Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, December 13, 2017
Gleacher Center – Chicago, IL

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

Program

Host: University of Chicago
Wednesday, December 13, 2017
Gleacher Center, Chicago

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *All activities will take place on the 6th Floor of the Gleacher Center*
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** Slide viewing/posters
9:00 a.m. - 10:00 a.m.	**Basic Science/Residents Lecture** "Infectious Dermatopathology Clues" *Tammie Ferringer, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:15 p.m.	**Resident Case Presentations & Discussion;** **MOC Self-Assessment Questions**
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors**
12:55 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**General Session** LORINCZ LECTURE - "Clinicopathologic Correlation" *Tammie Ferringer, MD*
2:00 p.m.	**Meeting adjourns**

Mark the Date!

Illinois Dermatological Society Coding/Practice Management Workshop
Wednesday, January 24, 2018; Stephens Convention Center, Rosemont
More information: www.Illinois DermSociety.org

Next CDS monthly meeting – Hosted by Stroger/Cook County Hospital
Wednesday, April 18th; Gleacher Center, Chicago

Watch for details on the CDS website: www.ChicagoDerm.org
Save time and money – consider registering online!

Guest Speaker

TAMMIE FERRINGER, MD

Section Head, Dermatopathology
Director, Dermatopathology Fellowship Program
Geisinger Medical Center, Danville, PA

Dr. Ferringer is the dermatopathology section head for the Geisinger Medical Center in Danville, PA. She also serves as the director of the Dermatopathology Fellowship Program. Dr. Ferringer earned her medical degree at the Medical College of Pennsylvania in Philadelphia and completed her residency in dermatology at Geisinger. Dr. Ferringer completed a fellowship in dermatopathology at the Medical University of South Carolina in Charleston. She is board-certified in dermatology and dermatopathology. Dr. Ferringer is the associate editor of Cutis, and is the assistant editor of the Journal of the American Academy of Dermatology. She serves on numerous committees and has many publications to her credit.

CME Information

This educational activity is jointly provided by the Chicago Dermatological Society in partnership with the Indiana Academy of Ophthalmology

Overview

The Chicago Dermatological Society was established in 1903 and has strived to provide meaningful educational opportunities to dermatologists in the Chicago area for more than a century. Guest speakers from across the country share their expertise with CDS members, as well as residents in training medical students doing their dermatology rotation. CDS schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. In addition to two lectures given by the guest speaker, the residents of the host institution present cases which are offered for audience discussion. In addition, live patients, posters and microscopic slides prepared by the residents are made available during the "clinical rounds" portion of the meeting. CDS also offers a session that qualifies for "Maintenance of Certification" self-assessment questions under the auspices of the American Board of Dermatology.

Target Audience

This activity has been designed to meet the educational needs of dermatologists. CDS members, residents in training and medical students engaged in their dermatology rotation are invited to attend.

Learning Objectives

At the conclusion of the 2017/18 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for allergic conditions, viral diseases and bacterial infections.
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.

Physician Accreditation Statement

This activity is planned and implemented by Indiana Academy of Ophthalmology (IAO) and the Chicago Dermatological Society. IAO is accredited by the Indiana State Medical Association to provide continuing education for physicians.

Credit Designation for Physicians – IAO designates this live activity for a maximum of 4.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form upon departure from the conference. Please leave your form, along with the evaluation form, at the registration table when you leave the meeting. Thank you for your attention to this important item.

Disclosure of Conflicts of Interest

The IAO and CDS require instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by IAO and CDS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are asked to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk.

Neither the guest speaker, Tammie Ferringer, MD, nor any of the planning committee members have any conflicts of interest to disclose.

Continued next page

Contact Information

For information about the physician accreditation of this program please contact the CDS administrative office at: 847-680-1666; email: Rich@RichardPaulAssociates.com

Americans with Disabilities Act

In compliance with the Americans with Disabilities Act, we will make every reasonable effort to accommodate your request. For any special requests, contact CDS at: Rich@RichardPaulAssociates.com

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Dislosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

AT THE FOREFRONT
UChicago Medicine

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CASE #1

PRESENTERS
Juliana Gao, MD; Christopher R Shea, MD; Adena Rosenblatt, MD.

