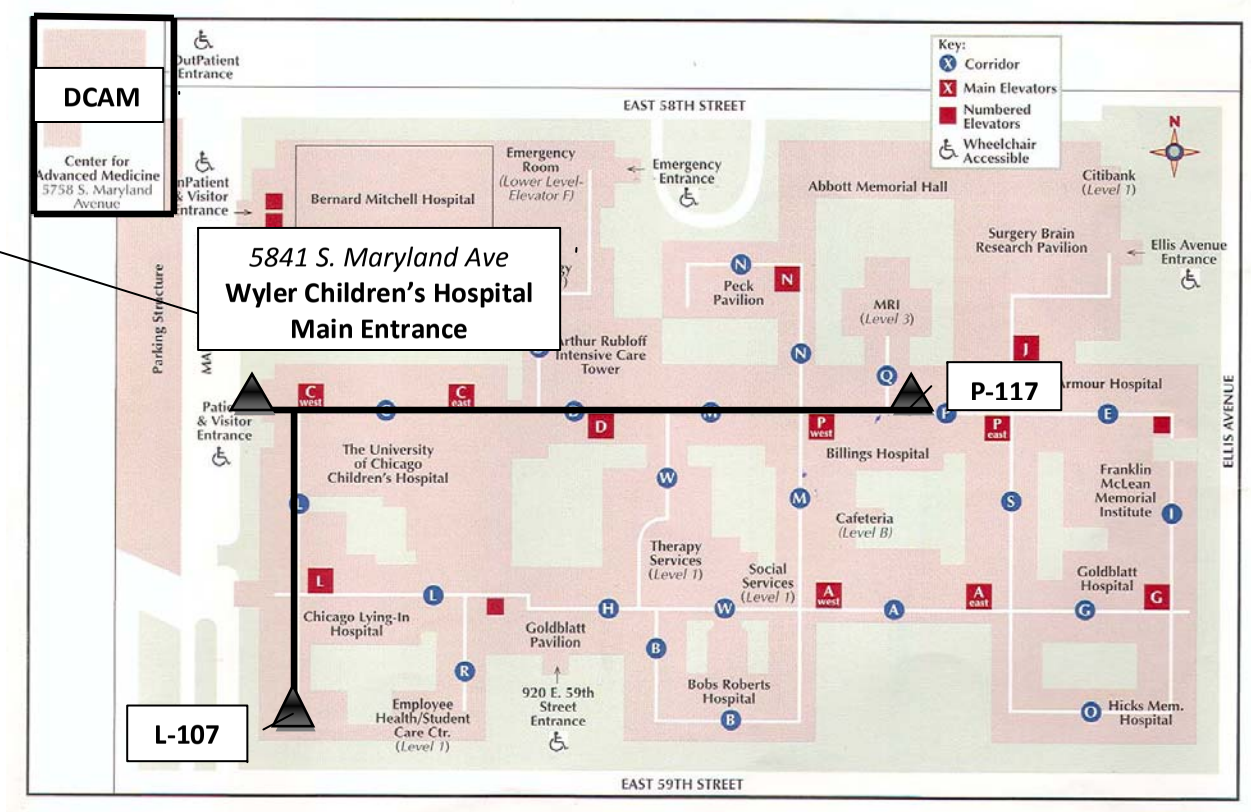
Enter through **Wyler Children's Hospital** main entrance at 5841 S. Maryland Avenue and follow map to:

<u>Billings Auditorium P-117</u> for:
Lectures
Business Meeting
Lunch
Case Discussions

<u>Rm L-107</u> for:
Slide Viewing



Note: The CDS conference registration desk will be located in the main lobby of the DCAM (Duchossois Center for Advanced Medicine). This is where you will pick up your meeting materials, and then proceed to patient viewing, slide viewing, resident lecture and general sessions. DO NOT go directly to the Billings Auditorium. We strongly recommend that you utilize the valet parking service at the front entrance of DCAM.

CME Information

This activity is jointly sponsored by the Chicago Medical Society.

Accreditation Statement:
This activity has been planned and implemented in accordance with the Essential 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.

Designation Statement:
The Chicago Medical Society designates this educational activity for a maximum of 4 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Commercial Support: There were no educational grants secured for this CME activity. We are pleased to acknowledge the participation of our exhibitors, Centocor and Graceway Pharmaceuticals.

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 sign the CME sign-in sheet located at the Chicago Dermatological Society registration desk. 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!

CME Disclosure of Financial Interests

Speaker: Dr. Yosipvitch is an investigator for UCB Pharma, and he serves on the advisory boards for Steifel and Unilever.

Program Planning Committee Participants:
- Benjamin Dubin, MD, program chair, has no significant financial relationships to disclose.
- Richard Paul, CDS executive director, has no significant financial relationships to disclose.
- Roger L. Rodrigues, MD, Chairman, Chicago Medical Society's CME Subcommittee on Joint Sponsorship, has no significant financial relationships to disclose.
- Bapu P. Arekapudi, MD, Member of Chicago Medical Society's CME Subcommittee on Joint Sponsorship, has no significant financial relationships to disclose.
- M. Anita Johnson, MD, Member of Chicago Medical Society's CME Subcommittee on Joint Sponsorship, is a shareholder with the following: Pfizer, Merck, Abbott Laboratories, Bristol Meyers Squibb, and Zimmer Holdings, Inc.
- Marella L. Hanumadass, MD, Member of Chicago Medical Society's CME Subcommittee on Joint Sponsorship, has no significant financial relationships to disclose.
- Hugo A. Alvarez, MD, Member of Chicago Medical Society's CME Subcommittee on Joint Sponsorship, has no significant financial relationships to disclose.
- Cecilia Merino, Chicago Medical Society, Director of Education, has no significant financial relationships to disclose.

Guest Speaker

Allan Lorincz Lecture

GIL YOSIPOVITCH, MD

- Professor, Department of Dermatology, Neurobiology & Anatomy, and Regenerative Medicine
- Director, International Fellowship Program; Director of Skin Physiology Laboratory

Wake Forest University Medical Center
Winston-Salem, NC

Born in Jerusalem, Dr. Yosipovitch attended Hadassah Hebrew University Medical School in Jerusalem and in 1990, earned his MD at the Sackler Faculty of Medicine, Tel Aviv University. He also earned a Masters Degree in Internal Medicine at the Sackler School of Medicine. Dr. Yosipovitch completed a residency in Internal Medicine in 1993 at Beilinson Medical Center, Petah Tiqva, Israel. He was a Fellow in the Department of Dermatology, University of California-San Francisco from 1994-95.

At Wake Forest, Dr. Yosipovitch lists his clinical and research as itch research, skin physiology, and international training.

TABLE OF CONTENTS

PRESENTERS
Diana Bolotin, MD, PhD, Justin Wasserman, MD, Keith L. Duffy, MD, Christopher R. Shea, MD and Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS
This 28-year old woman, with a history of Takayasu arteritis involving the vertebral and carotid arteries and Crohn's disease, on azathioprine, infliximab and low-dose prednisone (7.5 mg daily), presented with a three-month history of tongue and left buccal mucosa ulcerations. These painful lesions began as small ulcers but grew in size despite acyclovir therapy initiated by her primary care physician. The patient denied fever, abdominal pain, or changes in bowel habits. Her enteric Crohn's disease was well controlled on her regimen of immunosuppressant therapy.

PAST MEDICAL HISTORY
Crohn's disease (diagnosed in 1998), pyoderma gangrenosum on bilateral upper and lower extremities (2003), Takayasu arteritis (diagnosed in 2005), aortic, mitral, and tricuspid valve repair, aortic dissection with graft repair, diabetes mellitus

REVIEW OF SYSTEMS / FAMILY HISTORY / SOCIAL HISTORY / ALLERGIES
Non-contributory

MEDICATIONS
Azathioprine (175 mg daily), infliximab (10 mg/kg monthly), prednisone (7.5 mg daily), clopidogrel, metoprolol, glipizide, alendronate

PHYSICAL EXAMINATION
The patient was afebrile. An edematous macerated plaque with fissured surface was present on the left buccal and lower lip mucosa. A round, indurated plaque with a central ulcer and raised edge was noted on the right lateral tongue.

DERMATOPATHOLOGY
A shave biopsy specimen from the cheek lesion revealed extensive ulceration with an absence of the surface epithelium. The submucosa contained abundant infiltrates of plasma cells and lymphocytes. Several large multinucleated giant cells were also noted within the infiltrate. A 4-mm punch biopsy specimen from the edge of the tongue lesion showed squamous epithelium with extensive ulceration. The submucosa again revealed a dense infiltrate made up of lymphocytes, plasma cells, and multinucleated giant cells.

An anti-CD68 immunostain labeled increased numbers of interstitial macrophages and several collections of multinucleated giant cells. Anti-HSV1 and HSV2 immunostains were negative as was anti-*Treponema pallidum*. Lambda light chain and kappa light chains exhibited expression in normal proportions within the inflammatory infiltrate.

The periodic acid-Schiff, Gomori methenamine silver, and Fite stains of both specimens were negative. The Gram stain demonstrated Gram-positive bacteria on the surface only. Tissue cultures were negative for viral, fungal and acid-fast organisms. Bacterial cultures of the tissue grew methicillin-susceptible *Staphylococcus aureus*.

LABORATORY DATA
CRP: 18 [< 5 mg/L]
ESR: 59 [0-20 mm/hr]

Infliximab level: 10.0 [<1.4 mcg/ml];
Normal: Comprehensive metabolic panel, complete blood count, angiotensin converting enzyme level (ACE), serum protein electrophoresis, ANA, anti-dsDNA, anti-Smith, anti-RNP, C3, C4
Colonoscopy with biopsies: Numerous pigment-laden macrophages in the colon and rectum and mild patchy colitis in the left colon.
CT angiogram: Complete occlusion of the left vertebral artery. Stable <50% stenosis of right internal carotid artery and stable mild stenosis of the left common carotid artery.

DIAGNOSIS

Mucosal Crohn's disease

TREATMENT AND COURSE

The patient was initially treated with topical clobetasol and nystatin solution for *Candida* prophylaxis. The patient's prednisone dose was raised to 40 mg daily; azathioprine and infliximab were continued. However, the oral lesions continued to progress in size and became increasingly painful. She reported a twenty-pound weight loss due to a decrease in oral intake. Therefore, her gastroenterologist adjusted the immunosuppressant regimen to adalimumab, methylprednisolone and azathioprine. Two weeks later, she was admitted to the intensive care unit with fever and acute respiratory failure due to pulmonary histoplasmosis. Despite aggressive antifungal and supportive therapy, the patient developed acute hepatic and renal failure and subsequently expired.

DISCUSSION

Crohn disease (CD), a granulomatous inflammatory bowel disease, was initially described as regional enteritis by Crohn *et al.* in 1932. This condition can affect any part of the gastrointestinal tract, from the mouth to the anus. Most often, patients present with symptoms of CD during the second to fourth decade of life and a slight female predominance has been noted. Mucocutaneous involvement is the most frequent extraintestinal manifestation of CD. Of interest, cutaneous lesions appear to have an increased frequency in the setting of colonic involvement as compared to ileal involvement alone. In some cases, mucocutaneous CD may precede bowel involvement by several years.

Cutaneous manifestations of CD can be divided into involvement by specific granulomatous lesions and reactive manifestations. Mucosal lesions of CD characteristically present as ulcerations, fissured cheilitis, lip swelling, and mucosal cobblestoning. Cutaneous CD lesions are defined by the presence granulomatous infiltration of the skin at sites anatomically separated from the gastrointestinal tract in a patient with CD. Concomitant active intestinal CD has been noted in up to one third of adult patients and half of the cases in children. Histopathologic findings in mucocutaneous CD include non-caseating granulomatous inflammation with a mixed inflammatory cell infiltrate, as in our case. Infectious etiologies, especially with mycobacterial agents, must be ruled out with cultures and special stains.

Reactive cutaneous manifestations of inflammatory bowel disease include oral apthae, episcleritis, pyoderma gangrenosum, Sweet syndrome, pyoderma vegetans (more common with ulcerative colitis), erythema nodosum, polyarteritis nodosa, epidermolysis bullosa acquisita, and nutritional deficiency dermatoses. These conditions lack the granulomatous inflammation component characteristic of CD. While some of the reactive dermatoses parallel the clinical activity of the intestinal disease, others such as pyoderma gangrenosum run a course independent of the bowel involvement.

Treatment of cutaneous CD is often unsatisfactory. A range of immunosuppressant medications have been used. Oral metronidazole can be an effective treatment for mucosal CD. Topical and systemic corticosteroids, azathioprine, and/or TNF-α inhibitors remain the mainstay of therapy for more extensive involvement.

Our case also demonstrates an interesting but rare association between CD and Takayasu arteritis (TA), documented in a number of case reports and series. Both CD and TA are chronic granulomatous processes, albeit with different target organs. Both diseases present more commonly in young female patients, have a Th_1-cell-mediated cytokine profile, and respond to similar treatments. TA is most prevalent in Asia, whereas CD has a much higher prevalence in Northern Europe and North America. To date, no common human leukocyte antigen (HLA) genotype has been found to link the two diseases. While TA is a granulomatous vasculitis affecting large vessels – the aorta and its main branches, pulmonary and coronary arteries – CD is primarily a disease of the gastrointestinal tract wall. Though a common immunologic basis has been speculated, a definitive pathophysiologic link between these two entities is yet to be established, and the question of the difference in the preferred site of tissue injury remains unexplained.

