Chicago Dermatological Society

May 2015
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, May 20, 2015
Stephens Convention Center - Rosemont

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

Program

Stephens Convention Center
5555 N. River Rd., Rosemont, IL
Level 2, Conference Center

Registration Area – Foyer between Ballroom 41 and 42

Program Events

8:00 a.m.	**Registration begins for all attendees** Continental breakfast & visit with exhibitors *Ballroom 41*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** *Ballroom 42* "Liver Toxicity from Dermatologic Drugs: The Basics" *Stephen E. Wolverton, MD*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** - Slide & Poster Viewing; Visit with Exhibitors *Ballroom 41 and Foyer area*
11:00 a.m. - 12:00 p.m.	**General Session** MALKINSON LECTURE "Antimicrobial Resistance: Sorting Out the Facts and Fiction" *Stephen E. Wolverton, MD*
12:00 p.m. - 12:40 p.m.	**Lunch & Visit with Exhibitors** *Ballroom 42*
12:40 p.m. - 12:50 p.m.	**CDS Business Meeting** *Ballroom 42*
12:50 p.m. - 2:30 p.m.	**Case Discussions** *Ballroom 42*
2:30 p.m. - 3:00 p.m.	**Maintenance of Certification** - Self-Assessment Questions *Ballroom 42*
3:00 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting – Wednesday, June 3, 2015; hosted by Loyola University at the Stephens Convention Center in Rosemont.

Guest Speaker

STEPHEN E. WOLVERTON, MD

Theodore Arlook Professor of
Clinical Dermatology
Department of Dermatology
Indiana University
Indianapolis, IN

Delivering the Frederick Malkinson Lecture

Stephen E. Wolverton, MD, received his undergraduate degree at Ball State University with a B.S. as a Pre-Med major in 1975. Subsequently he attended medical school at the Indiana University School of Medicine, receiving an MD degree in 1979. Dr. Wolverton initially pursued a career in Family Practice, completing his residency at St. Elizabeth Medical Center in Dayton, Ohio in 1982. After considering a switch in specialty, Dr. Wolverton initiated his dermatology career by completing his residency at Wright State University, also in Dayton, Ohio. Subsequent faculty positions have included Wright State University, Ohio State University, and the long-term faculty position in the Department of Dermatology at the Indiana University School of Medicine (since 1990) where he was recently named the Theodore Arlook Professor of Clinical Dermatology. Dr. Wolverton's long-term academic interest has been systemic drug use in dermatology, focusing on all aspects of drug safety. He is best known for his series of four books concerning dermatologic drug therapy: Systemic Drugs for Skin Diseases and Comprehensive Dermatologic Drug Therapy.

CME Conflict of Interest Disclosure: Dr. Wolverton has no conflicts of interest to disclose.

CONTINUING MEDICAL EDUCATION CREDITS

Chicago Dermatological Society

Presents

"Chicago Dermatological Society Monthly Meeting Series"

May 20, 2015 *Rosemont, IL*

Please be sure to complete and return the attendance/CME claim form and the evaluation form before you leave the meeting. The information collected in the evaluation form represents an important part of the CME planning process. A certificate of credit will be mailed to you following the conference. Participants must attend entire session to receive full credit. SynAptiv will retain a record of attendance on file for six years.

JOINT SPONSOR STATEMENT

This educational activity is jointly provided by SynAptiv and the Chicago Dermatological Society.

GOAL / PURPOSE

To broaden the clinical knowledge of dermatologists in a number of areas relating to management of patients and new therapy options.

EDUCATIONAL OBJECTIVES

Upon completion of this activity, participants will be able to:

1. Discuss key factors in the diagnosis and treatment for a variety of dermatologic diseases and conditions, including psoriasis, hair disorders, and dermatological symptoms of systemic diseases.

2. Describe the manifestation of skin cancers and the efficacy of treatments available to the dermatologist.

3. List the therapeutic options available to the dermatologist for a variety of skin diseases, both medical and surgical, and discuss how new emerging treatments can be successfully incorporated into a dermatology practice.

Continued next page

CREDIT STATEMENTS

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of SynAptiv and Chicago Dermatological Society. SynAptiv is accredited by the ACCME to provide continuing medical education for physicians.

SynAptiv designates this live activity for a maximum of 4.5 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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DISCLOSURE STATEMENTS

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Fee Information - There is no fee for this educational activity.

Case

Presentations

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 1**

Presented by Todd Rickett, MD, PhD and Arthur Rhodes, MD, MPH
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 52 year-old white male presented to the emergency department with a 2 year history of swelling and firmness of his penile shaft. This presentation initially occurred only at the penile base, but had later spread along the length of the penile shaft. Over the prior 10 months, he had also experienced blistering and occasional pustules of the penile shaft, eventually, developing into exquisitely painful ulcers that were very slow to heal. He also describes the healing process "like a snake shedding its skin". Two months prior to presentation, he developed cellulitis of the penis requiring hospitalization and treatment with IV ceftriaxone and micafungin. A wound culture grew coagulase-negative staphylococcus aureus. Biopsies obtained by urology were interpreted as paraffinoma, though the patient repeatedly denied penile or pelvic injections. Since discharge from the outside hospital, he has had persistent inguinal lymphadenopathy. Prior to admission, he developed fevers to 102.9°F, dysuria, hematuria, and abdominal pain.

PAST MEDICAL HISTORY

Hypercholesterolemia
Sleep apnea
MRSA cellulitis following knee arthroscopy 3 years prior to presentation

PAST SURGICAL HISTORY

Left knee arthroscopy 3 years prior to presentation
Vasectomy 2 years prior to presentation

MEDICATIONS

No home medications
For present illness: Vancomycin IV, Piperacillin-tazobactam IV, hydrocodone-acetaminophen

ALLERGIES

None known

FAMILY HISTORY

Diabetes in his father and a "stroke" in his mother.

SOCIAL HISTORY

Denied use of alcohol, tobacco, or illicit drugs. Patient states that he is heterosexual. He is divorced from a prior relationship, but is currently engaged to be married and sexually active with his female partner. He denies sexual involvement with anyone else.

PHYSICAL EXAMINATION

At the time of our initial examination, the patient was afebrile and well-appearing. His penis was notable for marked thickening with firm, circumferential bands of tissue at the base and mid-shaft. On the dorsal shaft of the penis was a 25 mm horizontal fissure. The base of this fissure was notable for yellow granulation tissue, slight crusting, and surrounding erythema. There were two additional ragged ulcers and several scars. There were no intact vesicles or bullae. There were no lesions or irregularities of the penile glans or scrotum. There was moderate bilateral enlargement of the inguinal lymph nodes.

HISTOPATHOLOGY

Two punch biopsies from the left and right surfaces of the penile shaft demonstrated numerous vacuoles of varying size, with extensive sclerosis of the intervening stroma and a patchy lympho-histiocytic infiltrate. The findings were consistent with sclerosing lipogranuloma.

LABORATORY EVALUATION

CBC within normal limits
CMP within normal limits
HIV negative
Chlamydia/Gonorrhea PCR negative
RPR non-reactive
HSV PCR negative
Aerobic bacterial culture from penile ulcer: *Staphylococcus aureus*
Urine culture: *Escherichia coli*

IMAGING

Magnetic resonance imaging (MRI) of the pelvis revealed bilateral indeterminate inguinal lymphadenopathy and diffuse subcutaneous penile edema without focal penile masses.

DIAGNOSIS

Sclerosing lipogranuloma of the penis, and *E. coli* urinary tract infection

TREATMENT AND COURSE

From the onset of symptoms through his prior admission at another hospital, and up to the second day of admission at Rush University Medical Center (RUMC), the patient denied injections or other manipulations or interventions to his genitalia. Numerous diagnoses had been considered by the primary care team, including Behcet's disease, pemphigus, and blastomycosis. During consultation by the Dermatology Service, the patient's children and fiancée were asked to leave the room for a private discussion and a thorough mucocutaneous examination. Once the patient could be questioned in private, he readily admitted that he had received a mineral oil injection to his penis shortly before the onset of symptoms.

Biopsy of the penis did not identify any other pathologies likely contributing to his condition. Upon receiving IV antimicrobial treatment, his fevers resolved, and his urinary symptoms improved rapidly. He was discharged to home on oral cephalexin. After following up examination with urology, he underwent penile degloving with excision of circumferential penile paraffinoma with reconstruction of penile skin through a local flap and split thickness skin graft from left thigh. His recovery following surgical reconstruction has been uncomplicated. He has not experienced additional penile ulceration or urinary tract symptoms.

DISCUSSION

Lipogranulomas (also known as oleomas, eleomas, or oil tumors) are granulomatous, foreign-body reactions to lipids or lipid-like materials, usually following injections of exogenous oily substances. A wide variety of substances have been used for skin injection, including paraffin, liquid silicone, petrolatum, mineral oil, lanolin, automobile transmission fluid, and beeswax. Though these substances may be injected into the skin or subcutaneous tissues of any body part, the most commonly reported sites include the penis, breast, and face.

Injections of paraffin have been used to augment male genitalia for more than 100 years. Originally pioneered by physicians as a cosmetic medical therapy similar to modern soft tissue

fillers, the practice was abandoned because of unacceptable inflammatory and fibrotic reactions. Nonetheless, the procedure is still commonly performed, mostly by non-medical personnel, in Eastern Europe, the Middle East, and Asia. Such procedures are generally performed to enhance masculinity, enlarge penile size to increase attraction to potential sexual partners, to enhance pleasure for sexual partners, or at the recommendation of acquaintances.

Once injected into the dermis or subcutaneous fat, the oil may deposit at the site of injection or spread beyond the genitalia. Long-chain hydrocarbons, such as mineral oil or paraffin, cannot be metabolized. Consequently, the oil persists and may replace the normal fatty layers. Ultimately, exogenous oil will elicit a foreign body reaction that can include chronic granulomatous inflammation and fibrosis. Histopathological specimens are often notable for thickening of the reticular dermis and classic “Swiss cheese” appearance of the cystic vacuoles, as seen in our patient. This appearance is the result of loss of non-polar materials during standard tissue processing, though the lipid may be retained through frozen sections or other preparations. Histiocytes may be foamy, enlarged, and multinucleated. Lymphocytic and eosinophic infiltrations are common.

The clinical presentation of penile paraffinomas is variable. Sclerosing lipogranulomas often manifest as firm subcutaneous nodules. Fibrosis may result in phimosis, erectile dysfunction, and dyspareunia. Involved sites may also display edema, ulceration, atrophy, and painful woody induration. Signs and symptoms may occur shortly after injection of the oil, or may be delayed by up to 40 years.