PATIENT A

HISTORY OF PRESENT ILLNESS
An 83 year old African American male with myelodysplastic syndrome on lenalidomide was admitted to the hospital for symptomatic anemia and pancytopenia. Dermatology was consulted for evaluation of an expanding purpuric and necrotic lesion on the vertex scalp. The patient was unsure how long the lesion had been present. He suffered a fall several months prior to this admission but denies any recent trauma to the area. His review of system was notable for fatigue and weakness, but he did not have any fever or chills.

PAST MEDICAL HISTORY
Myelodysplastic syndrome
Hypertension

FAMILY HISTORY
Non-contributory

MEDICATIONS
Lenalidomide 10 mg daily
Amlodipine 10 mg daily
Folic acid 1 mg daily

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
On the posterior vertex scalp, there was a 1 cm dusky very soft plaque with surrounding rim of purpura. The remainder of the exam was unremarkable.

DERMATOPATHOLOGY
Biopsy from the central dusky plaque showed skin with superficial and deep perivascular mixed inflammatory cells with associated focal areas of dermal necrosis. There was necrotizing vasculitis in the deep dermis with numerous bacilli in and surrounding the walls of the blood vessels and also among the collagen bundles. The Gram stain was positive for gram-negative bacilli.

LABORATORY DATA
Complete blood count: Leukocytes 0.6 K/µL (3.5-11.0), hemoglobin 5.2 g/dL (9.8-17.6), platelets 16 K/µL (150-450).
Differential: Absolute neutrophil count 0.25 K/µL (1.12-6.72)
Infectious: Tissue culture from vertex scalp grew *Pseudomonas aeruginosa*; blood culture negative x 2

DIAGNOSIS
Ecthyma gangrenosum

TREATMENT AND COURSE
On admission, patient was initially placed on acyclovir, levofloxacin and fluconazole for neutropenia

prophylaxis and later started on IV cefepime for pseudomonal coverage. Due to his severe and persistent pancytopenia, a repeat bone marrow biopsy was performed and showed transformation to acute myeloid leukemia. Given his overall low performance status, an extensive goal of care discussion took place and the patient and family elected to proceed with home hospice.

PATIENT B

HISTORY OF PRESENT ILLNESS

A 19-year-old male with recurrent acute lymphoblastic leukemia (ALL) with central nervous system (CNS) involvement currently on chemotherapy was admitted to the hospital for septic shock. Dermatology was consulted for evaluation of a painful purple plaque with overlying bullae on the right flank. It started initially as a painful sensation, and the skin finding developed within hours of the symptom onset. Patient denied any previous trauma or subcutaneous injection to the area. Heparin for deep venous thrombosis prophylaxis was only given through his port.

PAST MEDICAL HISTORY

Pre B-cell ALL
Asthma

FAMILY HISTORY

Mother had ALL at age 8
Older brother recently diagnosed with ALL
Maternal grandmother had breast cancer at age 75

MEDICATIONS

Methotrexate dosing per chemotherapy cycle
Vincristine dosing per chemotherapy cycle
Dexamethasone 5 mg BID
Pegaspargase dosing per chemotherapy cycle
Albuterol inhaler
Budesonide inhaler
Clindamycin 300 mg QID
Sulfamethoxazole-trimethoprim-DS 800-160 mg BID on Saturday and Sunday
Famotidine 20 mg daily
Magnesium oxide 400 mg BID
Scopolamine patch 1 patch every 3 days

ALLERGIES

Chlorhexidine
Nuts

PHYSICAL EXAMINATION

On admission, the patent was febrile to 38.8 C, tachycardic with heart rate of 160 and hypotensive with systolic blood pressure in the 70s-80s. Examination of the skin revealed a purpuric indurated plaque with retiform border and central duskiness on the right flank. There was a large central tense bulla as well as several smaller more flaccid bullae overlying the plaque. Surrounding erythema extended from just superior to the purpuric plaque to a third of the way down the lateral right thigh. There was tenderness to palpation within areas of erythema but not beyond.