REFERENCES

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2. Farrant, M., et al., Takayasu's arteritis following Crohn's disease in a young woman: any evidence for a common pathogenesis? World J Gastroenterol, 2008. 14(25): p. 4087-90.
3. Lester, L.U. and R.P. Rapini, Dermatologic manifestations of colonic disorders. Curr Opin Gastroenterol, 2009. 25(1): p. 66-73.
4. Palamaras, I., et al., Metastatic Crohn's disease: a review. J Eur Acad Dermatol Venereol, 2008. 22(9): p. 1033-43.
5. Ruocco, E., et al., Crohn's disease and its mucocutaneous involvement. Skinmed, 2007. 6(4): p. 179-85.

PRESENTERS
Ingrid Polcari, MD, Shaily Patel, MD, Justin Wasserman, MD, and Sarah L. Stein, MD

PATIENT A

HISTORY OF PRESENT ILLNESS
A full-term baby boy was transferred to our facility at 2 days of life for evaluation of absence of skin on the bilateral feet.

PAST MEDICAL HISTORY
Pregnancy was complicated by gestational diabetes but the patient's mother did not take any medications or supplements during pregnancy. The delivery was uncomplicated.

FAMILY HISTORY
No known history of skin fragility or blistering disorders.

MEDICATIONS/ALLERGIES
None

PHYSICAL EXAMINATION
The bilateral plantar feet had sharply demarcated angulated symmetric defects measuring about 1 cm by 5 cm. The contour of the feet was abnormal with exaggeration of the normal plantar concavity. The remainder of his physical examination was normal.

HISTOPATHOLOGY
The placenta was examined and did not show any evidence of infarct.

DIAGNOSIS
Aplasia cutis congenita of the bilateral plantar feet

TREATMENT AND COURSE
The feet were treated with wound care including 3% Bismuth Tribrophenate-petrolatum (Xeroform) gauze. Occupational therapy was consulted and provided splints to correct the foot deformity. At 9 days of age, the ulcerations were noted to be healing and he had no blistering of the skin or evidence of skin fragility. Duoderm dressings were advised. At 3 weeks of age the feet were noted to be healed. The mid-plantar feet showed linear, well-demarcated angular depressions with well-epithelialized overlying skin with a collarette of desquamating skin around the periphery. The contour of the feet was still mildly abnormal but had improved. The patient continues to lack evidence of skin fragility.

PATIENT B

HISTORY OF PRESENT ILLNESS
A full-term baby boy was born with areas of absent skin on the bilateral lower legs. Shortly after birth, he developed blisters on his hands, lips and inside the mouth.

PAST MEDICAL HISTORY
Pregnancy and delivery were uncomplicated.

FAMILY HISTORY/SOCIAL HISTORY
No known history of skin fragility or blistering disorders. No history of consanguinity; parents state they are from two small neighboring towns in Mexico.

MEDICATIONS/ALLERGIES
Ampicillin, gentamicin, and fentanyl in the newborn period. No known drug allergies.

PHYSICAL EXAMINATION
The right leg from the knee distally and the left ankle and foot had sharply demarcated deep defects with a shiny red base. There were erosions on the tongue and lower lip and small bullae and crusted erosions on his left dorsal hand. The remainder of his physical examination was normal.

LABORATORY RESULTS
Immunoflourescent mapping was performed on an induced blister from the right leg. The cleavage plane was below the epidermis, with antibodies to type IV collagen, type VII collagen, keratin 14, laminin 332, alpha 6-beta 4 integrin, type XVII collagen, and plectin localized to the basement membrane zone of the roof of the vesicle. The location of the split plus the presence of type VII collagen suggested the diagnosis of recessive dystrophic epidermolysis bullosa, non-Hallopeau Siemens type or dominant dystrophic epidermolysis bullosa (from a spontaneous mutation since family history is negative).

DIAGNOSIS
Aplasia cutis congenita of the bilateral lower legs in the setting of dystrophic epidermolysis bullosa (Bart's syndrome)

TREATMENT AND COURSE
Wound care consisted of Mepitel covered with secondary gauze dressings. The NICU staff exercised gentle handling and minimized interventions to prevent further blistering. Despite periodic blistering in the mouth, the infant was able to bottle feed. He developed blisters on the abdomen where his umbilical line was secured and blisters on his thigh. He was discharged home at 4 weeks of life. At 6 weeks of age the legs showed evidence of continued healing with milia at the periphery of the defects. Small vesicles were noted on the tip of the tongue but no other blistering was noted. He had thin scars at the sites of previous bullae.

PATIENT C

HISTORY OF PRESENT ILLNESS
A full term infant was noted at birth to have scattered skin erosions, blisters, and ankle strictures.

PAST MEDICAL HISTORY
The pregnancy was uncomplicated. Antibiotics were administered prior to delivery for maternal colonization with Group B Streptococcus.

FAMILY HISTORY
No known history of skin fragility or blistering disorders.

MEDICATIONS/ALLERGIES

Clindamycin, vancomycin, gentamicin, vancomycin, and morphine in the newborn period. Current medications include gabapentin, lorazepam, lansoprazole, multivitamin, sucralfate, and mupirocin 2% ointment. No known drug allergies.

PHYSICAL EXAMINATION

The bilateral hands, feet and posterior scalp had small superficial erosions. The ankles were tapered with large overlying erosions. There were stellate defects with a red shiny base over the knees. Natal teeth were noted. The fingernails were dystrophic.

LABORATORY RESULTS

Immunofluorescence mapping was performed on an induced blister from the right anterior thigh. The cleavage plane was within the lower epidermis, with antibodies to type IV collagen, type VII collagen, laminin 5, alpha 6-beta 4 integrin, type XVII collagen, and plectin localized to the floor of the vesicle. Keratins 5 and 14 antibodies bound to both the roof and the floor of the vesicle. The pattern of localization was consistent with epidermolysis bullosa simplex. Genetic analysis revealed a heterozygous mutation for E447K in the *KRT5* gene which is found in Epidermolysis Bullosa Simplex, Dowling-Meara type

DIAGNOSIS

Aplasia cutis congenita in the setting of Epidermolysis Bullosa Simplex, Dowling-Meara type (Bart's syndrome)

TREATMENT AND COURSE

Mepitel was applied to erosions under secondary gauze dressings. The knees showed evidence of slow healing. Despite gentle handling, the infant continued to develop new bullae in response to the slightest trauma, especially along the diaper line, at the site of umbilical catheter dressings, and on the upper extremities. He had persistent oral erosions which were painful and despite the use of analgesics he was unable to meet his caloric needs through bottle-feeding. A gastrostomy tube was placed which allowed him to gain weight appropriately. The infant was discharged home at two and a half months of age. At the most recent visit at 14 weeks he was noted to have erosions on bilateral extremities and lower abdomen with relative sparing of the face, buttocks, chest and back.

DISCUSSION

Aplasia cutis congenita (ACC) is a condition in which localized or widespread areas of skin are absent or scarred at birth. It may be an isolated condition or may be associated with developmental anomalies or skin disorders. ACC has no single cause. It is best to think of ACC as a common endpoint after disruption of intrauterine skin development. Factors responsible for such disruption include genetic factors, compromised vasculature to the skin, trauma, and teratogens.

Clinical features of ACC vary from superficial erosions to deep ulcerations which can extend to the bone or dura. Scars may be present at birth if the lesions underwent healing *in utero*. The scalp is the most common location for ACC with an estimated 85-95% of solitary lesions occurring there. The most common form found on the scalp is membranous aplasia cutis, in which there is a discrete oval or round defect covered by a shiny membrane. Commonly there is a surrounding 'hair collar'. Membranous aplasia cutis is most often a sporadic condition without any associated abnormalities. More clinically dramatic types of ACC are found on the scalp and can be associated with a variety of syndromes that are beyond the scope of this discussion. The

scalp is also the most common site for teratogen-induced ACC. Specific drugs implicated include methimazole, misoprostol, and low-molecular-weight-heparin.

Extensive ACC or ACC localized to other body areas such as the trunk or extremities should raise suspicion for an insult in utero or epidermolysis bullosa. Uterine insults include intrauterine infection with varicella or herpes simplex or placental infarcts or other events. For example, the death of a twin fetus is thought to cause intrauterine disseminated intravascular coagulation. The mummified twin found at delivery is termed 'fetus papyraceaus' and has been associated with ACC in multiple areas.

All types of epidermolysis bullosa (EB) have been associated with ACC, sometimes termed congenital localized absence of skin (CLAS). Bart et al originally described a kindred with CLAS of the lower extremities thought to be a new EB subtype, termed Bart's syndrome. In retrospect these infants likely all had dominant dystrophic EB, however it is now recognized that ACC or CLAS is not specific to any subtype of EB. ACC in EB patients is thought to be caused, at least in part, by fetal movements inducing trauma, such as rubbing the leg against the uterine wall, and subsequent blistering and erosions. Two of our patients (Patients 2 and 3) demonstrated typical features of Bart's syndrome in that the involvement was confined to the lower extremities and other signs of skin fragility were present. Interestingly, Patient 2 had larger areas of ACC but clinically has demonstrated a much milder phenotype than Patient 3 who continues to have extensive blistering. We are following Patient 1 closely for any sign of skin fragility which might suggest the additional diagnosis of EB.

REFERENCES

1. Bart BJ, Gorlin RJ, Anderson VE, Lynch FW: Congenital localized absence of skin and associated abnormalities resembling epidermolysis bullosa: A new syndrome. Arch Dermatol 93: 296-304, 1966.
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3. Frieden IJ. Aplasia cutis congenita: A clinical review and proposal for classification. J Am Acad Dermatol. 1986;14:646-60.
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PRESENTERS
Shani F. Smith, MD, Christiane Querfeld, MD, Christopher R. Shea, MD, Vesna Petronic-Rosic, MD, MSc, David Pitrak, MD, Aisha Sethi, MD

HISTORY OR PRESENT ILLNESS
A 47-year-old African-American man presented to clinic with a three-week history of two slowly enlarging, non-tender nodules in the right inguinal area. Six weeks earlier he had a genital herpes outbreak with several small erosions and ulcers in the same area. He denied any constitutional symptoms.

MEDICATIONS
Lopinavir/ritonavir, lamivudine, abacavir, hydroxychloroquine, leflunomide, prednisone, colchicine, and latanoprost ophthalmic solution

ALLERGIES
None

PAST MEDICAL HISTORY
HIV-positive since 1996, AIDS (defined in 2006 when he developed *Mycobacterium avium* complex infection), chronic renal insufficiency, genital herpes simplex virus (HSV) type 2 infection, gout, glaucoma

PHYSICAL EXAMINATION
At the right-hand base of the scrotum were two fixed, non-tender, pink, crusted, friable, verruciform nodules. There was neither inguinal lymphadenopathy nor other pertinent cutaneous findings.

LABORATORY DATA
Most recent CD4 count at time of exam was 153/μL. Tissue culture was positive for HSV-2 resistant to acyclovir with an ID50 of 11.59 mcg/mL (sensitive < 2mcg/mL). HSV-1 was not detected. Fungal and atypical mycobacterial cultures were negative.

DERMATOPATHOLOGY
Biopsy revealed pseudoepitheliomatous hyperplasia with surface erosions, focal multinucleated keratinocytes, and a dense diffuse plasma-cell-rich infiltrate Special stains for mycobacteria, fungi, and spirochetes were negative. Immunohistochemistry was positive for herpes simplex virus type 1/2 and negative for *Treponema pallidum*.

DIAGNOSIS
Verruciform genital herpes

TREATMENT & COURSE
The patient was initially treated with oral valacyclovir, 500 mg BID for one week, subsequently increased to 1000 mg BID due to treatment failure. The nodules continued to grow despite therapeutic augmentation and were ultimately excised. Intravenous foscarnet was considered, but not used because of potential renal toxicity. No inguinal recurrence was seen after eight weeks; however, an ulcerative penile outbreak recurred following valacyclovir discontinuation. Subsequent tissue culture was positive for acyclovir-sensitive HSV-2. The patient was restarted and currently remains on oral valacyclovir 1000 mg daily with chronic penile ulceration, but without recurrence of verruciform nodules.

DISCUSSION

Genital herpes is the most common cause of genital ulceration worldwide. Its association with concomitant HIV infection is well known. The clinical presentation of genital herpes simplex virus infection in immunocompetent patients is well recognized; however, atypical presentations have been described in immunocompromised individuals. These hypertrophic, nodular, and verruciform growths have pseudoepitheliomatous hyperplasia and dense lymphoplasmacytic infiltrates.

The pathogenesis of this unique, exaggerated inflammatory response remains unknown; an immune reconstitution phenomenon has been proposed. Immune restoration disease occurs in approximately 10-50% of patients after antiretroviral initiation. It results from the recovery of a pathogen-specific immune response and presents as tissue inflammation or cellular proliferative disease. Histopathologic studies reveal a proliferation of factor XIIIa-positive dendritic cells in hyperkeratotic lesions associated with HIV disease and suggest that increased production of TNFα may trigger keratinocyte proliferation and result in hyperkeratosis and acanthosis.