Treatment of sclerosing lipogranulomas is almost exclusively surgical. Patients with minimal adverse signs and symptoms may elect to pursue non-surgical treatments with antibiotics or intralesional glucocorticoid injection. However, phalloplasty remains the standard of care as it allows for evacuation of exogenous material that has caused fibrotic reaction and interference of normal penile function. Complete or near total removal of the oil is recommended to reduce the potential of ongoing granulomatous reaction and recurrent symptoms.

Assessment is straightforward when patients provide an accurate history, but can be complicated by reticence to disclose attempts at genital augmentation. Biopsy is generally considered the gold standard in confirming the diagnosis of sclerosing lipogranulomatosis. Imaging modalities, including ultrasound, computed tomography (CT), and MRI, may be used to assist in diagnosis or to characterize the extent of fibrosis. Our patient had an extensive and protracted medical course, even after an accurate biopsy diagnosis.

This patient's presentation illustrates the importance of interviewing patients in a non-judgmental manner while isolated from well-meaning loved ones.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 2**

Presented by Andrew Nesterovitch, MD, Bryan Sofen, MD and Arthur Rhodes, MD, MPH
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 52-year-old white female was hospitalized with a flare of Crohn's colitis. Presentation was remarkable for fever, diarrhea and hypotension. There were erythematous annular plaques on the dorsal hands, arms, anterior thighs and left dorsal foot. Skin lesions were slowly enlarging for the previous 10 days, with occasional itching and tenderness. The patient has a long standing history of severe Crohn's disease, beginning at age 14 years. She has been treated with weekly adalimumab (Humira) injections for the past 6.5 years.

The patient had developed similar skin lesions on her left dorsal hand and right lateral leg 7 month prior to admission, during a flare of Crohn's colitis. She reported that the adalimumab 40 mg injections had been increased from bi-weekly to weekly about 3 months before first appearance of the skin lesions. A skin biopsy on the right lower leg showed septal panniculitis, consistent with erythema nodosum; biopsy of the left dorsal hand revealed a granulomatous dermatitis, consistent with Crohn's disease. The patient continued to take adalimumab, ciprofloxacin, ibuprofen with a short course of oral clindamycin and skin lesions resolved within 2 months.

PAST MEDICAL HISTORY

Crohn's disease complicated by rectovaginal and perianal fistulas, s/p seton stitch placement; Anemia; Corticosteroid induced psychosis; Melanoma of right anterior thigh, s/p removal in 2003 (SSM/III/0.73 mm/2 mitoses/mm2/no regression)

MEDICATIONS

Adalimumab, magnesium oxide, cyanocobalamin, probiotics, ciprofloxacin, pseudoephedrine, ergocalciferol, ibuprofen, loratadine, folic acid

ALLERGIES

Penicillins, sulfamethoxazole-trimethoprim, sulfasalazine, metronidazole, codeine, hydrocodone, latex

FAMILY HISTORY

Brother - melanoma

SOCIAL HISTORY

No illicit drug use, alcohol or tobacco

PHYSICAL EXAM

On dorsal hands, left lateral upper arm, right lateral forearm, right lateral upper arm, right medial leg and right lateral leg, left dorsal foot were 1 - 8 cm erythematous annular plaques with firm, raised borders, trailing scale, and central clearing. There were a total of 11 distinct lesions, comprising about 5% body surface area. There was no palpable cervical, submental, preauricular, or supraclavicular lymphadenopathy.

HISTOPATHOLOGY

Four punch biopsies were performed (for H&E and cultures): left thigh, proximal and distal, and right distal thigh. The histologic changes are essentially similar in all specimens, consisting of an interstitial infiltrate of predominantly mononuclear and occasional multinucleated histiocytes, and varying numbers of neutrophils. Areas of myxoid stromal change were evident. The overall histpathologic changes were descriptively interpreted as an interstitial (neutrophilic and) granulomatous dermatitis. PAS and DyLight Fluor stains are negative for microorganisms.

LABORATORY RESULTS

WBC and eosinophil count within normal limits
Liver function within normal limits
Skin cultures from biopsy: negative for microorganisms, including AFB and fungal.
ESR 78 mm/hr [0-27]
Hgb 7.9 g/dl [12-16]
Hct 27.5 % [37-47]

RADIOLOGY AND DIAGNOSTIC TESTING

Colonoscopy showed diffuse severe erythema, friability, and ulcerations in the rectum and sigmoid colon, consistent with markedly active Crohn's disease. The endoscope was not advanced beyond 20-25 cm due to severity of disease, and bleeding caused by scope- and biopsy related trauma. Given the severity of inflammation seen, the entire colon was believed to be affected with severe inflammation. Chest X-ray was unremarkable.

DIAGNOSIS

Interstitial Granulomatous Drug Reaction (IGDR) to adalimumab

TREATMENT AND COURSE

The patient was treated with 40 mg prednisone taper together with risperidone (for corticosteroid induced psychosis), with complete resolution of the skin lesions. However, skin lesions reappeared after the second injection of adalimumab while concurrently on a 20 mg daily dose of prednisone. Adalimumab was discontinued, and all of her skin lesions slowly resolved.

DISCUSSION

Interstitial granulomatous drug reaction (IGDR) is a rare entity presenting as erythematous to violaceous non-pruritic plaques, often in an annular configuration, on inner aspects of the arms, medial thighs, trunk and groin. Erythema nodosum-like lesions on lower legs have also been described. The major diagnostic criteria for diagnosis of IGDR is resolution of skin lesions within 2-3 months after cessation of the implicated drug, and reappearance of skin lesions after drug re-challenge. In general, a drug reaction is not usually suspected in this situation because the culprit medication may have been taken for many months to several years.

Drugs implicated in the etiology of IGDR include calcium channel blockers (diltiazem, verapamil, nifedipine); statins (simvastatin, pravastatin, lovastatin); furosemide; beta-blockers (labetalol, metoprolol, atenolol, propranolol); antihistamines (famotidine, cimetidine, ranitidine, brompheniramine); ACE inhibitors (enalapril, lisinopril); Tumor Necrosis Factor-α inhibitors (infliximab, etanercept, adalimumab; lenalidomide, thalidomide) and Interleukin-1-receptor antagonist (anakinra). Less common drugs causing IGDR include hydrochlorothiazide, carbamazepine, diazepam, bupropion, darifenacin, sennoside and ganciclovir.

Histopathologically, IGDR shows an interstitial granulomatous dermatitis pattern with pandermal or "bottom-heavy" infiltrate that contains histiocytes, with or without an interface change. The

infiltrate can feature small “rosettes” of palisading histiocytes surrounding tiny foci of basophilic degenerated collagen, with piecemeal fragmentation surrounded by variable numbers of neutrophils and eosinophils. Dermal mucin is usually absent.

Anti-tumour necrosis factor alpha inhibitors have been described to induce different types of granulomatous infiltration: granuloma annulare-like, sarcoid-like or interstitial granulomatosis. In contrast to histopathologic changes described with IGDR related to medications, metastatic Crohn’s disease in the majority of the reported cases has been described as a granulomatous infiltration of the sarcoidal type.

Drug discontinuation and re-challenge is the most reliable method to differentiate between granulomatous drug reaction in the setting of a primary granulomatous disease such as Crohn disease.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 3**

Presented by Magdalena Kobierska, MD and Lisa M. Arkin, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

This 10 year old African American female presented to clinic for evaluation of a "scar" on the middle of her nose, which was first noted as a “brown stripe” at least one year prior. Since then, this hyperpigmented linear plaque has progressed down her nasal bridge to involve her philtrum, upper cutaneous lip and ipsilateral gum. The patient denied associated symptoms including pruritus or pain. There has also been progressive “softening” of the nasal cartilage and development of appreciable facial asymmetry, per mom. She has not had headaches, staring spells, blurry vision, ocular pain, or history of seizures, or weakness.

PAST MEDICAL HISTORY

Otherwise healthy

FAMILY HISTORY

Family history significant for maternal aunt with RA and maternal grandmother with thyroid disease. No family history of systemic lupus, sarcoidosis, inflammatory bowel disease, JIA, scleroderma, dermatomyositis, psoriasis or vitiligo. No FH of atopy, psoriasis, skin cancer or melanoma.

PHYSICAL EXAM

At the time of the initial examination, patient presented with a well demarcated, hyperpigmented linear sclerotic plaque just slightly to the right of midline on the nose. Originating at approximately the level of the nasal supratip the linear plaque extends inferiorly to involve the columnella, philtrum, upper cutaneous lip and upper gingiva. At the level of the philtrum, the linear plaque becomes more hypo-pigmented and sclerotic in appearance. There is an obvious architectural distortion of the midline nasal tip with loss of the underlying cartilaginous structures as well as some subtle but appreciable nasal alar asymmetry with apparent subcutaneous loss of the right nare relative to the left. There is significant gingival recession (both free and attached gingiva) ipsilateral to the lesion abutting the right upper incisor. Superior to the supratip, the nose and remaining facial structures are spared and normal in appearance, including the forehead and scalp. Lower cutaneous lip is also unaffected and apparently normal. There are no other associated cutaneous findings of note.

HISTOPATHOLOGY

None

LABORATORY RESULTS

CBC with differential within normal limits
CMP within normal limits
Quantiferon gold negative

DIAGNOSIS

En coup de Sabre (linear facial morphea) with subcutaneous atrophy suggestive of Parry Romberg Syndrome

TREATMENT AND COURSE

A combination therapy of 25 mg subcutaneous methotrexate (MTX) and 1 mg/kg oral prednisone was initiated. Additionally, patient was also started on topical therapy with desonide and calcipotriene ointment. The prednisone was slowly tapered after 6 weeks but she developed a new active lesion on the nasal bridge, prompting re-initiation of a full 3-4 months of oral prednisone. The new area of activity has resolved on this regimen and she has significantly improved. She is seeing oral maxillary facial surgery for evaluation of the gingival recession, and has been followed by ophthalmology as well. Our plan is to treat her with subcutaneous methotrexate for 1-2 years and to wean her oral steroids after 3 months.

DISCUSSION

Morphea (also known as localized scleroderma) is an idiopathic, inflammatory disorder of the skin and its underlying mesenchymal structures. It is characterized by overabundance of collagen deposition in the skin with variable degrees of involvement of the subcutaneous fat, muscle, fascia, bone and/or cartilage. En Coup de Sabre (ECDS) and Parry-Romberg Syndrome (PRS) were historically thought to represent opposite ends of the disease spectrum in linear morphea, with ECDS marked by significant epidermal change and PRS manifesting mostly subcutaneous atrophy. Both are now recognized to occur in long-standing disease.