DERMATOPATHOLOGY

A punch biopsy from the edge of purpura and erythema showed an interstitial infiltrate of neutrophils

within the mid to deep dermis. There were associated degenerative changes and karyorrhectic debris. The Gram stain was negative for Gram-negative organism. The periodic acid-Schiff stain was negative for fungi. The Fite stain was negative for mycobacteria.

LABORATORY DATA

Complete blood count: Leukocytes 0.4 K/μL (3.5-11.0), hemoglobin 13.1 g/dL (9.8-17.6), platelets 32 K/μL (150-450).
Differential: absolute neutrophil count 0.15 K/μL (1.12-6.72)
Infectious: blood culture and tissue culture grew *Escherichia coli*

DIAGNOSIS

Ecthyma gangrenosum

TREATMENT AND COURSE

Patient was initially admitted to the PICU with aggressive fluid resuscitation and started on vasopressors along with broad spectrum antibiotics including vancomycin, ceftazidime and gentamicin. He had initial improvement but became febrile and hypotensive again several days later. The primary team was concerned that the wound on the right flank was necrotizing fasciitis so the patient was taken to the operating room for debridement and the wound was left to heal by secondary intention with the aid of a wound vac. The debridement occurred one year ago and now the wound has completely healed. He is still receiving chemotherapy and doing well.

DISCUSSION

Ecthyma gangrenosum (EG) is caused by bacterial invasion of the blood vessels in the deep dermis, which lead to secondary thrombosis, and subsequent tissue necrosis. Histopathology is characterized by necrosis of the epidermis and the upper dermis with surrounding hemorrhage. A necrotizing vasculitis with thrombosis is typically present in the deeper dermis with gram-negative bacteria in the media and adventitia of the blood vessel walls. Gram-negative bacteria can also be seen in between collagen bundles [1]. The clinically morphology of EG typically begins as erythematous to purpuric macules that progress to papules, then vesicles and eventually evolves into necrotic eschars. The most commons sites are the extremities, and intertriginous folds such as the axilla, gluteal cleft and perineal regions [2].

Ecthyma gangrenosum can occur either by direct inoculation of the bacteria through the skin, or more commonly by hematogenous seeding from a distant source. It typically affects immunocompromised individuals, especially those with underlying malignancy. Although EG is most commonly associated with *Pseudomonas aeruginosa*, and less often with *Escherichia coli*, other infectious agents such as Gram-positive bacteria and opportunistic fungi have also been reported [1, 2]. The diagnosis of EG relies on skin biopsies for tissue culture and blood culture, the latter of which is only positive for a fraction of the patients. In one meta-analysis of 123 cases of *Pseudomonas* EG, blood culture was only positive in 58.5% of the cases. This is in contrast with EG not associated with *Pseudomonas*, in which only 1.2% of cases (n=29) had positive blood culture [2]. Hence, the skin biopsy should be done promptly, and a sufficiently large biopsy should be obtained for bacterial, fungal and mycobacterial culture.

Prognosis of patients with ecthyma gangrenosum depends on their overall immunologic status, particularly the degree and duration of neutropenia, as well as the presence or absence of bacteremia. In patients with positive bacteremia, mortality is quite high, ranging from 38 to 96% [3, 4]. In patients with negative blood cultures, mortality is much lower but not insignificant at 16% according to one small case series [5]. Treatment involves use of antibiotics or antifungal medications depending on the infectious organism. Delay of appropriate antibiotic therapy increases the mortality rate from 46 to 74% [6]. Surgical debridement is often needed. In the same meta-analysis mentioned previously, 128 out of 167 (76.6%) cases required surgical intervention ranging from simple to aggressive debridement, and some

even required reconstructive skin graft [2].