Acyclovir, valacyclovir, and famciclovir are first line therapies for primary and recurrent genital herpes simplex in patients with HIV infection, and increased dosages may be required to suppress outbreaks in this population. Acyclovir-resistant genital herpes has a higher prevalence in the AIDS population, particularly in chronic hyperkeratotic lesions. These lesions have been successfully treated with intravenous foscarnet, topical cidofovir, and imiquimod.

HIV-1 infection is a known modifier of the natural course of HSV-2 disease. Co-infection usually results in more chronic, atypical presentations of HSV-2 genital infection, especially with significant immune suppression present. Recent randomized, double-blind, placebo-controlled trials have explored the synergistic relationship between HSV and HIV and demonstrate that HSV-2 infection may facilitate HIV-1 acquisition. Therefore, effective recognition of atypical genital HSV-2 infection presentations can lead to early diagnosis and definitive suppression therapy, which could have significant implications for HIV-1 disease control.

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5. French, MA. Disorders of immune reconstitution in patients with HIV infection responding to antiretroviral therapy. 2007 Curr HIV/AIDS Rep 4:16-21

PRESENTERS
Carlos Paz, MD, PhD, Christopher R. Shea, MD, Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS
A 61-year-old man presented with a two-year history of multiple erythematous papules with atrophic hypopigmented centers on the torso and lower extremities. Two years prior to presentation the patient had been treated with topical steroids for a presumed arthropod assault, and then one year later with oral antibiotics for presumed folliculitis. Despite these treatments, the lesions have persisted without change in size, quality or quantity.

REVIEW OF SYSTEMS
The patient denied abdominal, neurologic, or ophthalmologic symptoms.

PAST MEDICAL HISTORY
Testicular cancer status-post chemotherapy; osteoarthritis of the cervical, thoracic and lumbar spine; dysphagia status-post dilatation of lower esophageal ring; nasoseptal deviation and bilateral turbinate hypertrophy status-post septoplasty and somnoplasty of bilateral turbinates; and chronic insomnia.

MEDICATIONS
Ibuprofen, esomeprazole, triazolam

ALLERGIES
None

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
The patient is a retired computer support manager. He does not smoke tobacco or drink alcohol, and denies recreational drug use. His travel history was unremarkable.

PHYSICAL EXAMINATION
Multiple erythematous papules and plaques with "porcelain white" atrophic centers were present on the abdomen and both legs. Several lesions had a subtle rim of telangiectases.

LABORATORY DATA
A complete blood cell count with differential, comprehensive metabolic panel, and fasting lipid panel were all within normal limits.

IMAGING STUDIES
GI esophogram (2002): A chronic-appearing erosion/ulcer was found in the distal esophagus.
Colonoscopy (2008): The colonic mucosa appeared entirely normal. There were no masses, polyps, or vascular abnormalities noted.

HISTOPATHOLOGY
Two 4-mm punch biopsy specimens from lesions on the abdomen demonstrated orthokeratosis and parakeratosis overlying an atrophic epidermis. Dermoepidermal separation was noted focally. There was a sparse superficial and deep perivascular infiltrate of lymphocytes and plasma cells. The dermis appeared devitalized and had a basophilic staining quality. The periodic acid-Schiff (PAS) stain showed focal areas of reduced or absent basement membrane

overlying areas of inflammation or sclerosis. The PAS stain was negative for fungi. The colloidal iron stain demonstrated increased interstitial dermal mucin.

DIAGNOSIS

Degos disease (malignant atrophic papulosis)

TREATMENT AND COURSE

The patient is currently being followed by the Dermatology, Neurology, Ophthalmology, and Gastroenterology services at the University of Chicago. To date, the patient has not exhibited extracutaneous symptoms of Degos disease.

DISCUSSION

Degos disease (DD) is small- and medium-vessel occlusive disease affecting the skin, gastrointestinal tract, central nervous system, and other organs. DD has a wide clinical spectrum, from a benign cutaneous variant to a fatal systemic condition. Since DD was described in 1941, approximately 200 cases have been reported in the literature.

The benign cutaneous variant is found in approximately 15% of patients with DD. These patients present with erythematous papules with white atrophic centers but no signs of systemic disease. Patients with the systemic variant develop a number of extracutaneous complications, including gastrointestinal perforation, neurologic hemorrhage, and visual deficits within a few months to years of the appearance of the cutaneous lesions. Death, usually from gastrointestinal perforation, typically occurs within 2-3 years from the onset of systemic symptoms.

The etiology of DD is unknown, although scant evidence suggests that it might be related to a viral infection, autoimmune condition, or coagulation defect. DD is primarily diagnosed based on physical examination and histopathology. DD has no predilection for age, sex, or race. On exam, patients present with the pathognomonic erythematous papules with “porcelain white” atrophic centers and telangectatic rims located on the torso and extremities. Histologically, these lesions can exhibit hyperkeratosis, epidermal atrophy, dermoepidermal separation, dermal necrosis, a superficial and deep perivascular infiltrate, and increased interstitial mucin.

Because DD is rare, a clear consensus on the appropriate work-up has yet to be reached. A history and physical examination focusing on gastrointestinal, neurologic, and ocular symptoms is appropriate, as are consultations from the gastroenterology, neurology, and ophthalmology services. A complete blood count, autoimmune studies and a coagulation panel may be obtained.

Unfortunately, early detection of systemic involvement has not led to a significant improvement in overall survival. No effective treatment for DD is known. Anti-coagulation and immunosuppressive medications have been tried without effect. Care is primarily supportive for those with systemic DD.

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PRESENTERS
Christiane Querfeld, MD and Christopher R. Shea, MD

UNKNOWN CASE

A 50-year-old man with past medical history of Wegener granulomatosis and status-post kidney transplant for severe renal involvement presented with a pruritic, slowly enlarging, oozing plaque on the left upper dorsal arm.

PRESENTERS

David J. Mann, MD, Emily A. Green, MD, Jason Cheng, MD, PhD, Irene J. Vergilis-Kalner, MD, Jerome Dickstein, MD, PhD, Vesna Petronic-Rosic, MD, MSc, and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS

Dermatology was asked to evaluate a 4-year-old Hispanic male with T-cell acute lymphoblastic leukemia *(*T-ALL) diagnosed in June 2007 who had widespread asymptomatic skin lesions present for seven months. One week prior to admission, the patient developed a cough, increased emesis, decreased appetite, and weight loss. A chest x-ray demonstrated a 9 x 7 cm mediastinal mass in the left upper lobe with multiple 1-2 cm noncalcified nodular masses in the middle and lower lungs.

PAST MEDICAL HISTORY

T-cell acute lymphoblastic leukemia (in remission), hypogammaglobulinemia (on monthly IVIG), pancytopenia, seizures secondary to intrathecal methotrexate toxicity. Immunizations up to date.

FAMILY HISTORY

No childhood cancer or leukemia.

SOCIAL HISTORY

Lives with his parents, no siblings, and is not in daycare.

MEDICATIONS AT THE TIME OF PRESENTATION

Bactrim, cytosine arabinoside and etoposide (T-ALL maintenance chemotherapy)

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

Scattered over the face, trunk, arms, legs, palms, and soles were numerous discrete erythematous papules, some surmounted by vesicles, others with central erosion, ulceration and hemorrhagic crust. Post-inflammatory hyperpigmentation at sites of old lesions. No lymphadenopathy or hepatosplenomegaly.

LABORATORY AND IMAGING DATA

CBC: WBC: 20.0 K/μL [4.0-13.8], H/H: 9.3/28.2 [11.3-13.2]/[34-40], platelets: 427 [150-450]
CMP: Carbon dioxide: 21 mEq/L [23-30], creatinine: 0.4 mg/dL [0.5-1.4], alkaline phosphatase: 94 U/L [100-390], SGOT: 19 U/L [8-37], SGPT: 12 U/L [8-35], PT:15.7s [12.0-14.5], PTT: 38.8s [24.0-34.0]
Normal: HBV, HCV, quant Ig, amylase, lipase, uric acid
CT Chest/Abdomen/Pelvis: 8.4 x 5.9 cm anterior mediastinal mass extending into the left hemithorax. Additionally, innumerable nodules in both lungs of varying sizes were seen, a few of which were subpleural. Three hypoattenuating lesions were found in the liver.
Bone scan: normal bone scintigraphy. No evidence of bony disease.
Osseous survey: multifocal vague lucencies of right femoral neck that may represent lesions of Langerhans cell histiocytosis, MRI recommended for further evaluation.
MRI pelvis (right femoral neck): no findings to correlate with the lucencies seen on plain films.

DERMATOPATHOLOGY

H & E: a biopsy from the right leg showed irregular hyperplasia of the epidermis surmounted by a purulent and hemorrhagic scale crust. A dense interstitial infiltrate composed of monomorphous

histiocytes with kidney-shaped nuclei and abundant cytoplasm was present in the dermis. Occasional eosinophils were also present. S-100 and CD1a strongly stain all the neoplastic cells. CD3, CD7, and terminal deoxynucleotidyl transferase (TDT) are essentially negative (ruling out the possibility T-ALL). CD34 stains dermal dendritic cells in slightly elevated numbers.

PULMONARY HISTOLOGY

H & E: core biopsies of the lung showed sheets of medium to large neoplastic cells with abundant cytoplasm and eccentric nuclei. The nuclei were round to ovoid in shape with numerous folds. Eosinophils were also scattered through the infiltrate. CD68, CD4, CD11b, CD11c, and CD14 strongly stain the neoplastic cells. S-100 is focally positive. CD1a is negative. CD3 is negative.

DIAGNOSES

Skin: Langerhans cell histiocytosis (LCH)
Pulmonary: Histiocytic neoplasm, not otherwise specified

TREATMENT AND COURSE

Given the new diagnoses of LCH and pulmonary histiocytic neoplasm, in the setting of T-ALL, a chemotherapy protocol that combined T-ALL maintenance with LCH treatment was instituted. The initial regimen included etoposide, cytosine arabinoside, vinblastine, and high-dose prednisone. Poor response in both skin and pulmonary disease prompted a change to cladribine, vincristine, and decadron. Consideration is being made for surgical debulking of the pulmonary mass when feasible.

DISCUSSION

Langerhans cell histiocytosis (LCH) is an idiopathic reactive disorder characterized by the proliferation of antigen presenting cells known as Langerhans cells which are derived from the bone marrow. The accumulation of these cells may occur in various organs, including the skin, lungs, and bone, among others. Staging of patients depends on the degree of organ involvement and the evidence of damage. LCH is a rare disease with an incidence estimated from 0.5-5.4 cases per million persons per year with a 2:1 male-to-female ratio. Most published data is derived from children though LCH may occur at any age.

Currently, the Histiocyte Society has divided histocytic disorders into three groups: (1) dendritic cell histiocytosis, (2) erythrophagocytic macrophage disorders, and (3) malignant histiocytosis. LCH falls into the first category whereas histiocytic sarcomas would fit into the last. However, the characterization and categorization of histiocytic proliferations remains a controversial topic as the pathogenesis remains unknown. In 1998, an association between T-ALL and LCH was reported in twelve cases by the Langerhans-Cell Histiocytosis-Malignancy Group. In five of these cases, the LCH presented 3.5-7 years before a diagnosis of T-ALL, whereas in seven cases, the LCH presented 6-12 months after a diagnosis of T-ALL. These authors theorized that the former situation may be attributed to LCH chemotherapy promoting a secondary malignancy. On the other hand, these authors suggested that the latter group of patients may be the result of a chance occurrence, or perhaps such individuals possess a genetic predisposition, with or without the immunosuppression associated with the leukemia therapy, ultimately leading to the expression of disseminated LCH.

A report by Feldman *et al* described two additional cases of LCH associated with a precursor T-lymphoblastic leukemia/lymphoma. A 5-year-old with a T-cell lymphoblastic leukemia developed cutaneous LCH on the penis 2-years after the leukemia diagnosis. The second case involved an 8-year-old with a 2-month history of a skin rash. Biopsy demonstrated LCH and

imaging studies at that time detected mediastinal and renal masses. Mediastinal biopsy showed precursor T-lymphoblastic lymphoma. Flow cytometry and immunohistochemical analyses showed a similar immunophenotype for precursor T-lymphoblastic leukemia/lymphoma in both patients. The LCH tumors in both patients had similar histology and were S100 and CD1a positive. PCR for analysis of rearrangements in the gene for T-cell receptor showed bands of similar molecular weight from the samples of precursor T-lymphoblastic leukemia/lymphoma, and LCH in each patient. The authors concluded that the two diseases may derive from a common neoplastic progenitor cell. Or perhaps these cases serve as further evidence of lineage switching, a concept previously demonstrated by data from Xie *et al* which showed differentiated B cells could be reprogrammed immunophenotypically and functionally into macrophages. While this case report was very brief, both cases apparently needed aggressive therapy for response even in the skin disease.