Cases of contiguous extension into deeper underlying structures like the gingivae or CNS are not uncommon. Unlike systemic sclerosis, morphea lacks the distal findings of acral sclerosis or Raynaud's phenomenon and, most importantly, no true visceral fibrosis is seen. However, extracutaneous manifestations including joint contractures, neurologic and ocular involvement, have been reported in up to 40% of patients, most commonly in those with linear morphea who present before the age of 10. Pediatric linear morphea patients also tend to have an overall longer disease course with higher recurrence rates. One study found the mean disease duration to be nearly twice as long for juvenile linear morphea when compared to the adult onset-variant (13.5 vs. 5.8 years), with recurrence rates as high as 28-44% at 16-20 months. Periods of relapse and remission were seen in 20-30% of childhood morphea patients, in some cases, lasting up to 20 years after initial disease onset.

Clinicians face many difficulties when treating children with morphea. First, there is paucity of randomized treatment studies to help identify optimal therapeutic approaches and, until recently; no standardized treatment protocols existed to help guide management. Additionally, no validated treatment response criteria have been established to help guide optimal treatment duration and response to therapy. Another major challenge for clinicians is differentiating active disease from inactive damage, as treatment is only effective for active disease. This process is further complicated by the lack of objective tools for quantifying disease activity as there are no specific biomarkers or reliable diagnostic laboratory studies for morphea. Autoantibodies are not useful for diagnostic purposes and do not correlate well with disease severity.

Markers of activity include erythema, specifically an erythematous or violacious/ lilac border, pruritus and presence of expanding/ new lesions. Over time, edema and increased collagen deposition ensue with a progressive shiny white discoloration and induration as disease damage progresses. Markers of burnt-out lesions are characterized by dyspigmentation and atrophy (epidermal as noted by venous prominence; dermal which gives rise to the "cliff drop" appearance and subcutaneous fat atrophy which is lipoatrophy to the fascia).

In terms of development of more systematic treatment guidelines, much is owed to the relatively new consensus recommendations from the Childhood Arthritis and Rheumatology Research Alliance (CARRA) which in 2012 proposed 3 standardized treatment plans for patients with linear morphea and rapidly progressive disease. These include Methotrexate (1 mg/kg) for a

year either as monotherapy or in conjunction with three month course of systemic steroids as either intermittent, pulsed IV doses or three month, daily oral steroid taper (starting at ~1 mg/kg).

We present our patient to highlight the characteristic aspects of linear facial morphea complicated by ipsilateral gingival recession. In the previously reported cases in the literature progressive recession of the gingivae with alveolar bone resorption ensued. There are no reports of improvement with systemic immunosuppression, and we do not expect her to regain the gum she has lost. However, given the concern for re-activation of her disease with operative trauma, we hope to postpone surgical intervention for as long as possible with close follow up with oral surgery.

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Presented by Bryan Sofen MD, James Ertle MD, and Arthur Rhodes MD
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Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 5**

Presented by Emily Garritson, MD and Warren Piette, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

The patient is a 47-year-old black male who presented to clinic with an 8 month history of insidious skin changes. He noted swelling of his glabella, ears, and perioral area, as well as, small bumps on his trunk and extremities. All of the cutaneous changes were asymptomatic. He endorsed a sensation of tightness involving his hands and perioral area. At the initial visit, the patient was not using any treatment, but he stated he was given a topical corticosteroid by another dermatologist. He also had two punch biopsies of his right earlobe and right lower abdomen performed two weeks prior to his first visit at Rush. A review of systems revealed myalgias and neuropathy of the upper extremities. He specifically denied any dysphagia or respiratory difficulties.

PAST MEDICAL HISTORY

He has no significant past medical history.

MEDICATIONS

He was not taking any prescribed or over-the-counter medications at the initial visit.

ALLERGIES

The patient has no known drug allergies.

FAMILY HISTORY

There are no known family members with similar cutaneous findings.

SOCIAL HISTORY

The patient is a non-smoker and does not drink alcohol.

PHYSICAL EXAM

On initial examination, the patient's ear lobules, glabella, forehead, and perioral area were indurated with mild overlying erythema giving an overall Leonine facies appearance. His dorsal hands appeared normal, but his trunk and proximal extremities were covered with dozens of small 1-2 mm follicular papules.

HISTOPATHOLOGY

Two 4 mm punch biopsies were obtained by an outside dermatologist of the right earlobe and right abdomen. Both specimen demonstrated proliferation of fibroblastic cells with thickening of the collagen. These findings were accompanied by an increase in dermal mucin, which was highlighted by Alcian Blue staining.

LABORATORY RESULTS

TSH: 2.015 [0.350-4.940 uIU/ml]
Immunofixation Electrophoresis: Monoclonal IgG kappa detected
Immunoglobulins:

- IgG 1739 (ref 596-1584 mg/dl)
- IgA 44 (ref 35-213 mg/dl)
- IgM 140 (ref 59-292 mg/dl)
- Beta-2 Microglobulin 2.49 (0-3 mg/L)

Bone marrow biopsy: Slight plasmacytosis of 10% of cells but no definitive plasma cell dyscrasia. The majority of the plasma cells are reactive, and the specimen was negative for amyloid.
Skeletal survey: No lytic bone lesions.

DIAGNOSIS
Scleromyxedema

TREATMENT AND COURSE
The patient was referred to hematology/oncology for further evaluation and treatment. A bone marrow biopsy and skeletal survey were both negative for multiple myeloma. He was started on prednisone 100 mg daily and tapered off over the course of 3 weeks. In addition, he began monthly treatments with IVIG. Initially, the IVIG was planned to be given as 1 mg/kg on days 1 and 2 of each 28 day cycle. However, he experienced headaches and fevers after the first treatment, so the protocol was modified to limit the symptoms of serum sickness. He has completed his fourth cycle of IVIG, which is now dosed at 0.4 mg/kg administered on 4 sequential days each month. He has seen significant improved in his skin, myalgias and neuropathy.

DISCUSSION
Scleromyxedema, a rare mucin deposition disorder, is one of the three subtypes of lichen myxedematosus as classified by Rongioletti. All subtypes are defined by the presence of dermal fibroblast proliferation, mucin deposition, and increased collagen histologically. Scleromyxedema is the generalized and most severe subtype that occurs in conjunction with a monoclonal gammopathy and/or systemic involvement. There are several variants in the localized subtype, which lack the associated gammopathy and visceral disease. The atypical or intermediate subtype is composed of patients with presentations that do not directly correspond to the diffuse or localized subtypes. In all forms of lichen myxedematosus, the manifestations must occur in the absence of a thyroid disorder.

Scleromyxedema affects both sexes equally, but it tends to be a disease primarily of adults older than age 30. The pathogenesis of this disease remains unknown, and the role of the associated paraproteinemia remains controversial. Serum from a scleromyxedema patient has been shown to stimulate fibroblast proliferation in vitro, but the IgG isolated from the same patient did not result in a similar proliferative state.

Patients with scleromyxedema present clinically with a symmetric distribution of numerous small (2-3 mm), waxy, flat-topped papules that can coalesce into large plaques. The papules are often linearly arranged. Common sites of involvement include the face, neck, upper trunk, extensor extremities, and dorsal hands. The disease is chronic with progressive induration of the skin. Patients develop a shiny sclerodermoid appearance and may demonstrate a reduced range of motion of the hands or perioral area. Induration of the forehead and glabella contribute to the characteristic “leionine facies” of patients with scleromyxedma. In addition, involvement of the proximal interphalangeal joint can produce a phenomenon known as the “doughnut sign” with an elevated rim of skin surrounding a central area of depression. The cutaneous changes can be pruritic or asymptomatic.

Visceral disease is common in patients with scleromyxedema and is estimated to affect 70% of patients. Gastrointestinal involvement is seen most often with dysphagia being the most frequent complaint. The lungs are the second most common site of systemic involvement and can be manifested as either obstructive or restrictive pulmonary disease. Arthralgias and inflammatory myopathy are not uncommon, and at least ten percent of patients have carpal

tunnel syndrome. Patients can have disease activity in the peripheral and central nervous systems. The dermato-neuro syndrome describes patients with a flu-like prodrome, seizures, fevers, worsening cutaneous lesions, and unexplained coma. Systemic involvement can be fatal.

Approximately 80-90% of patients with scleromyxedema will have a monoclonal gammopathy during the initial work-up. Unlike our patient, it is usually a gammopathy of the IgG-lambda subtype. A bone marrow biopsy may reveal a plasmacytosis, but only 10% of patients evolve to multiple myeloma. The paraprotein levels have not been significantly associated with disease severity or progression.

A triad of features defines the histologic appearance of scleromyxedema. Biopsies demonstrate a proliferation of irregularly arranged fibrolasts, deposition of mucin in the upper and mid dermis, and increased collagen deposition. The overlying epidermis may be unremarkable to mildly atrophic. The histologic features of scleromyxedema are often diagnostic in suspected cases, but these same features are identical to those seen in cases of nephrogenic systemic fibrosis. However, patients with nephrogenic systemic fibrosis often have involvement of the fat and generally lack any cutaneous facial involvement or the associated gammopathy.

Treatment of scleromyxedema is challenging. Because the majority of articles published in the literature focus on small case series, there is little evidence to support a favored treatment modality. Melphalan was commonly utilized in the past as it targeted the plasma cell dyscrasia, but this treatment was also associated with increased induction of other hematologic malignances and sepsis. Now patients are often treated with various combinations of melphalan, thalidomide, prednisone, dexamethasone, bortezomib, lenalidomide, and IVIG. In a recent case series of 30 patients, IVIG was found to be effective as the sole therapy in 3 patients and as the second line agent in another 9 patients who failed alternative medications. IVIG is administered at 2 mg/kg per month and continued cycles are needed for remission. Rongioletti et al. favor IVIG as the treatment of choice for scleromyxedema as it is relatively safe and effective for both the cutaneous and visceral manifestations.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 6**

Presented by Todd Rickett, MD, PhD and Lisa Arkin, MD
Department of Dermatology, Rush University Medical Center

HISTORY OF PRESENT ILLNESS

A 58 year-old white female with a significant medical history of chronic immunosuppression following renal transplantation was hospitalized for a myocardial infarction and found to have a warm, painful, red plaque on her right thigh. The patient noted that the rash had initially appeared 3-4 weeks prior to admission but had gradually enlarged and become increasingly tender. She denied recent travel history, fever, chills, or any systemic symptoms. Empiric treatment for cellulitis was initiated with meropenem and vancoymycin. Dermatology was consulted when minimal improvement was noted after a few days of therapy.