Of note, the majority of the large case series in literatures focused on ecthyma gangrenosum secondary to *Pseudomonas* alone. The prognoses for those with *E. coli* or other organisms are less well known. It should also be noted that since many of the EG series date back to the 1970s and 1980s, and broad spectrum antibiotics with antipseudomonal coverage such as cefepime and piperacillin-tazobactam were not introduced until 1994 and 2005, respectively. Therefore, the actual mortality today may be lower than in the past with the availability of these antibiotics. More recent studies on pseudomonas bacteremia showed mortality rate around 20% to 40% when appropriate antibiotics were initiated early on which is significantly lower than those reported in literatures from decades prior [7, 8].

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CASE #2

PRESENTERS

Laura B. Buford, MD, MS; Diana Bolotin, MD, PhD; Vesna Petronic-Rosic, MD, MSc

UNKNOWN CASE

A 26-year-old male presented to the adult urgent care clinic complaining of an itchy rash on the right side of his abdomen. Dermatology was consulted for further evaluation.

CASE #3

PRESENTERS
Emily Lund MD, Vesna Petronic-Rosic MD, MSc; Sarah Stein MD

PATIENT A

HISTORY OF PRESENT ILLNESS
A 9-year-old male with a history of Crohn disease diagnosed at age 4 years presented to dermatology for scrotal and penile swelling. Swelling associated with redness began 4 months earlier. The patient denied pain, pruritus, difficult or painful urination. He was previously evaluated by allergy and urology without establishing a reason for the swelling. The GI manifestations of Crohn disease had been well controlled on subcutaneous methotrexate 12.5 mg weekly for the past three years.

PAST MEDICAL HISTORY
Crohn disease
Atopic dermatitis

MEDICATIONS
Methotrexate SQ 12.5mg weekly
Hydrocortisone 1% cream to affected areas of body PRN

ALLEGIES
No known drug allergies

FAMILY HISTORY
Mother and sister with atopic dermatitis

REVIEW OF SYSTEMS
Negative

PHYSICAL EXAMINATION
Examination revealed mildly erythematous, ill-defined, indurated plaques on the scrotum, penile shaft, and penile corona. The scrotal rugae were blunted.

LABORATORY DATA
CT scan and scrotal ultrasound prior to presentation were reportedly unremarkable.

HISTOPATHOLOGY
A punch biopsy from the patient scrotum revealed non-caseating granulomas with occasional multinucleated giant cells in the superficial dermis. Fite and methenamine silver stains were negative for organisms. Polaroscopy did not demonstrate refractile material.

DIAGNOSIS
Primary cutaneous Crohn disease

TREATMENT AND COURSE
Treatment was initiated with mometasone 0.1% ointment applied twice daily to the affected areas. Complete resolution of disease was observed at 3 months, and mometasone ointment was discontinued. One year later the patient had recurrence of scrotal and penile swelling. The family reinitiated mometasone ointment but did not appreciate improvement after 2 months of use. Topical therapy was

escalated to clobetasol 0.05% ointment with rapid resolution of swelling over a two-week period. Maintenance therapy with clobetasol ointment applied two times weekly was initiated. He has been symptom-free for 9 months.

PATIENT B

HISTORY OF PRESENT ILLNESS
An 8-year-old girl with Crohn disease presented with a 10-month history of labial swelling and erythema. Associated symptoms included pruritus, yellow vaginal discharge, and burning with urination. She had been treated with fluconazole 200mg daily for 14 days for presumed vaginal candidiasis without improvement. An MRI to evaluate for anorecto-vaginal fistula, demonstrated peri-rectal abscesses without fistula formation. The patient had been treated with oral ciprofloxacin and metronidazole for 14 days with resolution of the abscesses, but no change in the degree of vulvar swelling. The GI manifestations of Crohn disease were being managed with infliximab, prednisone and metronidazole with ongoing intermittent disease flares resulting in frequent hospitalizations.