While the pathogenesis of these cases remain uncertain, the relationship between T-ALL and LCH raised the question of whether or not our patient's third malignancy was also clonally related. Indeed, cytogenetic analysis of our patient's pulmonary histiocytic neoplasm was compared to that of the T-ALL and showed a common clone, again suggesting a common neoplastic progenitor.

Furthermore, Frater *et al.* described a case in which a patient had a histiocytic sarcoma of the tonsil that was CD1a negative with secondary involvement of the skin which expressed CD1a. The morphology and remaining phenotype of the two tumors was identical, leading the authors to suggest that the two were related. They proposed that the expression of CD1a by some of the tumor cells resulted in a subset of the tumor cells homing to the skin.

In summary, we believe that that this patient's three malignancies are the likely result of a common neoplastic progenitor cell. Investigating the associations of multiple malignancies in a single patient is an important endeavor which may ultimately deepen our understanding of neoplastic biology.

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PRESENTERS
John C. Fox, MD, Christiane Querfeld, MD, Keyoumars Soltani, MD, Christopher R. Shea, MD, Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS
A 44-year-old Caucasian man with a history of multiple myeloma, cryoglobulinemia, and undifferentiated spondyloarthropathy was hospitalized for a one-month history of increasing lower extremity rash and skin ulcerations despite pulse dexamethasone therapy and plasmapheresis for worsening cryoglobulinemia. Review of systems was positive for an associated new-onset peripheral neuropathy.

PAST MEDICAL HISTORY
Multiple myeloma
Cryoglobulinemia
HLA-B27 undifferentiated spondyloarthropathy
Asthma
Tobacco history (less than 1/2 pack per week, quit 18 years ago)

MEDICATIONS
Prednisone 60 mg daily
Pulse dexamethasone (4 days on, 4 days off cycle)
Plasmapheresis
Esomeprazole
Moxifloxacin
Estazolam
Acetaminophen

ALLERGIES
None

PHYSICAL EXAMINATION
Both legs exhibited a prominent, mottled, reticulated, violaceous discoloration in a vascular pattern. Numerous areas of non-inflammatory retiform purpura were also present along the distal lower extremities and dorsal feet, some with central ulceration and eschar formation.

LABORATORY DATA
Abnormal laboratory values: Cryoglobulin: <0.05%; however, cryoglobulin = 25% by volume, four days prior to admission, before plasmapheresis [reference range 0-0.05%]
WBC 12.3 K/microL, Hct 33.2%, IgG 1658 mg/dL, IgA 12 mg/dL, IgM 20 mg/dL
Serum protein electrophoresis (SPEP): monoclonal gammopathy
Normal: CMP, ionized Ca^{++}, ANA, anti-ds DNA, anti-SSA/SSB, lupus-like anticoagulant Ab, C_4, ESR, CRP, RPR, HIV, hepatitis panel

DERMATOPATHOLOGY
A punch biopsy specimen from the left lower leg exhibited extensive ischemic changes represented by a necrotic epidermis with separation of necrotic keratinocytes at various levels within the epidermis and frank necrosis of adnexal structures. Extensive extravasation of erythrocytes was present within the papillary dermis, and numerous fibrin thrombi were identified within the superficial dermal vasculature. Vascular endothelial cells exhibited swelling and focal necrosis, but only a sparse perivascular neutrophilic infiltrate was present, without frank leukocytoclastic vasculitis. The subcutis was unremarkable. Gram and methenamine silver stains

were negative for microorganisms, and the periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening.

Direct immunofluorescence of lesional skin demonstrated fibrinogen deposition within dermal vessels and epidermis.

DIAGNOSIS

Ischemic necrosis and thrombotic vasculopathy, consistent with Type I cryoglobulinemia

TREATMENT AND COURSE

Upon discharge, the rheumatology service initiated lenalidomide 25 mg daily (25 day cycle) with four days of pulse dexamethasone followed by four days of 30 mg oral prednisone, with a subsequent slow taper. The patient's cryoglobulinemia had resolved over the hospital course, and plasmapheresis was continued on an intermittent basis, without further elevation in plasma cryoglobulins. Ulcers continued to heal on a topical regimen of mupirocin ointment and Vaseline gauze dressings and completely resolved without recurrence. The patient ultimately underwent an allogeneic bone marrow transplantation and has done very well, with resolution of both the spondyloarthropathy and cryoglobulinemia; however, a persistent, low-level IgG gammopathy remains.

DISCUSSION

Cryoglobulins are plasma and serum immunoglobulins that reversibly precipitate at temperatures below 37ºC. They are detectable in a wide variety of diseases, including malignancies, infections, and systemic autoimmune disorders. Cryoglobulinemia describes the presence of circulating cryoglobulins and may cause disease through vascular occlusion or immune complex vasculitis

Cryoglobulins, and thus cryoglobulinemias, are classified into types I-III. Type I cryoglobulins are monoclonal immunoglobulins, most commonly IgM or IgG, though IgA and light chains have been described. Type II is a mixed cryoglobulinemia, in which cryoglobulins consist of a monoclonal immunoglobulin (IgM>IgG) that binds the Fc portion of polyclonal IgG, demonstrating so-called rheumatoid factor activity. Type III cryoglobulinemia is also mixed, but consists of polyclonal immunoglobulins that also have Fc-binding properties. Rare variants that do not fit this classification have also been described. Classically, type I cryoglobulinemia is associated with an underlying plasma cell dyscrasia or lymphoproliferative disorder, while the mixed cryoglobulinemias are associated with infections or autoimmune diseases, *e.g.*, hepatitis C, HIV, rheumatoid arthritis, lupus, and Sjögren syndrome).

Cutaneous manifestations of cryoglobulinemia most commonly affect acral sites susceptible to cold exposure and include purpura (often retiform), ulcerations, acral cyanosis, Raynaud phenomenon, and livedo reticularis. Type I cryoglobulins typically cause clinical symptoms through microvascular occlusion, forming non-inflammatory retiform purpura with areas of necrosis. Long-standing lesions may develop secondary vasculitis and present a more inflammatory picture. Mixed cryoglobulins more frequently induce lesions by immune complex mechanisms, leading to palpable purpura, often clustering in dependent body areas. Therapy for cryoglobulinemia includes minimizing cold exposure and controlling the underlying plasma cell dyscrasia or lymphoproliferative disorder to reduce the titer of monoclonal cryoglobulin.

Lenalidomide is an analogue of the immunomodulatory drug thalidomide, which has been demonstrated to be not only 100 – 1000 times more potent than its parent compound, but also to have a significantly lower incidence of neuropathy and sedation. In combination with

dexamethasone, lenalidomide has been shown to delay progression of relapsed or refractory multiple myeloma, and has various mechanisms of action which include down-regulation of pro-inflammatory cytokines TNF-α, IL-1, IL-6, IL-12, inhibition of angiogenesis, and direct anti-tumor activity.

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PRESENTERS
Shaily Patel, MD and Christopher R. Shea, MD

UNKNOWN CASE

This 24-year-old male with a history of dilated cardiomyopathy, status-post heart transplant, biventricular thrombi, and recent cardiac catheterization presented with a two-day history of extremely painful, rapidly enlarging lesions on the left thigh.

PRESENTERS
Brian E. Pucevich, MD, Diana Bolotin, MD, PhD, Christopher R. Shea, MD and Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS
This 48 year-old Caucasian male presented in May of 2009 for evaluation of a non-painful, non-pruritic eruption on his right chest. The rash was first noticed approximately 12 months prior to presentation. Initially, the patient observed a few red papules on his right chest that slowly increased in number and size over a period of a few months. After 6 months, the rash stabilized without waxing or waning. Review of systems was unremarkable.

PAST MEDICAL HISTORY
Seizure disorder, invasive ductal carcinoma diagnosed March 2009 stage IV on therapy with Tamoxifen

MEDICATIONS
Dilantin 400 mg daily, phenobarbital 120 mg daily, tamoxifen 20 mg bid, zoledronic acid 4 mg IV monthly

ALLERGIES
None

FAMILY HISTORY
The patient has a family history of breast cancer; both the paternal and maternal grandmothers were diagnosed with breast cancer in their 50's. Additionally, the patient had a paternal cousin who passed away from breast cancer at age 44. The patient's mother and father both had a history of lung cancer.

SOCIAL HISTORY
The patient is married, lives with his wife and two children, and works as a commodities broker. He denies illicit drug use and current tobacco use. He previously smoked 1 pack per week for about 15 years and occasionally consumes alcohol.

PHYSICAL EXAM
On the right chest there are discrete, non-tender, non-scaly, red to slightly violaceous papules measuring 0.5cm. The papules are grouped into larger plaques measuring 1 to 2cm in diameter with the large plaques having a deep nodular component upon palpation. There is visible retraction of the right nipple and diffuse swelling of the right pectoral area. There is a palpable non-tender right axillary node measuring 2.5cm and left non-tender axillary lymphadenopathy measuring 1.5cm in largest diameter. There was no detectable occipital, cervical, clavicular or inguinal lymphadenopathy.

HISTOPATHOLOGY
Right medial and lateral breast 4mm punch biopsies: Sections of skin with unremarkable epidermis. The reticular dermis contains and infiltrate of atypical epithelioid cells forming ducts, embedded within a densely desmoplastic stroma. High grade cytologic atypia and prominent mitotic figures are noted.

DIAGNOSIS
Infiltrative adenocarcinoma, consistent with metastatic mammary carcinoma.

LABORATORY, RADIOLOGIC and SURGICAL PATHOLOGY

CBC, BMP, LFT's: Within normal limits
CA 15-3: 217.2 (normal range 0-30)
Mammography, right breast: 2.6x2.8cm spiculated mass with 1.2cm right axillary mass.
MRI Chest: 2.8x2.9cm right breast mass with a 3.6cm right axillary mass and a 1.5x1.7cm left axillary lymph node.
Right breast core needle biopsy: Invasive ductal carcinoma with perineural invasion, estrogen and progesterone receptor positive, HER2/neu negative by FISH.
CT Thorax, abdomen, pelvis with PET: Multiple small pulmonary nodules largest nodules measuring 1.1cm on the right and 1.3cm on the left, with multiple liver lesions the largest of which was 1.6cm lesion see in the left lobe. Positive FDG avid uptake in the lungs, liver, breast, bilateral axillary, mediastinal, hilar, and retroperitoneal nodes
MRI brain: No metastatic foci visualized
Bone scan: Positive uptake seen in the T3, T4 and T12 vertebral bodies

TREATMENT

Due to the patients widespread metastatic disease at diagnosis, surgical and radiation therapy were not pursued. Hormonal therapy with tamoxifen 20mg bid and zoledronic acid 4mg IV monthly for the patient's bone metastases were continued by oncology. Tamoxifen was stopped due to progression of disease and an alternative estrogen receptor antagonist, fulvestrant, was begun at 250mg IM monthly. CA 15-3 levels have remained elevated and unchanged. Most recent CT imaging has shown an increase in size of the patient's bone and liver metastases with a new T12 pathologic fracture. Currently, oncology is considering a switch to multi-agent chemotherapy.

DISCUSSION

Breast cancer in men is rare. On average, men who develop breast cancer are 67 years old, about 10 years older than their female counterparts. The American Cancer Society (ACS) estimates that there will be 1910 new cases of invasive breast cancer in men in the United States in 2009. The ACS also estimates that 440 deaths in 2009 will be attributed to male breast cancer. Incidence of male breast cancer has remained unchanged for the previous three decades. The overall life-time risk of men developing breast cancer is estimated to be 1/1000.

Ionizing radiation exposure has been shown to increase risk of breast cancer in men. Twenty percent of men with breast cancer have a family history of breast cancer and imposes a 4 fold increase in lifetime risk of breast cancer development. BRCA2 gene mutation is seen in 10% of male breast cancer. BRCA2 cancers typically exhibit early onset in men prior to age 60. Androgen receptor mutations have been described in male breast cancer. Decrease in protective androgenetic effect on male breast tissue has been postulated to contribute to male breast cancer oncogenesis.

Clinically, male breast cancer presents most commonly as a unilateral painless sub-areolar mass. Associated presenting signs in up to 50% of patients include: nipple retraction, bleeding, discharge, ulceration and/or pain. There is a delay between onset of symptoms and evaluation/diagnosis of breast cancer. The delay is thought to explain the fact that men present at later stages of disease compared to women.

Ninety percent of male breast cancers are invasive carcinomas. Infiltrating ductal carcinoma accounts for more than 80% while papillary carcinoma for 5% of male breast cancers. The 10% that are non invasive are almost all ductal carcinoma in situ. Lobular carcinoma in situ is rarely seen owing to the absence of terminal lobules in normal male breast tissue. Pooled analysis of

several studies found estrogen receptor expression in 81% of cancers and progesterone receptor positivity in 74% of tumors. Conversely, relatively few male breast cancers exhibit HER2/Neu protein over-expression.

Treatment depends on stage at diagnosis. Non-metastatic disease is treated with modified radical mastectomy and axillary dissection. Therapy with tamoxifen in non-metastatic therapy is considered beneficial. Over a 5-year period, 61% of patients treated with tamoxifen survived versus 44% who did not receive tamoxifen. Metastatic disease is treated first line with tamoxifen. When used to treat estrogen receptor positive tumors, 69% of patients respond to treatment with tamoxifen.