PAST MEDICAL & SURGICAL HISTORY

Acute on chronic diastolic heart failure
Congenital hypoplastic kidneys s/p renal transplant in 2010 complicated by thrombotic microangiopathy s/p plasma exchange, now on eculizumab
Pneumocystis jirovecii pneumonia (5 months prior)

MEDICATIONS

Leflunomide, Prednisone, Atovaquone, Nystatin, Valganciclovir, Meropenem, Mycophenolate Mofetil, Tacrolimus

ALLERGIES

Azithromycin (Rash)
Penicillin (Rash)

FAMILY HISTORY

The patient's family history was significant for Wegener's granulomatosis, diabetes, MI, and stroke in her mother and hypertension, asthma, and heart failure in her father.

SOCIAL HISTORY

The patient is a former smoker, having quit cigarettes 31 years prior. She drinks alcohol rarely, and denies ever using recreational drugs.

PHYSICAL EXAM

The patient was an obese but frail white woman who appeared older than her stated age. She was afebrile. She had bilateral 2+ pitting edema of her lower legs to the knees. Dorsalis pedis pulses were palpable bilaterally. On her lateral distal right thigh, a poorly-circumscribed erythematous, warm plaque was noted, which was exquisitely tender to palpation. There was no cervical, axillary, or inguinal lymphadenopathy.

HISTOPATHOLOGY

Punch biopsy of the lesion center demonstrated acute inflammation containing fungal forms. PAS and GMS stains were positive for fungi consistent with blastomycosis.

LABORATORY RESULTS

WBC within normal limits
Lymphocytes: 10% [18-52%]
Urine Blastomycosis antigen positive

DIAGNOSTIC PROCEDURES AND TESTS

Aerobic Bacterial Culture, Bronchial Lavage, Blood, Pleural Fluid, and Skin Biopsy: No growth
Anaerobic Bacterial Culture, Bronchial Lavage, Blood, Pleural Fluid, and Skin Biopsy: No growth
Fungal Culture, Bronchial Lavage, Blood, and Pleural Fluid: No growth
Acid-Fast Bacilli Culture, Pleural Fluid and Skin Biopsy: No growth
Fungal Culture, Skin Biopsy: Growth of Dimorphic Fungi
DNA Probe Assay, Skin Biopsy: *Blastomyces dermatidis*
Radiograph, Chest: Bilateral patchy airspace opacities in the lung bases
Non-Contrast CT Scan, Lungs: No changes suggestive of fungal consolidation
MRI, Brain: No intracranial masses or lesions
MRI, Right Femur: No evidence of osteomyelitis

DIAGNOSIS

Blastomyces dermatitidis cellulitis

TREATMENT AND COURSE

Anti-fungal induction therapy was initiated with liposomal amphotericin B, with significant improvement after a few days, with reduction of erythema, induration, and pain. She completed 10 days of amphotericin before being transitioned to oral itraconazole

DISCUSSION

Fungal infections can be serious complications of immunosuppression following organ transplantation. *Blastomyces dermatidis* is a rare pathogen in this population. Blastomycosis has also been known as North American blastomycosis, Gilchrist's disease, or Chicago disease. *B. dermatidis* is endemic to the Central and Southeastern regions of the United States—particularly the Ohio and Mississippi river valleys—the Great Lakes region, and the coastal portions of Canada.

The causative organism exists in nature as a mold that proliferates in warm soil, decaying wood, or other moist organic matter. Infection most commonly arises from inhalation of fungal conidia, which become aerosolized when soil containing the mold is disturbed. Once inhaled, the fungal conidia transform to the yeast phase in the lung, where they proliferate if the host's cellular immune response is unable to clear the pathogen rapidly. While the vast majority of cases of systemic blastomycosis originate in the lung, there are reports of isolated cutaneous *B. dermatidis* spread by direct physical inoculation such as in puncture injuries, dog bites, and laboratory/autopsy accidents.

Cutaneous blastomycosis infections typically appear as ulcers, abscesses, or verrucous papules/plaques, often studded with pustules at the border. Our patient's presentation with a cellulitic plaque is unusual, as fungal cellulitis is rare. Cellulitis is a recognized presentation for Candida, Cryptococcus,and Histoplasma, but occurs less commonly in other dimorphic fungi. Only a single case report has described presentation of Blastomycosis as cellulitis.

The primary source of her infection remains uncertain. Imaging studies revealed no evidence of pulmonary, CNS, or bone involvement. She may have developed primary cutaneous blastomycosis due to direct inoculation of the skin or hematogenous dissemination from a sub-clinical pulmonary infection, which resolved spontaneously prior to imaging. The presence of blastomycosis antigens in serum or urine detects 93% of patients with the disease, and is thought to be more sensitive in those with disseminated infections. Therefore our patient's positive urine study would argue against a primary cutaneous infection and support the presence of systemic disease. Up to 30% of some populations in endemic areas have experience subclinical infections.

Histopathology demonstrates dermal and epidermal neutrophilic microabscesses with suppurative, granulomatous infiltrate. Causative organisms can often be visualized directly in or around blood vessels on slides treated with periodic acid-Schiff (PAS) or Grocott's methenamine silver (GMS) stains. *B. dermatidis* appear as multi-nucleate yeasts with double cell walls and characteristic broad based buds. Besides biopsy, blastomycosis may be visualized on KOH stains of sputum, skin scrapings, or pus. Polymerase chain reaction (PCR) can also be used to detect blastomycosis DNA. Despite advances in diagnostic techniques, the most sensitive test and diagnostic gold standard remains isolation of *B. dermatitidis* on fungal culture.

Treatment is appropriate for all patients with clinically symptomatic disease. Mild to moderate disease in immunocompetent hosts may be treated with itraconazole for 6-12 months. For more severe systemic disease or in immunocompromised hosts, more aggressive treatment is necessary with amphotericin B induction followed by at least 12 months of oral itraconazole to prevent relapse. This case demonstrates the importance of considering atypical pathogens and uncommon presentations in the immunocompromised host.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 7**

Presented by Blake Troiani, MD, and Lady Dy, MD
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PATIENT A

HISTORY OF PRESENT ILLNESS
In 2011, a 14-year-old white female presented to clinic for the evaluation of hair loss that began around the age of 8 or 9. At the time her hair loss began, her parents noticed small discrete round patches of hair loss localized only to the scalp. She was treated by an outside dermatologist for alopecia areata with topical and intralesional steroids. These treatments led to resolution of individual patches of hair loss; however, new patches continued to develop. Eventually, hair loss became apparent in the eyebrows and eyelashes. Other areas of the body remained with normal hair intact.

PAST MEDICAL HISTORY
No contributory history

MEDICATIONS
None

ALLERGIES
None

FAMILY HISTORY
No family history of atopy. The patient's sister has experienced the same type of hair loss.

SOCIAL HISTORY
The patient lives with her family. No one in the household is a smoker. She is otherwise happy and performs well in school.

PHYSICAL EXAM
At the time of her presentation to our clinic, her hair loss had progressed to involve almost the entire surface of the scalp. Eyebrows and eyelashes were also affected bilaterally with minimal retention of hair shafts. Her nails were not involved.

HISTOPATHOLOGY
None

LABORATORY RESULTS
None

RADIOLOGY
None

DIAGNOSIS
Alopecia totalis

TREATMENT AND COURSE
Initially, treatment was attempted with intralesional steroids to the scalp and eyebrow areas, resulting in minimal hair growth. Considering the lack of significant improvement with intralesional steroids alone, systemic immunosuppression was initiated with methotrexate.

Over the subsequent months, the patient's methotrexate dose was increased to a maximum of 20 mg weekly with sporadic improvements noted at follow up appointments. Throughout treatment with methotrexate, the patient continued to receive focal intralesional steroid injections. Methotrexate was continued for approximately 6 months before being discontinued due to lack of overall efficacy. She remained with diffuse hair loss over the scalp and with sparse eyebrows and eyelashes.

Treatment with squaric acid as a topical immunotherapy was then initiated starting at a dilution of 0.1% applied weekly to the scalp. Although initially, new regrowth was noted, eventually this growth was lost despite increased frequency of application and then increased strength of application up to a dilution of 2%. Accordingly, squaric acid was discontinued after about 1 year in favor of restarting methotrexate.

After restarting methotrexate and eventually reaching a dose of 25 mg weekly, again new hair growth was noted on the scalp that subsequently was lost despite continued treatment. Squaric acid was restarted in conjunction with methotrexate after 6 months of treatment. As before, periods of new growth and then loss were experienced.

During the course of her treatments, the patient had begun to wear prosthetic hair pieces, including prosthetic eye lashes. Other treatments attempted in conjunction with immunomodulation included minoxidil to the scalp and bimatoprost solution to the eyebrows and eyelashes.

After another 6 months of frustrating results with combined methotrexate and squaric acid treatments, she was referred to an outside dermatologist who was able to obtain tofacitinib. After 2 months of receiving tofacitinib, she had begun to demonstrate a response with new short terminal hairs visible. She was treated with 5 mg by mouth daily with an increase to 5 mg twice daily after 4 weeks. Increasing the frequency of dosing did not lead to enhanced response to the drug. She continues taking tofacitinib today in the hopes that she will continue to respond. Other treatments have not been continued. She is tolerating tofacitinib well with no adverse effects noted at the time this protocol was written.

PATIENT B

HISTORY OF PRESENT ILLNESS
The sister of patient A presented at the age of 12 with a similar history of hair loss starting with discrete round patches of hair loss localized only to the scalp. As in her sister, hair loss progressed to involve the entire scalp. Eventually, hair loss became apparent in the eyebrows and eyelashes. Other areas of the body remained with normal hair intact.

PAST MEDICAL HISTORY
No contributory history

MEDICATIONS
None

ALLERGIES
None

FAMILY HISTORY
No family history of atopy. The patient's sister has experienced the same type of hair loss.

SOCIAL HISTORY
The patient lives with her family. No one in the household is a smoker. She is otherwise happy and performs well in school.

PHYSICAL EXAM
At the time of her presentation to our clinic, her hair loss had progressed to involve almost the entire surface of the scalp. Eyebrows and eyelashes were also affected bilaterally with minimal retention of hair shafts. Her nails were not involved.

HISTOPATHOLOGY
None

LABORATORY RESULTS
None

RADIOLOGY
None

DIAGNOSIS
Alopecia totalis

TREATMENT AND COURSE
This patient's treatment course parallels that of her sister's. After failing intralesional steroids, systemic immunosuppression with methotrexate, topical immunotherapy with squaric acid, and a combination of methotrexate with squaric acid, she was referred to an outside dermatologist who was able to obtain tofacitinib.

After 6 months of receiving tofacitinib, she had begun to demonstrate a significant response with new pigmented terminal hairs covering the entire scalp and some recovery of hair follicles in the eyebrows. She received 5 mg by mouth daily throughout the course of treatment. She continues taking tofacitinib today in the hopes that she will continue to respond. Other treatments have not been continued. She is tolerating tofacitinib well with no adverse effects noted at the time this protocol was written.