PAST MEDICAL HISTORY
Crohn disease
Atopic dermatitis
Asthma

MEDICATIONS
Infliximab 250mg IV q6-8 weeks
Prednisone 10mg daily
Metronidazole 125mg BID

ALLERGIES
No known drug allergies

FAMILY HISTORY
Mother – Crohn disease, atopic dermatitis
Brother – asthma

REVIEW OF SYSTEMS
Notable for vaginal discharge and painful urination

PHYSICAL EXAMINATION
Examination revealed an erythematous to violaceous edematous plaque with overlying scale extending from the mons pubis to the superior aspect of the gluteal cleft, with involvement of the labia majora, clitoris, perineum, and bilateral buttocks. Fissuring was present at the superior aspect of the labia majora and within the gluteal cleft.

DIAGNOSIS
Primary cutaneous Crohn disease

TREATMENT AND COURSE
Topical therapy was initiated with mometasone 0.1% ointment twice daily. The lesions were responsive to topical therapy, and the patient was weaned to a maintenance regimen of desonide 0.05% ointment twice daily. Her cutaneous disease continued to wax and wane over the next year requiring intermittent mometasone application with decreasing benefit. The patient's intestinal Crohn disease was poorly controlled on infliximab monotherapy, requiring frequent courses of oral prednisone; methotrexate was

added with escalation of dose in an attempt to decrease flares of both intestinal and cutaneous disease. Topical therapy was transitioned to clobetasol 0.05% ointment twice daily. Worsening control of both gastrointestinal and skin disease prompted initiation of ustekinumab. Seven weeks after the first administration of ustekinumab, the skin findings were significantly improved.

DISCUSSION

Crohn disease was first described by Dr. Burrill Bernard Crohn and his colleagues at Mount Sinai Hospital in New York City in 1932 [1]. It is a systemic inflammatory disease characterized by segmental granulomatous inflammation of the gastrointestinal tract [2]. Extraintestinal sites, including the eyes, joints, liver, and skin (mucocutaneous), may also be affected. Joints are most commonly involved, with arthritis or arthralgia occurring in up to 50% of patients [3]. Mucocutaneous findings are also common, with estimated prevalence ranging from 20-45 % [2].

Mucocutaneous manifestations of Crohn disease fall into three categories: primary disease, related reactive disorders, and associated dermatologic conditions [3]. Primary disease lesions have the same histopathologic findings as the gastrointestinal disease and include oral and contiguous perianal disease, as well as distant non-contiguous, or so-called metastatic, cutaneous sites of involvement. Related reactive disorders, such as erythema nodosum and pyoderma gangrenosum, are signs of immune system dysregulation, demonstrating a pathology distinct from that of granulomatous inflammation. Associated dermatologic conditions are defined as conditions which co-occur with Crohn disease due to genetic linkage, therapy side effects, or sequelae of the disease.

While oral and perianal Crohn disease are relatively common mucocutaneous manifestations, non-contiguous cutaneous lesions are rare, particularly in the pediatric population [2,4]. The mean age of presentation of such disease is 35 years, and women appear to be more commonly affected than men [2]. Cutaneous Crohn is characterized by granulomatous infiltration of skin non-contiguous with the gastrointestinal tract. In 20-35% of cases, cutaneous disease precedes intestinal symptoms, and very rarely, it may precede histopathological evidence of Crohn disease in the gastrointestinal tract [2,5,6]. While the terminal ileum is the most commonly affected part of the intestinal tract, cutaneous Crohn disease is more often associated with colonic disease [4].

In the pediatric population, up to two-thirds of cutaneous Crohn disease cases affect genital skin, compared to half of adult cases [4]. The condition typically presents as scrotal or vulvar swelling, often with erythema and fissuring [2]. Extragenital disease may occur on the extremities including the palms and soles, trunk, face, and intertriginous areas, manifesting as dusky erythematous plaques and nodules with ulceration, and, even more rarely, as sterile pustules, lichenoid papules, or abscess-like lesions [4,6]. It is important to note that the severity and clinical course of cutaneous Crohn disease is not related to the activity or severity of the gastrointestinal disease [6,7].