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PRESENTERS
Tunisia Finch, MD, Shaily Patel, MD, Sarah L. Stein, MD

PATIENT A

HISTORY OF PRESENT ILLNESS
An 11 year old male presented with a four month history of asympomatic white raised lesions on bilateral palms which were accentuated after his hands were submerged in water. The application of over-the-counter lamisil cream, aluminum chloride pads, and desoximetasone cream did not result in any improvement of the condition.

PAST MEDICAL HISTORY
None

REVIEW OF SYSTEMS/FAMILY HISTORY/SOCIAL HISTORY
Review of systems was negative for hyperhidrosis and trauma. Family history was negative for cystic fibrosis and atopy. Social history was non-contributory.

MEDICATIONS
Desoximetasone cream, aluminum chloride pads

ALLERGIES
None

PHYSICAL EXAMINATION
Macerated, white, hyperkeratotic plaques with visible puncta were present on the central palms bilaterally.

DIAGNOSIS
Aquagenic Palmoplantar Keratoderma

TREATMENT AND COURSE
The patient had complete clearance of the lesions after the application of aluminum chloride hexahydrate 20% solution for 10 days. The patient is no longer applying aluminum chloride hexahydrate 20% solution and has had no recurrence of symptoms on reexposure to water.

PATIENT B

HISTORY OF PRESENT ILLNESS
A 13 year old male with a history of cystic fibrosis and psoriasis presented with a several year history of asymptomatic white lesions on bilateral palms that were accentuated when his hands were soaked in water. The application of mometasone ointment to the lesions did not result in improvement of the condition.

PAST MEDICAL HISTORY
Cystic fibrosis, nasal polyps and chronic sinusitis, psoriasis, seasonal allergies

REVIEW OF SYSTEMS/FAMILY HISTORY/SOCIAL HISTORY
Review of systems revealed that the palms were intermittently moist and bothersome. Family history was positive for atopy. Social history was non-contributory.

MEDICATIONS
Mometasone ointment, pancrelipase, ranitidine, vitamins A,D,E and K, amoxicillin/clavulanate, cetirizine

ALLERGIES
None

PHYSICAL EXAMINATION
Ill-defined lacy white plaques with visible puncta on the central palms as well as on the edges of fingers. The hands did not feel moist.

DIAGNOSIS
Aquagenic Palmoplantar Keratoderma in the setting of cystic fibrosis

TREATMENT AND COURSE
The patient had complete clearance of the lesions after the application of a urea containing cream for a few weeks. The patient is no longer using the urea containing cream and has had no recurrence of symptoms on reexposure to water.

DISCUSSION
Aquagenic palmoplantar keratoderma (APPK) also known as 'transient reactive papulotranslucent acrokeratoderma' and 'aquagenic syringeal acrokeratoderma' is an acquired and transient punctuate keratoderma in which patients develop whitish to transluscent, pebbly, papular thickening of the palms and soles 3-10 minutes after exposure to water. The cutaneous changes disappear after drying within minutes to an hour. It typically develops during the second decade of life. Patients may present with the 'hand in bucket' sign, presenting to the physician with a hand immersed in a bucket of water to demonstrate the physical findings. APPK is known to spontaneously remit and patients may have periods of complete remission during which no reaction results from water exposure.

The cause of APPK remains an enigma and has been postulated to be due to an aberration of the sweat duct, hyperkeratosis, friction, or defective barrier function of the stratum corneum. Increased water-binding capacity of keratinocytes mediated by increased sodium concentrations has also been suggested. Histologically, dilated eccrine ostia and a mildly orthokeratotic hyperkeratotic stratum corneum may be seen.

It is important to differentiate APPK from hereditary papulotranslucent acrokeratoderma (HPA) which is morphologically identical. HPA is an autosomal dominant condition characterized by bilateral, translucent yellowish white, smooth papules and plaques occurring primarily only along margins and pressure/trauma points of the hands and feet. This condition appears soon after puberty and is associated with an atopic diathesis and fine textured scalp hair. Unlike APPK, HPA lesions persist and gradually increase in size and number over time.

The relationship of APPK to cystic fibrosis (CF) is unclear. Cases of APPK have been reported in CF patients and cases of 'aquagenic palmar wrinkling' (APW) in CF patients have been reported. In the APW cases that have been reported, patients presented with an identical clinical and histological picture to those patients with APPK. Abnormal CF transmembrane conductance regulator (CFTR protein) regulation of cell membrane water channels (aquaporin 3) may mediate APW in patients with CF. APW has also been reported in a known carrier of CF. Further studies are needed to confirm the reliability of the association; however, consideration should be given to screening patients with APW and APPK for CF.

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PRESENTERS
Diana Bolotin, MD, PhD, Vesna Petronic-Rosic, MD, MSc, and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A 12-day old Hispanic male was seen in the neonatal intensive care unit (NICU) for red indurated lesions on his back and right cheek. The patient was a full term neonate whose delivery was complicated by meconium stained amniotic fluid. He was transferred to the NICU due to tachypnea and completed a 12-day course of ampicillin and cefotaxime for presumed meningitis. On the 6th day of life, the patient developed supraventricular tachycardia (SVT) that was treated with ice therapy and adenosine. The longest run of SVT, lasting 20 to 30 minutes, occurred on the 8th day of life and was treated with ice, adenosine and propranolol. Following ice therapy, the patient's body temperature was recorded at 35.7°C, but normalized under a heat lamp. There was no history of trauma. Within the following 72 hours, the nursing staff noted skin lesions on the neonate's back and cheek.

PAST MEDICAL HISTORY
Supraventricular tachycardia
Wolff-Parkinson-White Syndrome

REVIEW OF SYSTEMS / FAMILY HISTORY / SOCIAL HISTORY
Non-contributory

MEDICATIONS
Propranolol
Adenosine

ALLERGIES
None

PHYSICAL EXAMINATION
On physical exam, the baby was in no distress. Red, hard indurated plaques were present on the patient's upper central back and extending to the occipital scalp. A 5mm firm nodule was present on the patient's right cheek.

DERMATOPATHOLOGY
A 4mm punch biopsy from an upper back lesion showed a lobular mixed inflammatory cell infiltrate of eosinophils, neutrophils and histiocytes at the junction of the dermis and subcutis. No needle shaped clefting or deep subcutaneous fat involvement was present.

DIAGNOSIS
Cold panniculitis due to ice therapy for arrhythmia

TREATMENT AND COURSE
The skin lesions resolved within two weeks without treatment.

DISCUSSION
Cold panniculitis, also known as Haxthausen's disease, is most frequently seen in the neonatal period and in infancy. To date, four cases of panniculitis following ice pack treatment for SVT have been reported. Three of these were diagnosed clinically as cold panniculitis without pathologic confirmation of the diagnosis and one showed histopathology more consistent with

subcutaneous fat necrosis of the newborn (SFNN). Our case is the first histologically confirmed report of cold panniculitis following ice pack treatment for SVT.

Typically, cold panniculitis presents with red or flesh colored indurated plaques on the face, trunk, thighs or other fatty areas of the body exposed to cold. It is thought that this condition preferentially affects neonates because of the high proportion of saturated fatty acids in the newborn subcutis. Saturated fatty acids have a higher solidification point resulting in adipocyte damage after a short cold exposure. Although cold panniculitis can be clinically indistinguishable from SFNN, the two conditions do have different histopathologic findings. Biopsy of cold panniculitis classically reveals a mostly lobular panniculitis with intense mixed inflammatory infiltrates at the junction of deep dermis and subcutaneous fat. Unlike SFNN, cold panniculitis does not involve the entire subcutis and does not exhibit needle shaped crystals within adipocytes.

While skin findings in both of the above conditions usually resolve spontaneously, it is important to accurately determine the diagnosis given the known associations of SFNN with hypercalcemia and, less frequently, thrombocytopenia and hypertriglyceridemia. Our case demonstrates cold panniculitis as a side effect of ice-pack therapy for SVT and serves to advise practitioners about repeated prolonged ice therapy for treatment of SVT in neonates.

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PRESENTERS
David J. Mann, MD, Diana Bolotin, MD, PhD, Vesna Petronic-Rosic, MD, MSc, Keyoumars Soltani, MD and Christopher R. Shea, MD

PATIENT A:

HISTORY OF PRESENT ILLNESS
A 20-year-old African-American man with acute myelogenous leukemia, status-post haplo/cord stem cell transplant in January 2008, was seen in consultation for a necrotic left dorsal hand lesion. Present on admission to the intensive care unit seven days prior, the lesion remained unchanged and asymptomatic.

PAST MEDICAL HISTORY
Acute myelogenous leukemia, thrombotic thrombocytopenic purpura, graft versus host disease, fungal pneumonia, vancomycin-resistant enterococci bacteremia, and hypertension.

FAMILY HISTORY / SOCIAL HISTORY
Non-contributory

MEDICATIONS
Acyclovir, cefepime, hydrochlorothiazide, levetiracetam, methylprednisolone, metronidazole, posaconazole, rituximab, sulfamethoxazole and trimethoprim, vancomycin

ALLERGIES
Prochlorperazine

PHYSICAL EXAMINATION
A 2.5 cm necrotic plaque with central eschar and peripheral ecchymoses surrounded by a decompressed bulla was present on the left lateral dorsal hand. 3+ pitting edema was present on all of the extremities. Blanchable scaly lichenoid papules were noted on the face, chest and bilateral arms.

LABORATORY AND IMAGING DATA
CBC: WBC: 5.3 K/μL [3.4-11], H/H: 10.9/31.2 [13.5-17.5]/[41-53], platelets: 11 [150-450]
CMP: Chloride: 109 mEq/L [95-108], carbon dioxide: 18 mEq/L [23-30], blood urea nitrogen: 55 mg/dL [7-20], creatinine: 3.4 mg/dL [0.5-1.4], GFR estimate (Calc): 23 mL/min/BSA [>59], calcium: 8.1 mg/dL [8.4-10.2], total protein: 4.3 g/dL [6.0-8.3], albumin: 2.1 g/dL [3.5-5.0], bilirubin total: 1.1 mg/dL [0.1-1.0], bilirubin conjug.: 0.5 mg/dL [0.0-0.3], alkaline phosphatase: 616 U/L [30-120], SGOT: 54 U/L [8-37]
LDH: 1046 U/L [116-245]
BNP: 159,536 pg/ml [<125]
Blood cultures:negative x 2
CT Chest (2 weeks before presentation): pleural and pericardial fluid, nodular/necrotic lesions in left lower lung, ground glass opacities seen at right base.
CT Chest (1 day after biopsy): Large bilateral pleural effusions. Patchy, irregular spiculated consolidations were present in bilateral upper lobes, consistent with active fungal infection.

DERMATOPATHOLOGY
H & E: a biopsy specimen from the left hand showed a completely necrotic epidermis and coagulative necrosis in the dermis. In the deep dermis and subcutis, collections of neutrophils and

fungal organisms with branched hyphae were noted, several of which had invaded the wall of a thrombosed and necrotic blood vessel.
PAS & GMS stains confirmed the presence of fungi at all levels within the tissue
Fite & Gram were negative for microorganisms
Tissue culture: few non-septate hyphae identified as *Rhizopus spp*

DIAGNOSIS
Mucormycosis

TREATMENT AND COURSE
Micafungin was added to the posaconazole, and silver sulfadiazine dressings were continued. Orthopedic debridement was considered but not performed given the patient's persistent thrombocytopenia which had failed trials of pulse steroids, rituximab and plasmapheresis. The patient's immunologic, respiratory, neurologic, and renal systems continued to worsen. Ultimately, the family elected palliative care and the patient died shortly thereafter.

PATIENT B

HISTORY OF PRESENT ILLNESS
A 47-year-old Caucasian woman with chronic myelogenous leukemia status-post matched unrelated stem-cell transplant in December 2008 was admitted from the hematology-oncology clinic for a red and tender left upper arm lesion. The patient was started on clindamycin for a presumed bacterial cellulitis one day prior to admission without response. The patient reported widespread non-tender eschars that "would crust and fall off" for several month prior to this admission that were attributed to skin fragility in the setting of thrombocytopenia. She denied recent fever or chills.

PAST MEDICAL HISTORY
Chronic myelogenous leukemia, vancomycin-resistant enterococci bactermia, hand-foot syndrome, diabetes, and hypothyroidism, pulmonary Nocardiosis

FAMILY HISTORY
Hemophilia in mother, father and brother

SOCIAL HISTORY
Non-contributory

MEDICATIONS
Amlodipine, clindamycin, dapsone, impinenem, levetiracetam, levothyroxine, quetiapine, valacyclovir, voriconazole

ALLERGIES
Codeine, sulfa

PHYSICAL EXAMINATION
The left arm had an edematous, indurated, painful red 2.0 cm plaque with a 1.5 cm round eschar. Multiple smaller dusky crusts and round eschars were noted on bilateral upper and lower extremities along with fine red scaly papules on the back.