DISCUSSION
Alopecia areata is the most common cause of inflammatory hair loss in the United States, where it has been estimated that approximately 4.5 million people are affected. The worldwide prevalence has been estimated at 0.1%-0.2%, and the calculated lifetime risk for developing alopecia areata is 2%. Both children and adults may be affected, and younger patients are more likely affected, with up to 66% of patients under the age of 30.

The typical clinical presentation of alopecia areata is that of rapid hair loss in well-circumscribed patches with normal underlying skin. The most common location of involvement is the scalp, but the beard region is also frequently affected. While most cases with remain with limited hair loss, some cases may progress to involve the total scalp (alopecia areata totalis) or even the

whole body (alopecia areata universalis). Characteristic clinical signs include exclamation-mark hairs, cadaver hair, nail pitting, and the growth of depigmented hairs in formely affected areas.

Recent work regarding the pathogenesis of alopecia areata continues to demonstrate evidence of the disease as an autoimmune process. Under baseline circumstances, the hair follicle represents a site of immune privilege, established mainly by the suppression of major histocompatibility complex antigen (MHC) class 1, which serve to present antigen to CD8+ T lymphocytes. A local immunoinhibitory signaling milieu also contributes to hair follicle immune privilege status. When that status is breached, by mechanisms as yet not entirely understood, the expression of follicle antigens to CD8+ T lymphocytes ensues, allowing for an immune response against these antigens. Antigens implicated thus far have included those involved with melanin synthesis. As only anagen hairs actively produce melanin, response to these antigens provides an explanation for the fact that only anagen hairs are affected. Given the autoimmune nature of alopecia areata, an increased frequency of other autoimmune conditions, such as thyroid disease, systemic lupus erythematosus, vitiligo and diabetes mellitus, has been well described in affected patients. In addition, a link to atopic dermatitis has been made.

Treatment of alopecia areata is well known to be difficult and often disappointing. Curative therapy does not exist, and the disease tends to run a chronic relapsing course. All treatments described for alopecia areata are aimed at affecting the autoimmune response, either directly with local or systemic immunosuppression or via immune-deviation strategies that manipulate the cutaneous inflammatory milieu. The best-tested treatment is intradermal injections of triamcinolone given ever 2-6 weeks. High potency topical steroids under occlusive dressings have also been shown to be effective. Systemic steroids may also be given, but their use is generally limited to avoid significant side effects associated with their use. In some cases, systemic immunosuppression has been attempted with steroid-sparing immunosuppressants with varying degrees of success. Immune-deviation may be accomplished with the topical application of squaric acid, typically applied weekly to the affected areas. Squaric acid application has been shown to provide regrowth in approximately 17% of alopecia areata totalis patients. Adjunctive treatments, including minoxidil and bimatoprost solution, may be added to facilitate anagen hair survival.

Alopecia areata pathogenesis is primarily mediated by CD8+ cytotoxic T lymphocytes in coordination with CD4+ helper T lymphocytes. Together, these cell types secrete cytokines typical of a Th1 response, to include IFN-γ and IL-2. Cytotoxic T cells are activated and maintained by the cytokines IL-2 and IL-15. In order to facilitate continued survival, these cells themselves begin to produce IL-2 and IL-15 via IFN-γ signaling. All three of these cytokines, IL-2, IL-15 and IFN-γ produce intracellular effects via a cell membrane-spanning janus kinase receptor. Tofacitinib acts by inhibiting signaling from janus kinase inhibitors, thereby blocking the effects of IL-2, IL-15 and IFN-γ on the cytotoxic T cells. Without these signals, cytotoxic T cell survival is no longer promoted, preventing the immune response causative of alopecia areata. A growing number of studies have demonstrated efficacy of janus kinase inhibitors, tofacitinib and ruxolitinib, in the treatment of alopecia areata, both via systemic and topical administration.

Tofacitinib has been approved by the Federal Drug Administration for the treatment of rheumatoid arthritis and is currently undergoing studies for treatment in psoriasis. Safety data for tofacitinib has been obtained from phase 1, 2 and 3 trials. As JAK signaling is integral to hematopoiesis, many adverse effects occur within this system. Modest, dose-dependent decreases in hemoglobin, hematocrit and red blood cell count may be seen. Dose-dependent transient decreases in neutrophil, eosinophil, NK cell, and T cell counts may be seen. Considering changes in immune cell counts, infection rates were examined and were not found

to be significantly higher in those receiving tofacitinib. Studies did demonstrate; however, a very small risk of reactivation of latent tuberculosis, prompting the recommendation that patients be screened prior to treatment. Other laboratory abnormalities noted included liver enzyme elevations, cholesterol (LDL and HDL) elevations and elevations in serum creatinine. Other adverse events included headache, diarrhea, nasopharyngitis, and hypertension.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 8**

Presented by Magdalena Kobierska, MD and Lisa Arkin, MD, Mark D Hoffman, MD, Julie Moore, MD & Warren Piette, MD
Department of Dermatology, RUSH University Medical Center

PATIENT A

HISTORY OF PRESENT ILLNESS

A 50-year-old white woman presented to clinic with one year history of bilateral upper eyelid edema and associated violaceous erythema of the periorbital skin and malar cheeks. There were no other skin manifestations. Patient did not complain of any fatigue, myalgias, arthralgias or respiratory symptoms at the time of initial presentation. Shave biopsy from eyelid for H&E staining revealed interface vacuolopathy with sparse lichenoid lymphocytic infiltrate as well as lymphocytic perivascular infiltrate within the superficial and deep dermis. Direct immunofluorescence was negative for both Lupus band and ANA in vivo reaction, leaving dermatomyositis in the differential. Baseline labs were unremarkable, including normal CMP, CPK, Aldolase, ESR and CRP. CBC revealed baseline microcytic anemia in the context of a known thalassemia trait.

Given her characteristic rash, absence of weakness on exam, and normal muscle enzymes, the diagnosis of clinically amyopathic dermatomyositis was made. The patient was initiated on treatment with Prednisone (20-40 mg/day) and Hydroxychloroquine with significant improvement. After three years, hydroxycholoroquine was discontinued and systemic steroids were tapered, with subsequent recurrence of the facial eruption. At this time, the patient also developed new-onset deep ulcerations on her bilateral hands and progressive diffuse non-scarring alopecia. Examination did not reveal any scaly tender palmar papules.

Biopsy of one of the hand lesions revealed a simple ulcer with no evidence of vasculitis or calcinosis. A myositis specific antibody panel was sent with concern for anti-MDA5 positive dermatomyositis and eventually confirmed. Subsequent pulmonary work up revealed interstitial lung disease. The patient had minimal response to resumption of higher-dose Prednisone, Hydroxycholorquine or Methotrexate. Ulcerations finally began to heal with initiation of IVIG and Sildenafil. Her pulmonary disease is currently being treated with oral tacrolimus and is stable.

PHYSICAL EXAM

Initial examination revealed bilateral upper eyelid erythema and edema and violaceous erythema of her malar cheeks. There were no other skin manifestations on initial presentation. Three years later, examination revealed similar facial findings, as well as multiple deep ulcerations with central crusting over her bilateral 2nd metacarpophalangeal joints, left 3rd and 4th proximal interphalangeal joints, and bilateral 2nd through 4th distal palmar digits.

LABORATORY WORKUP

IFA ANA titer: 1:30, repeat 1:50 [<1:40]
AST: 34 [3 – 44]
TSH: 1.53 [0.3-4.9]
SSA: positive
SSB: negative

IMAGING
Mammography – unremarkable
Gastroscopy – unremarkable
Colonoscopy – adenomatous polyps, otherwise unremarkable
CT of chest, abdomen and pelvis – unremarkable

DIAGNOSIS
Anti-MDA5 Antibody Positive Dermatomyositis

PATIENT B

HISTORY OF PRESENT ILLNESS
A 40-year-old Hispanic woman presented for management of edema, fever, and cough, with tender cutaneous ulcerations and generalized pruritus. Patient has a known history of treatment-resistant amyopathic dermatomyositis with severe cutaneous disease. Recently, patient had been undergoing aggressive immunosuppressive therapy with tacrolimus, MMF, AZA, MTX, and Inflixumab when she developed a listeria brain abscess. Since this complication, all immunosuppressants had been discontinued except for prednisone (15 mg daily), and IVIG infusions had been initiated with improvement of her skin disease.

Patient did not endorse any symptoms of proximal muscle weakness and her muscle enzymes were normal despite a previously abnormal EMG. A myositis specific antibody panel was sent and confirmed TIF-1 gamma antibody dermatomyositis. Initial work up revealed no evidence of underlying malignancy on a chest/abdomen/pelvic CT. Further malignancy workup, including mammography, colonoscopy and PAP smear screening have been delayed given patient's recent infectious complications. She has new onset pulmonary symptoms with work-up currently in progress, though per pulmonology most recent assessment, symptoms most consistent with recurrent episodes of aspiration pneumonia, persistent baseline atelectasis and persistent lung under-recruitment rather than interstitial lung disease.

MEDICATIONS
Prednisone, 15 mg G-tube daily
Hydroxychloroquine, 400 mg G-tube daily
Hydroxyzine, 25 mg G-tube TID
Gabapentin 300 mg G-tube TID

PHYSICAL EXAM
There was diffuse violaceous erythema of her face and poikiloderma of the patient's chest and back. She also had numerous shallow ulcerations on her upper extremities as well as pink infiltrated papules on her dorsal hands overlying joints. All ten fingers showed ragged cuticles with capillary loops and drop out.

LABORATORY RESULTS
TIFI Gamma (P155/140) EIA: 103 [>80 Units = Strong Positive]
MDA-5 (CADM-140) EIA: negative
CPK: within normal limits
AST: within normal limits
Aldolase: within normal limits

DIAGNOSIS
TIF1-gamma Antibody Positive Dermatomyositis

TREATMENT AND COURSE
Given recent active infection, all prior immunosuppressant medications were held except for prednisone, 15 mg PO daily and patient was started on hydroxycholorquine 200 mg BID. Monthly IVIG initiated and patient has received a total of 4 infusions and plans to continue, 1 g/kg each with some improvement in skin ulcerations but minimal improvement in pruritus.

PATIENT C

HISTORY OF PRESENT ILLNESS
The patient is a previously healthy 2-year-old African American male who presented for evaluation of a new-onset rash. Two weeks prior, the patient was ill with a likely coxsackie viral infection. Since then, all of his initial mucocutanous findings had resolved and mother noted appearance of a new rash on his dorsal hands, dorsal feet, elbows and knees. Mother also endorsed new-onset ragged cuticles and violaceous crusted papules on the helices of his ears bilaterally. During this time, he seemed increasingly lethargic per mom and was not interested in playing. He also seemed to be limping intermittently and whimpering when he walked. Mom again reported tactile fevers but not taken his temperature at home.