The varied presentations of primary cutaneous Crohn disease complicate its clinical diagnosis, and biopsy is often required to confirm the diagnosis. The histopathology of affected areas is identical to the gastrointestinal lesions, demonstrating sterile, non-caseating epithelioid granulomas with surrounding lymphocytes infiltrating the superficial and deep dermis and sometimes extending into the subcutaneous fat. Multi-nucleated Langhans-type giant cells and a perivascular lymphohistiocytic infiltrate may also be seen [2]. In the case of vulvar involvement, consultation with gastroenterology to determine the utility of imaging to rule out fistulating Crohn disease may also be warranted [8].

Primary cutaneous Crohn disease can be recalcitrant, and currently a medical consensus on the best approach to treatment does not exist [9]. Case reports have demonstrated anecdotal efficacy of topical corticosteroids, intralesional steroids, oral prednisone, azathioprine, cyclosporine, mycophenolate mofetil, thalidomide, metronidazole, adalimumab, and infliximab [2]. Topical corticosteroids are often first-line

therapy. Potent or superpotent topical corticosteroids are typically required, and often the initial response is not sustained [5]. Recently, a case of cutaneous Crohn disease affecting the vulva was reported to respond to ustekinumab [10]. Surgical excision can also be considered, although poor wound healing and recurrence are common complications [2].

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CASE #4

PRESENTERS
Jared Wishik, MD, Adena Rosenblatt, MD, PhD

HISTORY OF PRESENT ILLNESS
In December 2016, a 68-year-old woman with a history of monoclonal gammopathy of unknown significance (MGUS) and scleromyxedema, diagnosed in 2003, presented to the University of Chicago Dermatology Clinic with concerns of skin tightness over the back of her neck, around her mouth, and throughout both of her hands. It was difficult for her to extend her neck, open her mouth or smile, and to perform fine motor skills.

The patient originally presented in 2003 with small, monomorphic, waxy papules on her arms, legs, and face with associated skin tightness. She was diagnosed clinically with scleromyxedema at that time. Upon further workup, she was found to have an underlying IgG-kappa MGUS. She was treated initially with oral cyclophosphamide with resolution of her associated skin findings. She remained in remission until 2007 when she experienced her first recurrence of her cutaneous lesions. At this time, she received another round of oral cyclophosphamide with resolution of her skin disease a second time. In 2009, the patient was diagnosed with restrictive lung disease thought to be possibly secondary to scleromyxedema given a workup for interstitial lung disease was negative. Her scleromyxedema was quiescent for a number of years until she experienced a second recurrence in 2011. At that time, she was treated with a third course of chemotherapy in addition to an autologous bone marrow transplant (BMT) with subsequent clearance of both her scleromyxedema and her underlying monoclonal gammopathy. The patient's MGUS and scleromyxedema remained in remission for another 5 years until 3 months prior to her initial visit to our clinic in December 2016.

PAST MEDICAL HISTORY
Scleromyxedema complicated by restrictive lung disease
IgG-kappa MGUS
Graves' Disease status post total thyroid ablation in 2004
Idiopathic thrombocytopenic purpura
Peripheral arterial disease
Essential hypertension

FAMILY HISTORY
Sister with a history of scleroderma.

MEDICATIONS
Amlodipine 5 mg daily
Aspirin 81 mg daily
Enalapril 20 mg BID
Simvastatin 20 mg nightly

ALLERGIES
No Known Drug Allergies

PHYSICAL EXAMINATION
Examination revealed diffuse perifollicular, flesh-colored, waxy, monomorphic, dome-shaped papules with underlying induration coalescing into plaques on the face, bilateral upper and lower extremities, chest, and back. Lesions were most prominent over the bilateral upper extremities and glabella, giving the patient a leonine-appearance. The patient also had sclerodactyly of all ten fingers.

LABORATORY RESULTS
Immunoglobulin G 1176 (800-1700 mg/dL), kappa free light chain 2.81 (0.3300-1.94 mg/dL), lambda free light chain 1.47 (0.5700-1.94 mg/dL), kappa/lambda ratio 1.91 (0.2600-1.65), immunoglobulin A 88 (100-490 mg/dL), immunoglobulin M 43 (60-370 mg/dL)

DERMATOPATHOLOGY
A punch biopsy of a characteristic lesion from the left upper arm revealed an atrophic epidermis and thickened dermis with an increase in both dermal fibroblasts and collagen, and trapping of eccrine glands. A scant perivascular and periadnexal lymphohistiocytic infiltrate was present in the dermis. Colloidal iron stain highlighted significantly increased mucin within the papillary and adventitial dermis.