LABORATORY AND IMAGING DATA
CBC: WBC: 1.5 K/μL [3.4-11], H/H: 7.7/21.6 [11.5-15.5]/[36-47], platelets: 31 [150-450]

CMP: Creatinine: 0.4 mg/dL [0.5-1.4, calcium: 8.2 mg/dL [8.4-10.2], total protein: 5.7 g/dL [6.0-8.3], albumin: 3.4 g/dL [3.5-5.0], alkaline phosphatase: 145 U/L [30-120], SGOT: 60 U/L [8-37], SGPT: 98 U/L [8-35]
CK: < 20 U/L [9-185]
Blood culture: Coagulase negative *Staphylococcus spp*
Sinus CT: Chronic pansinusitis was noted without osteolysis

DERMATOPATHOLOGY
H & E: left arm debridement tissue showed ulceration with necrosis and fungal organisms morphologically consistent with *Rhizopus spp.* **GMS** stain was positive
Tissue culture: few non-septate hyphae identified as *Rhizopus spp*; bacterial and acid-fast bacilli cultures were negative

DIAGNOSIS
Mucormycosis

TREATMENT AND COURSE
Amphotericin B and posaconazole were started and a wide debridement of the lesion on the left arm was performed by plastic surgery. The tenderness and drainage slowly resolved and no evidence of systemic mucormycosis was identified by CT. Two weeks after discharge, at an outpatient plastic surgery appointment, the patient showed continued improvement of the wound without fevers or drainage. Unfortunately, she was readmitted from clinic two weeks later for nausea and vomiting and deteriorated rapidly. She passed away on hospital day twenty, after self-extubation. Autopsy showed evidence of sepsis, ARDS, and obstructive jaundice. Blood cultures were negative.

DISCUSSION
Mucormycosis is an invasive opportunistic infection caused by fungi belonging to the order Mucorales. While extremely rare in immunocompetent individuals, this condition can be devastating to the immunocompromised population with mortality as high as 90% in those with disseminated disease. One US cancer center calculated that twenty patients per 100,000 admissions had the disease, and reported an incidence of 0.7% at autopsy.

Rhizopus species are the most common cause of mucormycosis with *Mucor* and *Absidia* comprising the other genera. Classically, 50% of cases involve rhinocerebral disease; other sites of involvement include lung, skin, and gastrointestinal tract. Due to the lack of serologic laboratory tests, the diagnosis of mucormycosis can be quite difficult.

As in our cases, cutaneous mucormycosis may present clinically as a tender, indurated, large plaque with a dusky center. The lesion may result from primary or secondary processes that often involve states of immune dysfunction.

As dimorphic fungi, Mucorales organisms exist in the natural environment as molds that become hyphal forms when in tissue. Histopathologically, mucormycosis can appear quite variable, with different degrees of inflammation. The identification of fungal elements on H & E stains are of considerable help in confirming the diagnosis. Broad and non-septate hyphae branch at right angles and often invade vessel walls with resulting necrosis.

The goal of treatment is to combine surgical resection of infected tissue with oral antifungal therapy as quickly as possible. This is particularly essential in cases localized to the skin. A recent case report documented successful treatment of systemic mucormycosis with liposomal

amphotericin B and posaconazole without surgical intervention. Other studies have demonstrated the benefits of combination oral treatment using amphotericin B plus caspofungin vs. amphotericin B alone (100% success vs. 45%, respectively) along with increased survival time in patients with rhino-orbital-cerebral mucormycosis.

For patients at increased risk, such as ours, focusing on prevention is critically important. Two recent trials found posaconazole to be superior to both fluconazole and itraconazole at preventing infection. However, other reports have shown breakthrough infections despite this regimen as demonstrated in patient A.

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PRESENTERS

Shani F. Smith, MD, Christiane Querfeld, MD, Vesna Petronic-Rosic, MD, MSc and Christopher R. Shea, MD

HISTORY OR PRESENT ILLNESS

A 65-year-old Caucasian woman presented to clinic with a five-month history of swelling and thickening of the distal upper and lower extremities. She had previously undergone an extensive cardiovascular work-up, which was found negative for cardiovascular disease but revealed an enlarged right inguinal lymph node that was excised. A review of systems was notable for extremity swelling and stiffness of the elbows, knees, and hands resulting in loss of ability to close the hands. She denied any current constitutional symptoms but did report difficulty sleeping and a recent history of weight loss.

MEDICATIONS

Levothyroxine, furosemide, potassium, alendronate, multi-vitamin, vitamins C and D, calcium, *Acidophilus*, chromium picolinate, aspirin, sudafed prn

ALLERGIES

Penicillin, sulfa

PAST MEDICAL HISTORY

Lichen sclerosus et atrophicus in 2004 (resolved with topical corticosteroids), hypothyroidism

FAMILY HISTORY/ SOCIAL HISTORY

Non-contributory

PHYSICAL EXAMINATION

There was localized edema of the extremities with indurated, erythematous plaques on both volar forearms and both pretibial areas. Sparing of hands and feet was noted; however, there was diminished flexural range of motion observed in bilateral fingers, wrists, and ankles.

LABORATORY DATA

Complete blood count: Hemoglobin 15.7 g/dL [11.7-15.5], eosinophils 2288 cells/μL [<500]
Normal labs: Complete metabolic panel, thyroid studies, ANA, dsDNA, ANCA, SSA/SSB, Jo-1, centromere B, RNP, Scl-70, PM-Scl, RF, centromere, CCP, ESR and urinalysis
CMV IgG antibody titer: 3.55 [Positive: ≥1.10]
CMV IgM antibody titer: 1.25 [Positive: ≥1.10]

IMAGING

CT Chest: multiple lymph nodes with reniform shape and fatty hila in the axillary region, fatty infiltrate. Nonspecific.
CT Abdomen: positive bilateral small inguinal lymph nodes. Subcutaneous edema in proximal thigh noted.

SURGICAL PATHOLOGY

Right inguinal lymph node biopsy: reactive lymph node, some rare large cells and subtle linear fibrosis.

DERMATOPATHOLOGY

Biopsy revealed thickened and fibrotic fascia with a mixed inflammatory cell infiltrate rich in eosinophils.

DIAGNOSIS

Eosinophilic Fasciitis

TREATMENT & COURSE

The patient has received oral prednisone, 60 mg daily, and is participating in physical therapy. Her musculoskeletal function and skin continue to improve.

DISCUSSION

Eosinophilic fasciitis is a rare, sclerodermoid syndrome first described in 1974 by Shulman in patients with diffuse fasciitis and peripheral eosinophilia. The clinical spectrum of this disease is highly variable and expansive, making its clinical definition and prompt diagnosis challenging. Patients with eosinophilic fasciitis typically report initial swelling and induration and thickening of the skin of the arms and legs, which may progress to hyperpigmentation, induration, and skin tightening. Extracutaneous manifestations including joint contracture, inflammatory arthritis, restrictive lung disease, pleural effusion, and paraneoplastic phenomena are often present, posing significant overlap with scleroderma, polymyositis, hypereosinophilic syndrome, and vasculitides.

The current standard for diagnosis is a full-thickness, skin-to-muscle biopsy; recent studies have investigated MRI as a potential surrogate. Biopsy typically reveals dermal thickening from collagen deposition and a lymphocytic fascial infiltrate. Tissue eosinophils are occasionally seen on biopsy but are not required for diagnosis.

The etiology of eosinophilic fasciitis is uncertain. Reports of physical exertion, ingestion of l-tryptophan and statin drugs, trauma, arthropod bites and borreliosis have all been implicated in its pathogenesis. To date, there have been no known associations with *Cytomegalovirus* (CMV) infections and the onset of eosinophilic fasciitis. However, several herpesviruses, such as human herpesvirus 6, have been implicated in the development of a severe, drug-induced, systemic hypersensitivity reaction, such as drug rash with eosinophilia and systemic symptoms (DRESS).

Systemic corticosteroids remain the primary treatment for eosinophilic fasciitis, although various other drug regimens have been tried. Several steroid-resistant cases have been treated with hydroxychloroquine, cimetidine, azathioprine, and d-penicillamine, with variable results. Recent work has also suggested the potential use of anti-TNFα inhibitors to manage refractory cases not responsive to conventional therapy.

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PRESENTERS
Carlos Paz, MD, PhD, Diana Bolotin, MD, PhD, Vesna Petronic-Rosic, MD, MSc and Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS
A 49-year-old African American woman with a history of poorly-controlled diabetes mellitus presented with a five month history of a large vegetating verrucous plaque on her right submandibular area. Four months prior to presentation, the patient had seen an otolaryngologist who incised and drained the lesion her neck, and then treated her with broad spectrum antibiotics for a presumed bacterial infection. The antibiotics had no effect. Over the ensuing months, the patient developed similar verrucous plaques on her chest and bilateral lower extremities.

PAST MEDICAL HISTORY
Diabetes mellitus, anemia, hypertension, irritable bowel syndrome, and candida esophagitis

PAST SURGICAL HISTORY
Left ovarian resection for a suspected teratoma at the age of 15 with no recurrence, and three cesarian sections

MEDICATIONS
Lisinopril, atorvastatin, hydrochlorothiazide, metformin, glyburide, and aspirin

FAMILY HISTORY/ALLERGIES
Non-contributory

SOCIAL HISTORY
The patient is happily married and works as a valet parker. She has a remote 10-pack-year smoking history but denies any alcohol or illicit drug use. Her travel history was unremarkable.

PHYSICAL EXAM
A total body skin examination revealed a large vegetating verrucous plaque on her right submandibular area. In addition, several smaller dermal nodules with erythema and infiltration were found on the chest, and both thighs. No lymphadenopathy was noted.

LABORATORY DATA
Hemoglobin A_1C: 10.8% [Normal 3.9 – 6.1%]
Normal labs: complete blood count with differential, comprehensive metabolic panel
HIV1/HIV2 antibodies: negative
Fungal culture (tissue from neck biopsy): Blastomyces dermatitidis
Fungal culture (tissue from thigh biopsy): Blastomyces dermatitidis

IMAGING STUDIES
CT Chest: Multiple nonspecific micronodules measuring about 2mm in diameter were noted, mainly in the left lower lobe. The micronodules were thought to be related to a previous granulomatous infection. There was no specific evidence of active disease.

DERMATOPATHOLOGY
A 4mm punch biopsy of the right submandibular plaque showed pseudoepitheliomatous hyperplasia and a dense diffuse mixed inflammatory infiltrate of lymphocytes, neutrophils, plasma cells, eosinophils, and extravasated red blood cells. Intradermal abscesses were present,

as well. The PAS and GMS stains highlighted rare hyaline, non-encapsulated, thick (double contour)-walled yeast. The Gram, Fite, and mucicarmine stains were unremarkable

DIAGNOSIS
Disseminated blastomycosis

TREATMENT AND COURSE
The patient was treated with itraconazole and is currently being followed by dermatology and infectious disease service at the University of Chicago.

DISCUSSION
Blastomycosis is an infection with variable clinical presentations, from an asymptomatic subclinical condition primarily involving the lungs to a widely disseminated disease that can be fatal. In the United States, most cases of blastomycosis are found in midwestern, north central, and southeastern parts of the country. While infection shows no predilection for age, race, gender, or occupation, blastomycosis has been increasingly recognized in immunocompromised individuals.

Blastomycosis is caused by *Blastomyces dermatitidis*, a dimorphic fungus occuring in mycelial and yeast forms, the latter of which leads to infection in humans. Primary infection often occurs in the lung following inhalation of aerosolized spores normally found in soil. Once established in the lung, lymphohematogenous spread of yeast organisms to other organs may occur. The skin is the most common extrapulmonary site of disseminated blastomycosis, followed by bone, prostate, epididymis and the central nervous system. Cutaneous lesions present as minimally tender papules to verrucous plaques that may ulcerate.

Histologic diagnosis is based on identification of the characteristic thick-walled broad-based budding yeast cells in tissue, often in the setting of pseudoepitheliomatous hyperplasia and a dense mixed inflammatory infiltrate of lymphocytes, neutrophils, plasma cells, and eosinophils. Fungal culture may be required to establish the diagnosis of blastomycosis.

Disseminated blastomycosis can be treated with itraconazole 200mg daily for 6 months. Blastomycosis involving the central nervous system requires treatment with amphotericin B 30mg/kg for 10-12 weeks. The prognosis for blastomycosis depends on severity of infection, involvement of extra-pulmonary tissues, and whether or not the affected individual has a competent immune system. In general, the mortality rates in untreated or immunocompromised individuals ranges from 30-50%, whereas the mortality rates in appropriately treated individuals is 2-5%.

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PRESENTERS
Christiane Querfeld, MD, PhD, Vesna Petronic-Rosic, MD, MSc, Thomas Krausz, MD, and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A 14-month-old female presented for evaluation of a lesion on her left lower back, which was noticed at 1 month of age and has persisted since that time. Two skin biopsies were performed at an outside practice with a presumptive diagnosis of morphea. The patient is otherwise healthy.

PAST MEDICAL HISTORY
Full-term infant born by spontaneous vaginal delivery without complication.

MEDICATIONS
Fluticasone ointment to lesion prior to appointment.

FAMILY HISTORY/SOCIAL HISTORY/ALLERGIES
Non-contributory

PHYSICAL EXAMINATION
Well-appearing and well-developed 14-month-old infant with 2.5 x 2 cm violaceous-brown indurated, plaque with accentuated hair follicles on the lower back. No other significant skin findings.