On admission, he was noted to have a transaminitis (AST 312, ALT 112) with elevated CPK of 2225. He was irritable and limping, but there was no shortness of breath, cough, dysphonia or dysphagia. Inflammatory markers were notable for a slightly elevated ESR of 20 with normal CRP (<5). An EKG revealed 1st degree block but a follow up echocardiogram was normal.

PHYSICAL EXAM
On examination, the patient was fussy with a hesitant gait but was otherwise afebrile and non-toxic-appearing. He had numerous violaceous scaly papules and plaques on his bilateral ears, cheeks, dorsal hands and elbows. All 10 fingers with ragged cuticles, multiple fingernails with splinter hemorrhages and prominent dilated capillary loops with early drop out noted under dermoscopy.

LABORATORY RESULTS
CPK: 2225 [10-205]
Aldolase: 22.6 [3.4-11.8]
LDH: 970 [110-240]
AST: 312 [3-44]
ESR: 20 [0-17]
CRP: normal
ANA Screen: negative
Myositis Specific Antibody Panel – pending

DIAGNOSIS
Juvenile Dermatomyositis, Myositis Specific Antibody pending

TREATMENT AND COURSE
The patient was directly admitted from clinic to Lurie Children's, where he was managed by the pediatric rheumatology service and found to have widespread patchy uptake on MR consistent with severe myositis. He was started on pulse solumedrol, subcutaneous methotrexate and hydroxychloroquine and has improved significantly since presentation. His mother reports that his skin is much improved and he is now nearly back to his baseline strength.

DISCUSSION

Dermatomyositis is a systemic autoimmune disease characterized by involvement of the skin, muscle and occasionally lung. Clinically, however, DM is a widely heterogeneous disease with variable cutaneous, muscle and pulmonary manifestations. Recently, specific cutaneous phenotypes have been identified which correlate with particular myositis-specific antibodies (MSAs) and are helpful for risk stratification and prognosis. In certain subsets of DM, MSAs may be detectable in serum prior to symptom onset and titers may correlate with disease activity.

Approximately 60 to 70% of patients with DM have sero-positivity to such MSAs. Some of these MSAs, along with their distinctive clinical subsets, have long been recognized. For example, anti-ARS antibodies (aminoacyl-tRNA Synthetases) (~25-25% DM) [which include: anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo or anti-Ha] and are highly associated with the "anti-synthetase syndrome," characterized by myopathy, fever, interstitial lung disease (ILD), Raynaud's phenomenon, non-erosive arthritis and mechanic's hand. In contrast, anti-Mi-2 antibody (~10-30% DM) is associated with more "classic" manifestations of DM, lower rates of malignancy and interstitial lung disease (ILD) and a more favorable response to therapy. Several novel, DM-specific, MSAs and their respective clinical subtypes have recently been described, namely anti-MDA-5 (CADM-140) and anti-TIF1-Gamma (p155/140) antibodies.

MDA-5 is the autoantigen recognized by the anti-CADM-140 antibody. MDA-5 is anRNA helicase and a member of the RIG-I family and is involved in the innate immune response against intracellular viruses, cellular growth suppression and apoptosis. Found in ~10-30% of DM patients, anti-MDA-5 antibody positivity is associated with clinically amyopathic DM (CADM), rapidly progressive interstitial lung disease (RP-ILD) and a characteristic cutaneous phenotype consisting of skin ulcerations, tender palmar papules that show vasculopathy on histopathology, or both. Of note, the majority of original studies on MDA-5 DM come from Asian populations (Japanese, Korean and Chinese) where the frequency anti-MDA-5 positivity is reportedly higher (20-30%) vs. 10-20% in Caucasian DM patients and the severity of associated RP-ILD is thought to be worse. Recent study from US cohort confirmed this by showing less severe or even absent ILD even in the presence of MDA-5 Ab positivity. In addition, the study highlighted two additional features of the MDA-5 DM phenotype: presence of three of more features of the antisynthetase syndrome despite absence of anti-ARS antibodies and symmetric polyarthropathy clinically indistinguishable from Rheumatoid Arthritis.

MDA-5 is unique among the DM-specific autoantigens in terms of its cellular localization and function. Unlike some of the other DM-specific antigens (p155 or Mi-2), which are nuclear proteins involved in transcriptional or translational regulation, MDA-5 localizes to the cell membrane. It senses intracellular viral infection and subsequently upregulates type I interferons to suppress viral replication and modulate adaptive immunity. Viral infection has long been postulated as one of the potential etiologies of the idiopathic inflammatory myopathies, including DM. Adults with MDA-5 antibodies often experience an acute onset and a severe, treatment-resistant course. Children, on the other hand, tend to have lower rates of interstitial lung disease relative to adults, with an overall improved prognosis relative to other subtypes of JDM. Autoantibodies against TIF1-Gamma (p155/140) are associated with two distinct clinical DM subtypes based on age. In Juvenile DM (JDM), anti-TIF1-Gamma antibodies are particularly associated with widespread and severe cutaneous manifestations but not internal malignancy. In adult DM patients, TIF1-Gama positivity is associated with increased rates of malignancy (60-80%), lower rates of ILD and more widespread and severe skin disease. In particular, the diagnostic value of the anti-TIF1-gamma Ab is due to its very high negative predictive value Interestingly, TIF1-family of proteins are involved in carcinogenesis and are over expressed in

differed tumor tissues. Autoantibodies against these proteins might, thus, represent an initial anti-tumor response.

We present two adults with DM, each of whom demonstrates sero-positivity to one of the above-discussed novel MSAs in order to illustrate their respective, unique clinical phenotypes. The MSAs on our pediatric patient are still pending. He presented with typical cutaneous findings of JDM with severe widespread myositis at presentation.

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Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 10**

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PATIENT A

HISTORY OF PRESENT ILLNESS

A 67-year-old white woman with no personal or family history of skin cancer or melanoma presented for the evaluation of a large basal cell carcinoma involving the Right nasal sidewall, nasofacial sulcus, medial canthus and medial cheek. She had recently undergone surgical excision of a non-ulcerated desmoplastic melanoma measuring 1.6 mm in depth on the Right nasal bridge with otolaryngology. Sentinel lymph node biopsy was negative, and she did not receive adjuvant therapy for melanoma.

Both lesions had been present for several years prior to her seeking treatment. Given the location and the size of the tumor, the patient was felt to be a poor surgical candidate, and a plan was made to initiate treatment with vismodegib. After 1 month of treatment with vismodegib 150 mg daily, there appeared to be near-complete clinical resolution of the basal cell carcinoma.

Another month later, the patient presented to the clinic with a rash consistent with an exanthematous drug eruption that resolved after cessation of vismodegib and treatment with prednisone. One month later, vismodegib was restarted, with the subsequent development of new blisters on the bilateral dorsal hands that eventually became crusted erosions. She had no history of similar lesions in the past.

PAST MEDICAL HISTORY

Hypertension

MEDICATIONS

Metoprolol, acetaminophen

ALLERGIES

None

FAMILY HISTORY

No family history of skin cancer or melanoma.

SOCIAL HISTORY

She has never been a smoker. She states that she only rarely consumes alcohol.

PHYSICAL EXAM

Examination revealed an exophytic pink eroded tumor with hemorrhagic crust measuring 6 x 3 cm and 1 cm in height. The bulbar and palpebral conjunctivae did not appear to be involved. There was no cervical lymph node enlargement.

HISTOPATHOLOGY

H&E demonstrated a subepidermal separation lacking significant inflammatory infiltrate. Direct immunofluorescence was negative.

LABORATORY RESULTS
CBC with differential: within normal limits
CMP: within normal limits
Elevated urine porphyrins (uroporphyrins > coproporphyrins)
HIV: negative
HBV: negative
HCV: negative

RADIOLOGY
None

DIAGNOSIS
Porphyria cutanea tarda developing after treatment with vismodegib

TREATMENT AND COURSE
Vismodegib was once again discontinued. No specific interventions were made to treat porphyria cutanea tarda other than strict photoprotection. Within 4 weeks after discontinuation of vismodegib, her lesions had resolved, and plasma porphyrin levels were normal. Now almost 1 year later, she has not experienced a recurrence of either lesions consistent with PCT or the basal cell carcinoma for which vismodegib was initiated.

PATIENT B

HISTORY OF PRESENT ILLNESS
The sister of patient A presented at the age of 12 with a similar history of hair loss starting with discrete round patches of hair loss localized only to the scalp. As in her sister, hair loss progressed to involve the entire scalp. Eventually, hair loss became apparent in the eyebrows and eyelashes. Other areas of the body remained with normal hair intact.

PAST MEDICAL HISTORY
Chronic hepatitis C infection, Hypertension, Hypothyroidism

MEDICATIONS
Sofosbuvir, Simeprevir, Levothyroxine, Lisinopril

ALLERGIES
None

FAMILY HISTORY
No contributory family history.

SOCIAL HISTORY
He has never smoked. He does not consume alcohol.

PHYSICAL EXAM
Examination demonstrated one crusted erosion with dyspigmentation and scarring where previous lesions had resolved.

HISTOPATHOLOGY
H&E demonstrated a subepidermal separation lacking significant inflammatory infiltrate.

LABORATORY RESULTS

CBC with differential: within normal limits
CMP: within normal limits
Elevated urine porphyrins (uroporphyrins > coproporphyrins)
HCV RNA undetectable

RADIOLOGY

None

DIAGNOSIS

Porphyria cutanea tarda associated with chronic hepatitis C infection

TREATMENT AND COURSE

At the time of the patient's presentation, treatment had been initiated with sofosbuvir and simeprevir by hepatology for his hepatitis C infection. One month prior to presentation, HCV RNA was no longer detectable in his serum. No specific interventions were made to treat porphyria cutanea tarda other than strict photoprotection. Within 6 months of HCV RNA reaching undetectable levels in his serum, all lesions were resolved, and he no longer experienced recurrence.

DISCUSSION

Porphyria cutanea tarda (PCT) is the most common of the porphyrias. Its pathogenesis has been linked to dysfunction of uroporphyrinogen decarboxylase (UROD), the 5^{th} enzyme in the porphyrin synthesis pathway. This dysfunction leads to the accumulation of reactive porphyrin intermediates that are directly responsible for the clinical manifestations of PCT.

Because PCT is a heterogenous disease, it has been classified into 3 subtypes. Type 1, the most common type, is acquired PCT, accounting for up to 75-80% of cases. In this subtype, UROD dysfunction is limited to hepatocytes. Type 2 is hereditary, accounting for up to 20-25% of cases. In this subtype, there is partial deficiency, typically around 50%, in all tissue types. Type 3 is a rare subtype in which a genetic predisposition apparently leads to decreased UROD activity limited to hepatocytes.