DIAGNOSIS
Scleromyxedema

TREATMENT AND COURSE
After confirming the diagnosis of recurrent scleromyxedema along with the re-demonstration of the underlying monocolonal gammopathy, the patient was referred again to hematology-oncology and rheumatology. Due to recurrence after two courses of cyclophosphamide and a bone marrow transplant, the decision was made to start the patient on intravenous immunoglobulin (IVIG) therapy in February 2017. Treatment began with a loading dose of 1 gm/kg twice the first month, followed by 1 gm/kg/month thereafter. She had complete resolution of her skin lesions at a 4 month follow up. She continues to receive monthly infusions without recurrence of any cutaneous lesions.

DISCUSSION
Scleromyxedema, which is also known as Arndt-Gottron disease or generalized and sclerodermoid lichen myxedematosus, is a primary cutaneous mucinosis that usually occurs in association with a monoclonal gammopathy. The most common monoclonal gammopathies associated with scleromyxedema are IgG-lambda light chain, but IgG-kappa light chain has also been described. The most common presentation of this condition includes a widespread eruption of roughly 3-5 mm, firm, waxy papules that may coalesce into firm, indurated plaques. Scleromyxedema typically involves the hands, forearms, head, neck, trunk and thighs. Involvement of the glabella is rather typical, and can produce a leonine-appearing face, as was observed in our patient. Non-tender subcutaneous nodules and regional alopecia can occur as well. The condition can progress to induration, skin stiffening, and decreased range of motion in any affected location. Scleromyxedema has only been described in adults, usually between the ages of 30 and 80 years.

The pathogenesis of scleromyxedema is not clear. Some suggest that circulating cytokines (interleukin-1, TNF-alpha, and TGF-beta) stimulate glycosaminoglycan synthesis and deposition in the dermis as well as cutaneous fibroblast proliferation, while others have thought the circulating paraproteins may be pathogenic. Interestingly, paraprotein levels do not usually correlate with disease severity or progression. Histologically, scleromyxedema is characterized by the triad of dermal mucin deposition, fibrosis, and marked fibroblast proliferation.

Scleromyxedema can affect other organ systems as well. Neurologic, rheumatologic, and cardiac involvement has been reported in 30%, 25%, and 22% of patients, respectively. In one of the largest case series to date, extracutaneous manifestations were found in 20 out of 26 (77%) patients. One of the most feared complications of scleromyxedema is dermato-neuro syndrome, which is a potentially lethal neurologic condition characterized by fever, confusion, dysarthria, lethargy, convulsions and coma.

There have not been any randomized control trials for treatment for scleromyxedema since it is such a rare condition. Most of the treatment options are based on case reports, case series, and anecdotal

evidence. It has been suggested to initiate therapy with IVIG or thalidomide in combination with systemic steroids. Other options include: autologous bone marrow transplant, cyclophosphamide, melphalan, or bortezomib with dexamethasone. The latter medications carry significant adverse effects such as hematologic malignancies and opportunistic infections. Unfortunately, a large percentage of patients will experience relapses regardless of the chosen therapeutic intervention. A review of 17 cases treated with autologous BMT showed complete resolution in 10 patients, but only 2 of those patients remained in remission between 14 and 60 months of follow up. It has been suggested to initiate therapy with IVIG. Continued remission has been seen with long-term IVIG therapy, which our patient is currently receiving.

The prognosis for scleromyxedema remains unclear. In a 2013 observational study, 21 patients were followed up for a mean duration of 33.5 months after various therapeutic interventions were implemented. At that time, a total of 5 patients had passed away, 3 of which were related to complications from their scleromyxedema (two from dermatoneuro syndrome and one from inflammatory mucinous cardiomyopathy).
We present this case to highlight a rather rare condition that is associated with significant mortality and an unpredictable prognosis.