HISTOPATHOLOGY
The skin has a spindle cell proliferation in the reticular dermis extending to the subcutaneous fat with a prominent capillary network and hyalinized collagen. Spindle cells strongly express CD34 and factor XIIIa , and are negative for smooth muscle actin, S-100 protein, epithelial membrane antigen , CD1a, and CD31. CD117 highlights numerous mast cells. The epidermis is unremarkable.

DIAGNOSIS
Medallion-like dermal dendrocyte hamartoma

TREATMENT AND COURSE
An appointment with plastic surgery was made for complete excision. At six-month follow-up the patient presented with a well-healed mildly hyperemic scar.

DISCUSSION
Medallion-like dermal dendrocyte hamartoma (MDDH) is a novel connective tissue hamartoma that was first described by Rodríguez-Jurado and co-workers in 2004. Nine cases have been reported in the literature with remarkably similar clinical features of a solitary, red to brown, atrophic, medallion-shaped patch on trunk or extremities in most patients. On histology, epidermal atrophy coexisted with a dermal and subcutaneous spindle-cell proliferation involving adnexal structures. A mild increase in perivascular mast cells and variable loss of elastic fibers was also noted. CD34 was positive in each tumor, but factor XIIIa was not consistently expressed. Our patient presented with an erythematous indurated plaque with accentuated hair follicles, clinically different from the cases published, but with histologic findings of MDDH.

The etiology of dermal dendrocyte hamartomas remains unknown. While all reported lesions were congenital, variable histopathologic, and immunohistochemical characteristics were seen between individual lesions suggesting a heterogenous onset or different maturation stage of

disease. Recruitment of dendrocytes during embryogenesis in response to a traumatic event has been suggested. Furthermore, it has been speculated that, similar to a congenital nevus, the lesion may be composed of a clonal dendrocyte population.

The relationship between CD34 and factor XIIIa expression in dendrocyte hamartomas is not clear and may reflect different maturation stages or phenotypic alterations due to changes to the microenvironment. Type I dendrocytes are known to be $CD34^-$ and factor $XIIIa^+$. They are typically found in the papillary dermis and may play a role in inflammation, phagocytosis, wound healing, and collagen production. Type II dermal dendrocytes are $CD34^+$ and factor $XIIIa^-$ and reside in the reticular dermis, possibly regulating collagen synthesis. Studies in morphea have shown that CD34 expression correlates with inflammation, whereas factor XIIIa correlates with the degree of sclerosis.

The clinical course of MDDH is benign without evidence of histological regression, transformation or malignant degeneration. The differential diagnosis may include fibrous hamartoma of infancy, connective tissue nevus, hemangioma, and congenital dermatofibrosarcoma protuberans (DFSP). The treatment options include observation and local excision.

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PRESENTERS
Ingrid Polcari, MD, Vesna Petronic-Rosic, MD, MSc and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
An 11-year-old boy with well-controlled asthma presented with a several week history of bumps on his left leg. The first bumps appeared on his left medial knee where he sustained a minor abrasion from a soccer cleat. His pediatrician prescribed a course of oral clindamycin without improvement. Later he developed smaller but similar-appearing bumps on his left inner thigh. He denied itch or tenderness.

PAST MEDICAL HISTORY
Asthma and Seasonal Allergies

MEDICATIONS
Budesonide inhaler 2 puffs bid, cetirizine 10 mg daily, montelukast sodium 5 mg daily, albuterol inhaler prn

FAMILY HISTORY/ALLERGIES
Non-contributory

SOCIAL HISTORY
No recent travel

PHYSICAL EXAMINATION
On physical exam, the left medial knee had erythematous to violaceous papules and plaques, some with a white pustular collection. The left inner thigh had a violaceous plaque with surrounding minute erythematous papules. All lesions were non-tender. No lymphadenopathy was appreciated.

DERMATOPATHOLOGY
A 4mm punch biopsy from a knee lesion showed a dense nodular and diffuse mixed inflammatory cell infiltrate composed of numerous neutrophils, histiocytes, lymphocytes and eosinophils. The PAS, GMS and Von Kossa stains highlighted 1-2 micrometer cigar shaped spores as well as round spores approximately 8-10 micrometers in diameter. The gram stain was negative for microorganisms.

LABORATORY DATA
Tissue culture was negative for organisms.

DIAGNOSIS
Sporotrichosis

TREATMENT AND COURSE
The patient has been treated with Itraconazole 150 mg by mouth daily with near resolution of the lesions. A six-month course of therapy is planned.

DISCUSSION
Sporotrichosis is an infection of the skin and subcutaneous tissues caused by *Sporothrix schenckii*, a dimorphic fungus. *Sporothrix* is most commonly found in soil which explains its predilection for gardeners, florists, farmers or other persons exposed to contaminated soil. It has also been isolated from wood, grain, and animals such as cats, rodents and armadillos.

Sporotrichosis occurs worldwide but is more common in tropical and subtropical zone regions. Childhood infection does occur but is less common.

The classic presentation in adults is the lymphocutaneous form in which a painless, erythematous papule or nodule starts one to four weeks after inoculation via a penetrating injury from an object such as a thorn, splinter, or broken glass. Later more lesions appear proximally along dermal and subcutaneous lymphatics. This pattern of spread has been referred to as "sporotrichoid". Nodules can ulcerate and may produce cutaneous fistulae. Commonly there is coexisting lymphadenopathy but systemic symptoms are usually absent or mild. The "fixed cutaneous" form of sporotrichosis has localized skin lesions without spread along the lymphatics. This type is more common in children. Rarely sporotrichosis can become disseminated; this is more common in patients who are immunocompromised. The primary focus can be from skin or from the lung after inhalation of spores. Subsequent hematogenous spread leads to multiorgan involvement and high morbidity.

The differential diagnosis for lesions in a sporotrichoid distribution includes Leishmaniasis, atypical mycobacterial infections, nocardiosis, tularemia, chromoblastomycosis, foreign body granuloma and furunculosis. Tissue culture and histology will help guide the diagnosis.

Histologic sections of *Sporothrix* infection show pseudoepitheliomatous hyperplasia with intraepidermal neutrophils. A diffuse mixed dermal infiltrate composed of neutrophils, histioctyes, plasma cells and multinucleated giant cells is common, but the presence of eosinophils as in our patient's specimen is an unusual finding. PAS or GMS will stain 3-8 micron spores that are round, oval or cigar-shaped but these organisms are notoriously difficult to find in tissue sections. Fungal culture is recommended for definitive diagnosis. Although sporotrichosis grows easily in appropriate culture media, the sensitivity of culture is not 100%. This can be explained by the fact that organisms tend to aggregate within tissue and the specimen sent for culture must contain such aggregates to yield a positive result.

Sporothrix infection does not resolve spontaneously so will become chronic if left untreated. Historically the treatment for nondissemminated sporotrichosis in both adults and children has been orally administered saturated solution of potassium iodide (abbreviated SSKI) for four to six weeks after clinical resolution of lesions. The low cost of this medication makes it more suitable in endemic regions or in epidemic outbreaks. The mechanism of action of this treatment is unknown. The emerging treatment of choice is Itraconazole for a period of three to six months. Studies have shown a success rate of 90-100% with this treatment. The recommended adult dose is 200 mg daily. Children should receive 5 mg per kilogram of body weight per day. Amphotericin B is used for the initial treatment phase of disseminated disease.

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PRESENTERS
John C. Fox, MD, Christopher R. Shea, MD and Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS
An 83-year-old African-American woman presented with a two-year history of a slowly enlarging, occasionally pruritic growth involving her right upper back. She denied pain, bleeding, and antecedent trauma.

PAST MEDICAL HISTORY
Hypertension
Osteoarthritis

MEDICATIONS
Furosemide 40 mg daily, potassium 20 mEq daily, vitamins C, E, B_{12}

ALLERGIES
None

PHYSICAL EXAMINATION
Physical examination revealed a 30-mm by 32-mm firm, dark grey, nodular plaque with two exophytic papules at the inferior border. A slightly larger, rock-hard, subcutaneous extension of the lesion was also palpable.

LABORATORY DATA
CBC, CMP within normal limits

DERMATOPATHOLOGY
Step sections of a punch biopsy specimen revealed skin with unremarkable epidermis and papillary dermis. The reticular dermis contained a diffuse and nodular infiltrate composed of spindled cells arranged in fascicles with storiform patterning. Variable cytologic atypia was noted, with several areas displaying high-grade cytologic atypia and considerable nuclear pleomorphism.

Immunohistochemical studies revealed strong staining of almost all neoplastic cells with anti-vimentin. Within the more slender spindled cells in storiform arrangements, anti-CD34 showed strong reactivity among all cells, and anti-factor XIIIa labeled approximately 50% of such cells. The larger, more atypical cells generally exhibited markedly lower expression of these two markers. The neoplastic cell population was essentially negative for desmin, smooth muscle specific actin, S100 protein, and Melan-A expression. The COL1A1/PDGF-ß translocation was not identified by gene rearrangement study.

DIAGNOSIS
High-grade pleomorphic sarcoma arising within a dermatofibrosarcoma protuberans

TREATMENT AND COURSE
The patient was referred to oncology and general surgery for staging and wide local excision of the tumor with primary closure. Imaging studies did not reveal metastatic disease. Discussion with the patient, her family, and physicians of the Surgery, and Radiation Oncology Departments led to the decision not to utilize adjuvant local radiation therapy. The patient has recovered well from the surgery and has no clinical evidence of recurrence to date.

DISCUSSION

Dermatofibrosarcoma protuberans (DFSP) is a low-grade soft-tissue tumor clinically characterized by aggressive local invasion, high rate of local recurrence, and rare incidence of metastatic disease. Classically, lesions of DFSP present on the trunk and upper extremities of young to middle-aged adults and vary in appearance from small plaques and nodules to large, multi-nodular tumors. The classic histopathologic features include a monotonous, storiform growth pattern of uniform and cytologically bland spindled cells with hyperchromatic, elongated nuclei, infiltrating into the subcutaneous fat in a characteristic honeycomb pattern. Immunohistochemical stains are generally positive for vimentin and CD34.

A small number of DFSP tumors contain areas of high-grade sarcomatous change, and the prognostic significance of such variants remains controversial. Fibrosarcomatous loci are characterized by fascicles of spindle-shaped tumor cells with higher cellularity and increased mitotic activity, as well as increased cytologic atypia. Immunohistochemical staining generally reveals absence or, less commonly, focal and weakly staining areas of CD34 expression in areas of sarcomatous transformation; this tendency to lose CD34 expression has been proposed to represent tumor progression to frank fibrosarcoma, which is usually CD34-negative. Such transformed tumors have demonstrated similar rates of local recurrence when compared to ordinary DFSP; however, a higher rate of metastasis (14.7% vs. <1%) and tumor-related deaths have been observed in several studies.

Wide surgical excision with margin control is the treatment of choice for DFSP with areas of sarcomatous transformation. Although not demonstrated in our patient, most DFSPs have a chromosomal translocation that fuses the *COL1A1* promoter gene of chromosome 17 to the *PDGFß* gene of chromosome 22, producing a constitutively active platelet-derived growth factor ß receptor tyrosine kinase that leads to cellular proliferation and tumor formation. A growing body of literature continues to support a role for imatinib in reducing tumor burden by targeting the PDGFß receptor tyrosine kinase in DFSP.

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PRESENTERS
Shaily Patel, MD, John Fox, MD, Christopher R. Shea, MD and Sarah L. Stein, MD

PATIENT A

HISTORY OF PRESENT ILLNESS
A six-week-old female admitted for an apparent life-threatening event (ALTE) was noted to have a rash present from birth. The rash primarily involved her extremities and started with multiple blisters and red papules that resolved slowly over time. In addition, she had developed a few rough nodules and streaks of darker discoloration. The rash was asymptomatic and was being treated with bland emollients.

PAST MEDICAL HISTORY
Full-term infant born via cesarean section secondary to failure to progress
Gastroesophageal reflux disease

FAMILY HISTORY
Mother and maternal grandmother with similar rash in infancy
Mother with residual streaky discoloration of the lower legs and retained deciduous molar teeth
Mother with history of four first trimester miscarriages

MEDICATIONS
Famotidine

ALLERGIES
None

PHYSICAL EXAMINATION
The patient was a well-appearing and well-developed six-week-old female in no distress. Over the lower extremities most notably, but also involving the upper extremities and trunk, there were multiple streaky, hyperpigmented, linear macules and patches following the lines of Blaschko. Several hyperkeratotic verruciform nodules on the dorsal hands and feet were also apparent. No discrete vesicles were present, but scattered erythematous papules and linear plaques were noted. No alopecia, nail changes, erupted teeth, ocular or skeletal abnormalities were appreciated.

DERMATOPATHOLOGY
A 4mm punch biopsy specimen of an erythematous papule on the right thigh showed acanthosis of the epidermis with slight spongiosis, with a suggestion of papillomatosis. Numerous dyskeratinocytes and eosinophils were noted within the epidermis. The dermis had a sparse, superficial perivascular infiltrate of lymphocytes and numerous eosinophils. The subcutaneous fat was unremarkable.