In acquired cases of PCT, UROD dysfunction is believed to be related to is inhibition by oxidatively damaged pophyrin intermediates. These intermediates are formed iron-dependent oxidation, and uroporphyrinogen is a commonly implicated intermediate. Uroporhyrinogen has been shown to convert into uroporphomethene, which potently inhibits UROD. Other factors known to enhance this oxidation process include alcohol excess and estrogen therapy via activity of cytochrome P-4501A2. Although vismodegib does not appear to be capable of affecting UROD activity via this route, it has been shown to inhibit a member of the ATP-binding cassette family of drug transporters that is responsible for transporting endogenous and exogenous porphyrins. Although it is unclear how affecting this transporter may lead to a PCT phenotype, the relationship is interesting to highlight.

Regardless of the mechanism behind UROD dysfunction, uroporphyrins and hepta-carboxylated porphyrins accumulate in various tissues. These porphyrin intermediates absorb light in the range of 400-410 nm (the Soret band), exciting electrons to higher states. When these electrons return to their normal state, energy is transferred to oxygen molecules, creating reactive oxygen species. These molecules are directly responsible for the phototoxic damage characteristic of PCT.

PCT presents clinically with blisters, vesicles and/or milia days to weeks after sun exposure in exposed sites, especially the dorsal arms and hands. Chronic skin changes, such as scarring and changes in pigmentation, may be seen over time. Other features include hypertrichosis, usually involving the lateral aspects of the face, chloracne, sclerodermatous changes, dystrophic calcification, alopecia and onycholysis. Plasma porphyrin levels are elevated during active PCT, as are urine porphyrins, specifically with uroporphyrins in higher levels than coproporphyrins. Mild elevations in serum transaminase levels may be observed. Histopathology from a characteristic lesion will demonstrate a subepidermal separation without a concomitant inflammatory response.

PCT has long been strongly associated with hepatitis C viral infection. Although the link between HCV and PCT remains somewhat unclear, several mechanisms have been proposed, to include the contribution of HCV-related cirrhosis and alterations in iron metabolism secondary to inflammation leading to HCV-related iron overload. Interestingly, with new HCV-targeted antiviral therapies, patients with PCT related to HCV infection have demonstrated resolution of lesions as their HCV infection is cleared.

The management of PCT is usually accomplished first with strict photoprotection. In order to relieve the stress of iron overload, phlebotomy has become the first line treatment, usually targeting a specific ferritin level as an index of overall iron levels. Should phlebotomy not be an option, antimalarials may be employed. These drugs allow for the release of porphyrin intermediates from hepatocytes, facilitating their excretion from the body. Caution should be exercised when starting a patient with PCT on antimalarials, as over dosing may lead to an acute hepatitis as a manifestation of toxicity related to the overly rapid release of porphyrins. Usually these medications are initiated on a once weekly dosing schedule with the potential to titrate doses higher as tolerated with time to produce a clinical response.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 11**

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HISTORY OF PRESENT ILLNESS

The patient is a 22 year-old white man who presented to clinic for a routine acne follow-up visit. During the examination, he incidentally noted a bothersome phenomenon concerning his palms. Starting approximately 12 years ago, his palms would rapidly wrinkle within 2-3 minutes of any water exposure. In addition, his cheeks and glabella turn red and peel after any significant water contact. These cutaneous changes last for approximately 1-2 hours if he does not apply hydrocortisone 1% cream immediately after exposure. He notes a pruritic and uncomfortable sensation associated with the changes, which force him to significantly limit his exposure to water. The patient has not tried any other treatments for this condition. He has a 2 year history of mild sinus congestion, but he has never been hospitalized or treated for any serious sinopulmonary infections. A thorough review of systems also revealed a 3-4 year history of diarrhea and irregular bowel movements, which had not been evaluated by a physician.

PAST MEDICAL HISTORY

Hashimoto's thyroiditis, Inflammatory acne

MEDICATIONS

Minocycline, Metoprolol, Tretinoin, Hydrocortisone 1% cream

ALLERGIES

No known drug allergies.

FAMILY HISTORY

He has no family members with a history of similar cutaneous changes. His paternal grandfather has diabetes mellitus, but there is no known family history of cystic fibrosis, recurrent sinopulmonary infections, infertility, or pancreatitis.

SOCIAL HISTORY

The patient is a current every day smoker. He works in a restaurant.

PHYSICAL EXAM

During examination, the patient's palms appeared unremarkable at baseline with no erythema or primary lesions. After immersing his palms in tap water for 1 minute, his distal palmar fingers appeared white with evidence of a mild wrinkling. After 3 minutes of water soaking, both palmar surfaces were also white with an exaggerated wrinkled appearance

HISTOPATHOLOGY

None

LABORATORY RESULTS

CBC with differential: within normal limits

DIAGNOSIS

Aquagenic wrinkling of the palms

TREATMENT AND COURSE

The patient was instructed to consult his primary care physician regarding possible genetic testing for cystic fibrosis. He has not had any genetic testing as of yet. He has discussed his gastrointestinal concerns with his primary physician and is currently scheduled to see a gastroenterologist next month.

DISCUSSION

Aquagenic wrinkling of the palms is a rare phenomenon that is also referred to as acquired aquagenic palmoplantar keratoderma or aquagenic syringeal acrokeratoderma. It is characterized by the transient appearance of edematous white to translucent papules and plaques without erythema on the palmar surfaces after contact with water. Physiologic wrinkling of palmar skin occurs after an average of 11.5 minutes of water contact, while aquagenic wrinkling of the palms often occurs within 3 minutes of water exposure. Both longer duration of water contact and exposure to warmer water temperatures have been anecdotally associated with a more severe wrinkling response. The phenomenon is typically accompanied by an uncomfortable painful and/or pruritic sensation, which can significantly impact a patient's life. Resolution of the lesions generally occurs spontaneously after 20 minutes of drying time.

Patients are usually diagnosed with aquagenic wrinkling of the palms clinically during an office visit. Most patients have symmetric involvement of the palmar surfaces with the plantar surfaces involved less often. Atypical presentations have included patients with involvement of the dorsal fingers, heels, and unilateral involvement of one palm. Biopsy of active lesions reveals spongiosis of the stratum corneum, acanthosis with orthohyperkeratosis, and dilation of the eccrine acrosyringia. The dilated eccrine ostia can also be easily visualized with dermoscopy. Some patients experience improvement after continued use of topical aluminum chloride solution once to twice daily. Other therapeutic options reported in the literature include aluminum magnesium hydroxide stearate barrier cream, salicylic acid 20% in petrolatum, iontophoresis, and injections of Botulinum toxin A.

Aquagenic wrinkling of the palms is drawing increasing attention in the literature due to its association with cystic fibrosis. Elliott first described this association in 1974, and "three minutes and a bowl of water" was proposed as an easy method for screening children with possible cystic fibrosis. Subsequent reports have estimated that between 44% and 84% of patients with cystic fibrosis have aquagenic wrinkling of the palms. Furthermore, 25% of carriers of cystic fibrosis also display the phenomenon. Early reports suggested a preponderance of young females affected, but a recent population based study demonstrated an equal sex predilection. One study found a positive correlation between aquagenic wrinkling and measured levels of transepidermal water loss, but no significant genotype-phenotype correlations were found in patients with cystic fibrosis. It has been proposed that patients with excessive palmar wrinkling in less than 10 minutes should be genetically tested for possible cystic fibrosis or carrier status. In addition, consideration for genetic testing should be given to patients with transient episodes of aquagenic wrinkling associated with aminoglycoside or COX-2 inhibitors.

Several mechanisms have been proposed to explain the phenomenon of aquagenic wrinkling of the palms. Initial reports hypothesized that the hypertonic sweat of cystic fibrosis patients created an osmotic gradient for water to flow into the epidermis. Other studies proposed that aberrant expression of aquaporin 5 in the eccrine glands of cystic fibrosis patients is responsible for the transient edema. Furthermore, ineffective TRPV4 channels have been suggested to poorly regulate water influx in the epithelial cells of cystic fibrosis patients. The associated paresthesias seen with aquagenic wrinkling have supported a neurologic component involving the sympathetic nervous system. The true pathogenesis is likely multifactorial.

In addition to the association with cystic fibrosis, aquagenic wrinkling of the palms has been reported in patients with other diseases including hyperhidrosis, marasmus, and atopic dermatitis. The phenomenon has also been seen in patients taking nonsteroidal anti-inflammatory drugs, selective cyclooxygenase inhibitors, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and aminoglycosides. Even healthy patients without any identifiable underlying diseases have been reported to demonstrate exaggerated rapid wrinkling after water exposure.

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HISTORY OF PRESENT ILLNESS

A 30-year-old female presented with extensive facial crusting. Her past medical history was significant for marginal zone lymphoma s/p chemotherapy, systemic lupus erythematosus (SLE) on prednisone, and previous deep vein thrombosis (DVT).

Three months prior to this presentation, the patient was admitted for acute pancreatitis attributed to use of alcohol. At that time, dermatology was consulted for a papular eruption which primarily involved the face and mid upper chest. The patient denied pruritus but admitted to picking the lesions. While awaiting the results of a punch biopsy, she was started on hydrocortisone 2.5% ointment. Biopsy from the chest demonstrated suppurative folliculitis without evidence of interface or mucin deposition. The patient was discharged on prednisone 25mg daily for management of SLE and instructed to follow up with dermatology as an outpatient.

Three weeks after discharge, she presented to another institution. The lesions on her face had progressed to confluent mounds of crusting, with notable periorbital sparing. A punch biopsy for H&E, PAS, and GMS stains demonstrated numerous yeast forms within the stratum corneum associated with folliculitis, again with no interface changes or mucin deposition. A pathology consultant noted verrucous hyperplasia with neutrophils and erosive changes on the biopsy. A punch biopsy for deep tissue culture showed 4+ yeast**.** The patient was discharged with six weeks of itraconazole 200mg daily and ketoconazole cream. Prednisone 25mg daily for SLE was continued.

Six weeks later, the patient was transferred to Rush University Medical Center for treatment of a gastrointestinal bleed on subcutaneous heparin (see Treatment and Course for a summary of her hospital course). Dermatology was consulted for progression of the facial crusting on itraconazole. Several surface cultures, deep tissue cultures, and punch biopsies were obtained. Biopsies were significant for verrucous epidermal hyperplasia, again with suppurative folliculitis. A deep tissue culture from the right leg grew staphylococcus lugdunensis. Surface cultures from the face grew coagulase negative staphylococcus (speciation was not reported). Repeat surface cultures and deep tissue culture grew enterobacter cloacae (see Pathology and Microbiology section below for all pathology and microbiology results).

PAST MEDICAL HISTORY

Marginal zone lymphoma (s/p four cycles of chemotherapy; discontinued following DVT)
DVT in left upper extremity (attributed to port-a-catheter for chemotherapy)
SLE diagnosed 8/2014 (ANA+, dsDNA+, Smith+, arthritis, serositis with pleural/pericardial effusion, anemia, thrombocytopenia)
Hypertension

PAST SURGICAL HISTORY

Lymph node biopsy 11/2013

HOME MEDICATIONS

Prednisone, Carvedilol, Lisinopril, Folic acid, Enoxaparin SC, Allopurinol, Magnesium oxide

FAMILY HISTORY
There was no known family history of autoimmune disease.

SOCIAL HISTORY
Six beers once weekly.

PHYSICAL EXAM
There were extensive confluent mounds of hyperkeratotic crusting on the face with sharp demarcation and sparing of the periorbital region including the eyelids. There were hyperpigmented macules and minimally raised papules on the upper chest. Additional follicular based erythematous and non-erythematous crusted papules and plaques were present on the legs. The left lower leg and left upper arm were swollen, erythematous, and tender. There was a single bulla on the left arm.

LABORATORY RESULTS
Pertinent laboratory studies during the course of admission:

ELISA ANA	2.82	(normal 0.0 – 0.99)
IFA ANA titer	1:40	(normal <1:40)
Anti-DsDNA	94	(normal 0– 26)
Anti-Smith	1.21	(normal 0.00 – 0.89)
U1RNP	1.06	(normal 0-0.89)
Histone negative		
SSA/SSB negatives		
Dilute Russel Venon Viper Test	59	(normal <45)
C3	132	(normal 88-203)
C4	43	(normal 13-49)
CH50	>60	(normal 31-60)
AST	51	(normal 3 – 44)
ALT	111	(normal 0 – 40)
CMV DNA Quantification copies/mL	1105	(normal < 300)
Soluble IL-2 receptor (CD25)	840	(normal 45-1105)
NK cell activity (CD107A) - insufficient sample for diagnosis)		

Solumerol started

	2/25	3/7	3/11	3/14	3/18	Ranges
Ferritin	**3976**	**50669**	**5799**	**7611**	**5706**	**Nl 12-260**
ESR	**37**	**>140**				**Nl 0-27**
Triglycerides	**167**			**147**		**Nl 30-149**
Fibrinogen	**548**	**701**				**Nl 190 395**
WBC	**6.26**	**9.64**	**8.33**	**9.23**	**7.92**	**Nl 4-10**
HgB	**7.3**	**6.9**	**6.1**	**9.3**	**8.5**	**Nl 12-16**
Platelets	**119**	**106**	**116**	**119**	**147**	**Nl 150-399**
ALT	**71**	**111**		**26**	**15**	**NL 0-40**
AST	**20**	**32**	**25**	**26**	**15**	**NL 3-44**

PATHOLOGY AND MICROBIOLOGY

Date			
11/22/14	H&E.	Left upper chest	**Suppurative folliculitis**. There was a neutrophilic inflammatory infiltrate distorting the hair follicle.
12/24/14	H&E and PAS	Right jawline	**Pityrosporum folliculitis**. There were numerous fungal forms present in the stratum corneum with associated neutrophilic inflammation.
12/24/14	H&E Consultation	Right jawline	**CONSULTATION:** Verrucous hyperplasia with neutrophils and erosive changes.
12/24/14	Deep Tissue Culture	Right jawline	**4+ yeast.** No bacteria isolated.
2/9/15	Deep tissue culture	Right leg	**Light growth of staphylococcus lugdunensis**. Light growth of staphylococcus epidermidis. Negative fungus. Negative AFB.
2/9/15	H&E	Left arm	**Thrombotic vasculitis.** Punch biopsy of a left arm bulla (which was affected by a DVT) showed epidermal necrosis secondary to neutrophilic inflammation and subsequent fibrinoid necrosis of dermal blood vessels. Blood vessels in the subcutaneous fat were also involved.
2/9/15	H&E	Right leg	A **neutrophilic scale crust** with focal epidermal ulceration and marked hyperkeratosis is present. The underlying epidermis shows no significant pathologic changes.
2/9/15	Surface Swabs (HSV, aerobes, fungus)	Face	**Light growth of staphylococcus species (coagulase negative)** – no further speciation. HSV-1/2 PCR negative. No fungus isolated.
2/12/15	Repeat Surface Swabs (aerobes, fungus)	Face	**Light growth of staphylococcus species (coagulase negative)(more than one kind).** No fungus isolated.
2/12/15	H&E and DIF	Left lower face	**Suppurative folliculitis.** Stains for C1q, C3, IgA, IgG and IgM are negative within the epidermis, at the dermal epidermal junction, and around the dermal blood vessels.
2/12/15	H&E	Right lower face	**Ruptured folliculitis.** Perifollicular chronic inflammation and fibrosis, consistent with **ruptured folliculitis.** PAS negative.
2/26/15	Surface Swab Cultures	Jawline	4+ Enterobacter Cloacae, 4+ coagulase negative staphylococcus.
2/26/15	Deep Tissue Culture	Jawline	Polymicrobial (4+ Enterobacter Cloacae, 3+ E. Coli, Bacteroides Fragilis)
2/27/15	H&E x 2	Left lower jaw and left cutaneous lip	**Verrucous epidermal hyperplasia with associated acute and chronic inflammation**. There is marked papillomatous epidermal hyperplasia with associated hyper and parakeratosis. The underlying dermis shows varying degrees of acute and chronic inflammation.
3/6/15	Biopsy	Bone Marrow	Hypercellular (60%) marrow with erythroid hyperplasia. No dysplasia, lymphoma or increase in blasts. **There are scattered erythrophagocytic histiocytes in the aspirate and markedly increased iron.**

DIAGNOSIS

Crusted folliculitis with verrucous epidermal hyperplasia and possible hemophagocytic lymphohistiocytosis

TREATMENT AND COURSE

Warm soaks, urea, benzoyl peroxide, and manual debridement were used to remove the crusting. Bleeding and heme crust developed after debridement, but otherwise revealed normal epidermis. She received antibiotics including vancomycin, doxycycline, cephalosporins, trimethoprim-sulfamethaxazole, 120mg of pulse solumedrol, and hydroxychloroquine. Dapsone was started for PCP prophylaxis with the pulsed steroids.

During her hospital course she was found to have multiple acute and chronic DVTs, a subacute infarct in her left parietal lobe with hemorrhagic transformation, status epilepticus, fevers, and numerous lab abnormalities including anemia, thrombocytopenia, and a rising ferritin value from 1,000ng/mL to over 7,000ng/mL. Bone marrow biopsy demonstrated erythrophagocytocytic histiocytes with significant iron deposition concerning for hemphagocytic lymphohistiocytosis..

The patient's seizures were attributed to her subacute infarct with hemorrhagic transformation. The seizures were controlled with anti-epileptics. Lupus anticoagulants were initially negative, but repeat labs showed a positive dilute russel venom viper test. A diagnosis of hemophagocytic lymphohistiocytosis or macrophage activating syndrome in the context of SLE was favored given the rising ferritin levels, erythrophagocytosis in the bone marrow, bicytopenia, and fevers. The patient was started on high dose steroids--methylprednisolone 125mg daily with defervescence of her fevers and improvement in her ferritin level. She was discharged to a rehabilitation institute.

DISCUSSION

This case demonstrates an immunosuppressed patient who developed extensive crusted folliculitis. The sparing of the periorbital area is explained by the decreased size and density of the hair follicles on the eyelids. A consensus was not reached on a causative organism. The predominant seborrheic distribution of the initial eruption, 4+ yeast on deep tissue culture, and positive PAS and GMS stains were suggestive of pityrosporum. The verrucous epidermal changes seen on pathology might be suggestive of blastomycosis-like pyoderma (BLP). BLP is also known as pyoderma vegetans. It is caused by a prolonged primary or secondary infection in an immunocompromised patient. It is thought to be an exaggerated inflammatory tissue reaction. It presents as verrucous plaques clinically and pseudoepitheliomatous hyperplasia with microabscesses histologically. Bacteria usually causes BLP; however, it has also been reported to be caused by a mixed infection with staphylococcus epidermidis and trichophyton rubrum. It will not respond to antibiotics alone. Systemic retinoids have been used with success.

Deep tissue culture from the leg revealed staphylococcus lugudensis, a coagulase negative staphylococcus which was previously regarded as a commensal bacterium. However, infectious disease journals have shown S. *lugudensis* to be a highly virulent pathogen, capable of causing skin, joint, blood, and endocardial infections. It is most commonly isolated from the skin. It may behave similarly to staphyloccous aureus and cause nosocomial and community acquired infections. S. *lugdensis* may be underreported in the literature because some laboratories do not routinely speciate coagulase negative staphylococcus. As awareness of pathogenic potential increases and technology for speciation improves, a greater number of cases of *S. lugdunensis* may be reported. Another organism isolated in our patient, Enterobacter cloacae, is one of the two most commonly isolated pathogens among the genus Enterobacter. It is part of the normal gut flora and may cause nosocomial infections because it contaminates medical equipment.

The patient also met several of the criteria for a diagnosis of hemophagocytic lymphohistiocytosis (HLH). HLH can be primary and diagnosed by molecular identification of a

characteristic gene mutation or secondary, typically in the setting of malignancy or infection. When it is caused by underlying rheumatologic disorder, HLH is referred to as macrophage activating syndrome (MAS). There are no consensus criteria for MAS, but the diagnosis of HLH can be met with five of eight diagnostic criteria including persistent fever (>38.5 degrees Celsius), splenomegaly, ferritin ≥500 ng/mL, soluble CD25 (IL-2 receptor) ≥2,400 U/ml, low or absent NK-cell activity, cytopenias (≥2 of 3 lineages in the peripheral blood), hypertriglyceridemia (>265mg/dL) and/or hypofibrinogenemia, and hemophagocytosis in bone marrow, spleen, or lymph nodes. This was a challenging diagnosis because the patient had multiple comorbidities that could have explained some of her lab abnormalities. However, her rising ferritin level was suspicious, particularly in the setting of a low ESR at the start of admission. In a study of pediatric patients with HLH, ferritin values over 3000 were 90% sensitive and 77% specific for HLH; whereas ferritin values over 6000 were 90% sensitive and 90% specific. The etiology for HLH in this case was not clear as she had multiple possible causes including CMV infection, a skin infection with an exaggerated inflammatory tissue reaction, SLE, and recent malignancy.

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