LABORATORY DATA
Complete blood count: Leukocytes 11.3 K/µL (3.5-17.7), hemoglobin 14.1 g/dL (9.8-17.6), platelets 680 K/µL (150-450)
Differential: Neutrophils 17%, lymphocytes 62%, monocytes 10%, eosinophils 7%, bands 2%

DIAGNOSIS
Incontinentia pigmenti

TREATMENT AND COURSE
Neurologic evaluation including a head ultrasound and electroencephalogram was within normal limits. Ophthalmologic evaluation including a dilated-eye examination was unremarkable. Genetic counseling was provided to the family. The patient was subsequently discharged and seen in the outpatient dermatology clinic at seven weeks of age with continued expected evolution of the skin lesions.

PATIENT B

HISTORY OF PRESENT ILLNESS
An 11-week-old female presented to the outpatient dermatology clinic for evaluation of persistent discoloration of the legs, present from birth. Initially the lesions started as blisters and pustules that later crusted over and healed with dark discoloration. The rash was asymptomatic and no treatments had been utilized.

PAST MEDICAL HISTORY
Full-term infant born without complications

FAMILY HISTORY
Mother with similar rash in infancy, missing teeth, and residual streaky discoloration of the lower legs

MEDICATIONS
None

ALLERGIES
None

PHYSICAL EXAMINATION
The patient was a well-appearing and well-developed 11-week-old female in no distress. Over the lower extremities predominantly, and to a lesser extent on the upper extremities and trunk, there were reticulated and linear, whorled, hyperpigmented patches, some blue-gray in color, following the lines of Blaschko. The inner thighs had erythematous streaky plaques and papules. The dorsal feet had some hyperkeratotic verruciform nodules, but no vesicles were noted. No alopecia, nail changes, erupted teeth, ocular or skeletal abnormalities were appreciated.

DIAGNOSIS
Incontinentia pigmenti

TREATMENT AND COURSE
The patient was referred to ophthalmology and neurology for baseline examination, both of which were unremarkable. At her follow-up visits at both five and nine months of age, she continued to have normal development and expected evolution of the skin findings.

DISCUSSION
Incontinentia pigmenti (Bloch-Sulzberger syndrome) is a rare, X-linked dominant genodermatosis with cutaneous, neurologic, dental, ophthalmologic, and skeletal manifestations. The disorder is due to mutations in the nuclear factor-kappa B essential modulator (NEMO) gene, localized to the X chromosome, which serves to protect cells against apoptosis. In most affected individuals, the mutation is the result of a deletion that eliminates the activity of NEMO. There can be variable phenotypic expression, thought to be due to random activation of the affected X allele in the

involved tissues. Given its inheritance, it is antenatally lethal in boys, with the exception of those with Klinefelter syndrome or somatic mosaicism.

The disorder appears at birth or shortly thereafter and has four phases, which can overlap. In the initial vesicular phase, inflammatory vesicles and pustules develop in crops over the trunk and extremities and can persist for months. The verrucous phase follows, characterized by irregular, verruciform papules and nodules on the extremities, most often on the hands and feet; this phase usually resolves spontaneously within two years. Next, the characteristic hyperpigmented phase occurs, in which lesions appear as thin, linear whorls of brown to blue-gray discoloration on the extremities and trunk; these hyperpigmented lesions can progress until two years of age, then stabilize and fade to the final phase, characterized by hypopigmentation and atrophic streaks.

Ectodermal manifestations including cicatricial alopecia, nail dystrophy, nail tumors, supernumerary nipples, and absent sweat glands can affect 30-50% of patients. Noncutaneous manifestations include dental anomalies such as: delayed dentition, partial anodontia, and pegged or conical teeth. Approximately 30% of patients have CNS involvement, most commonly presenting as seizures, as well as spasticity and mental retardation. Ophthalmologic changes are present in 30-35% of patients and include strabismus, cataracts, optic atrophy, retinal neovascularization, retinal detachment, and even blindness. Finally, skeletal anomalies such as microcephaly, syndactyly, supernumerary ribs, hemiatrophy, lytic lesions of the distal phalanges, and shortening of the arms and legs can be seen.

Early diagnosis and investigation for any associated systemic involvement is the mainstay of treatment. Simple supportive care such as emollients for the skin lesions is usually adequate, as most of them will spontaneously resolve. Interdisciplinary care with baseline and longitudinal neurologic, ophthalmologic, dental and dermatologic examinations are recommended. Finally, genetic counseling should be provided to the family.

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PRESENTERS
Brian E. Pucevich, MD, John Fox, MD and Vesna Petronic-Rosic, MD

HISTORY OF PRESENT ILLNESS
This 82-year-old Asian male first seen in consultation in February 2008 at UCMC for drug induced hypersensitivity determined to be secondary to furosemide. He presented in March 2008 for post-hospital follow up and re-evaluation. He was noted to have a rash on his face and upper chest and back which he and his family state had began several months after the patient had started amiodarone therapy. The rash slowly worsened while the patient was continued on amiodarone, which eventually was stopped by the patient's cardiologist. The rash has persisted since discontinuation of the medication, but was asymptomatic. Review of systems was unremarkable.

PAST MEDICAL HISTORY
Diabetes, glaucoma, hypertension, GERD, aortic graft with MRSA infection

MEDICATIONS
Metoprolol, gabapentin, ciprofloxacin, rifampin, insulin glargine, atorvastatin, insulin lispro, odansastron, esomeprazole, docusate, niacin, gemfibrozil

ALLERGIES
Tramadol, furosemide, nafcillin

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
The patient is married and lives with his wife; denies tobacco, illicit drug, or alcohol use.

PHYSICAL EXAM
On the face, chest, back and abdomen there are non-blanching slate bluish/gray colored patches in a reticulated, psuedovascular pattern. Overall the skin is atrophic with fine wrinkling.

HISTOPATHOLOGY
Right trapezius 4mm punch biopsy: Sections are of skin with an atrophic epidermis and rare necrotic keratinocytes in the basal layer. Within the papillary dermis, there is a scant perivascular and interstitial lymphohistiocytic infiltrate and innumerable pigment laden macrophages highlighted with the Fontana-Masson stain, and therefore consistent with melanin. The iron stain highlights minimal amounts of hemosiderin in the papillary dermis. The PAS stains normal basement membrane.

DIAGNOSIS
Drug induced reticulated hyperpigmentation secondary to amiodarone.

TREATMENT
In clinical follow up, the blue/gray pigmentation was noted to have slowly faded from initial presentation in March 2008 to his last visit in April 2009. In speaking with his daughter in October 2009, she states that the discoloration has continued to fade since his last visit.

DISCUSSION

Amiodarone is well known to cause a characteristic blue-gray discoloration of the skin. This discoloration is often photo accentuated with prominent involvement of the face. Typically, it is uniformly distributed in affected areas with sparing of nasolabial folds, eyelids, deep wrinkles and other photo-protected sites. This dyspigmentation has been documented to occur in as many as 9 percent of patients treated with amiodarone.

The risk of pigmentation alteration is dependent upon dosage and duration of use of amiodarone. Higher risk is associated of doses greater than 800mg/day. Clinical apparent skin dyspigmentation typically begins after about 6 months of amiodarone therapy. Corneal discoloration has also been reported and tends to occur within the first month of therapy, much earlier than the skin changes.

The mechanism of discoloration is classically thought to be secondary to deposition of lipofuscin in the dermis with accumulation in dermal macrophages. This was postulated to result from the direct action of amiodarone on lysosomes and phototoxic induced lysosomal damage explaining the photo-accentuation of the pigmentation. More recently, however, presence of amiodarone granules has been demonstrated via liquid chromatography in the pigmented skin of a patient without demonstrable lipofuscin by electron microscopy.

Amiodarone induced dyspigmentation typically improves with time upon cessation of drug use. Therefore, treatment need not be aggressive. Use of Q-switched laser has been shown beneficial in hastening the resolution.

The reticulated pattern of pigmentation seen in this case is the interesting feature and to our knowledge not previously described in the literature. One possibility we considered to explain this morphology was the possibility that the lichenoid drug eruption occurring secondary to furosemide somehow altered the pattern of pigmentation. This, however, was not substantiated by the patient or the patient's family in that they could not recall nor did we observe a change in morphology of the pigmentation.

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PRESENTERS

Tunisia Finch, MD, Diana Bolotin, MD, PhD and Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS

Dermatology was asked to evaluate skin changes overlying the left hand in an 11-month old female with known kaposiform hemangioendothelioma involving the metacarpals and phalanges of the left hand. The patient had had a 4 month history of swelling and pain of the left hand. A magnetic resonsance imaging study (MRI) had demonstrated lytic lesions in the metacarpals and proximal phalanges. An incisional biopsy of the left fifth metacarpal was consistent with kaposiform hemangioendothelioma. The patient was begun on chemotherapy. Shortly thereafter, the skin changes were noted and dermatology was consulted.

PAST MEDICAL HISTORY

38-weeks gestation, no prenatal or postnatal complications.

REVIEW OF SYSTEMS/FAMILY HISTORY/SOCIAL HISTORY

The patient's maternal grandmother had a history of a schwannoma. Review of systems was remarkable for the patient choosing not to use the left hand and appearing sensitive to any significant contact with that hand. Social history was non-contributory.

MEDICATIONS/ALLERGIES

Tylenol as needed for pain. No known drug allergies.

PHYSICAL EXAMINATION

Edematous left hand with edema beginning abruptly at the level of the wrist and involving all digits, with the 4^{th} and 5^{th} digit being more edematous then the other digits. The overlying skin was violaceous to erythematous with multiple petechia scattered over the dorsal hand. There was a well demarcated faint line of erythema that extended over the dorsal wrist and ended toward the volar wrist.

HISTOPATHOLOGY

An incisional biopsy of the fifth metacarpal showed a solid proliferation of epitheliod to spindle shaped cells with large nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. Many cells contain Prussian blue positive hemosiderin pigment and resemble epitheliod histiocytes; however, subtle vascular lumen formation is present. No organisms are demonstrated with GMS stain. The mitotic rate is low and the MIB-1 index is 5%. Immunohistochemical evaluation shows strong positive reaction with CD34, CD31, and FLI-1 in the lesional cells. D2-40 appears positive, but difficult to interpret. AE1, myogenin, and CD1a are negative. SMA staining is demonstrated in cells surrounding the endothelial cells and vascular channels. HHV8 is negative.

LABORATORY/RADIOLOGIC DATA

Complete Blood Count at presentation: Hemoglobin 10.5 g/dL (NL 10.3-13.2), hematocrit 30.4 (NL 33-39) white blood cell count 9.8K/uL (NL 6.0-17.3), platelets 212 K/uL (NL 150-450)

MRI hand: Multiple lytic lesions in the 1^{st}, 4^{th}, and 5th metacarpals and 4^{th} and 5^{th} proximal phalanges of the left hand.

Plain X-ray hand: Multiple lytic lesions without internal calcificaitions are noted affecting the 4^{th} and 5^{th} metacarpals and proximal phalanges. There is associated soft tissue swelling.

MRI Brain: Normal contrast enhanced brain MR for age.

CT chest/abdomen/pelvis: Nonspecific subcentimeter micronodule in the right upper lobe.

DIAGNOSIS

Kaposiform Hemangioendothelioma of bone, also involving soft tissue and skin

TREATMENT AND COURSE

The patient is being managed in the pediatric hematology/oncology practice. The patient was initially treated with IV vincristine and actinomycin D for 8 weeks. Repeat MRI and plain X-ray showed disease progression, so interferon alpha 2B was initiated. Clinically, her pain and swelling of the hand has improved although she still has some discoloration on the lateral side of the hand. Interval changes on the most recent MRI and plain X-ray show increased sclerotic changes in the first, fourth, and fifth metacarpals consistent with a positive therapeutic affect.

DISCUSSION

Kaposiform hemangioendothelioma (KHE) is a rare, locally aggressive vascular tumor of the skin, deep soft tissue, and bone that mainly occurs during childhood. It appears as one or multiple masses, and may be associated with consumptive coagulopathy (Kasabach-Merritt syndrome (KMS)). KHE may be locally aggressive or extensive, but has not shown malignant potential. KHE typically presents during the first year of life although it may develop in adults. Cutaneous forms present as locally infiltrative vascular macules or plaques. Deeper lesions may present as bulging, indurated masses. Once developed, KHE shows no tendency to spontaneously involute.

The term 'kaposiform' relates to the histologic resemblance to Kaposi's sarcoma, with compact spindled tumor cells forming slit-like lumens. 'Hemangioendothelioma' implies the uncertainty regarding biologic behavior of the tumor which lies in between that of a hemangioma and a sarcoma. The diagnosis is made on clinical presentation, imaging studies, and histologic and immunohistochemical features. Differential diagnoses include: infantile hemangioma, tufted angioma, and Kaposi's sarcoma.

Seventy-five percent of patients with KHE present with a superficial or deep soft tissue mass on the extremities or trunk, and 18% of cases present with retroperitoneal involvement. Because retroperitoneal involvement has a grim prognosis, this distribution has been emphasized. KHE has a mortality rate of 30% overall; deaths are usually related to locally invasive effects, visceral location which is unresectable, the presence of KMS, or the presence of associated lymphangiomatosis. Favorable location, size and a positive clinical response to glucocorticoids and interferon predict a good outcome.

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