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CASE #5

PRESENTERS

Rebecca S. Kaiser, MD; Christopher R. Shea, MD; Keyoumars Soltani, MD

UNKNOWN CASE

A 71-year-old African American man presented to the dermatology clinic for evaluation of itchy bumps on his head, neck, and forearms, which he had first noted over a month before.

CASE #6

PRESENTERS
Ashley Jenkins, MD; Farah Abdulla, MD; Vesna Petronic-Rosic, MD, MSc

HISTORY OF PRESENT ILLNESS
A 58-year-old African American female presented to the dermatology clinic as an urgent add-on for a four-week history of a lower extremity "rash" consisting of red nodules which were only mildly tender. In addition to the nodules, the patient had also developed painful edema extending from her toes up to her mid-calves. She had been taking acetaminophen/hydrocodone and gabapentin for the severe pain in her legs; however, this provided minimal relief. Elevation of her legs only decreased her swelling partially. Review of systems was positive for worsening fatigue, shortness of breath, low-grade fevers, chills, and night sweats.

PAST MEDICAL HISTORY
Sarcoidosis – diagnosed in 1978, complicated by supplemental oxygen and severe renal and liver transplant, treated by renal and liver transplantation.

FAMILY HISTORY
Her mother died from lung cancer.

MEDICATIONS
Tacrolimus 1mg BID for organ anti-rejection, amlodipine, aspirin 81mg, a corticosteroid inhaler, gabapentin and hydrocodone/acetaminophen

ALLERGIES
Penicillin
High-dose prednisone intolerance – psychosis and depression
Mycophenolate mofetil intolerance – severe dysgeusia

PHYSICAL EXAMINATION
Examination revealed numerous, ill-defined, erythematous, slightly-elevated nodules ranging from 2-5cm in diameter along the anterior, medial, and lateral shins. She also had marked edema present to the mid-shins bilaterally.

LABORATORY DATA
Laboratory evaluation was significant for an elevated angiotensin-converting enzyme (ACE) level which was high at 126 U/L. Erythrocyte sedimentation rate and C-reactive protein were normal.

PATHOLOGY
A 6-mm punch biopsy of the left leg revealed scattered epithelioid histiocytes and multinucleated giant cells with a sparse lymphocytic infiltrate. Within the subcutaneous tissue, a large vessel was identified with granulomatous inflammation within the vessel wall. Necrosis was not present. Polaroscopy was negative for birefringent foreign material. The PAS, GMS, Gram, and Fite stains were negative for organisms.

DIAGNOSIS
Cutaneous sarcoidal vasculitis

TREATMENT AND COURSE
The patient was started on methylprednisolone 8mg per day, infliximab 5mg/kg infusions, and topical

clobetasol ointment. The patient started having severe mood symptoms within the first two days of taking methylprednisolone, so she self-discontinued the corticosteroid and her symptoms eventually resolved. She tolerated infliximab and, after the second loading infusion, the skin nodules started to diminish and her pain and swelling improved. She also reported improvement in her fatigue and shortness of breath have improved.

DISCUSSION

Sarcoidosis is a systemic inflammatory disease that often has cutaneous involvement. Despite extensive research, the etiology of sarcoidosis is still not known. Most evidence suggests that sarcoidosis is due to an exaggerated cell-mediated immune response, driven by an unidentified antigen (or possibly multiple antigens) in genetically susceptible individuals.

Sarcoidosis is characterized by the accumulation of sarcoidal granulomas in the affected organs, and the non-caseating epithelioid granuloma is the pathological hallmark of sarcoidosis. Sarcoidal granulomas are discrete, round to oval, non-confluent collections of epithelioid histiocytes and multinucleate giant cells. They are surrounded by only a sparse rim of lymphocytes and plasma cells, which is why they are considered to have a "naked" appearance. Although sarcoidosis can affect any organ, sarcoidal granulomas have a predilection for the lungs, lymph nodes, eyes and skin. Sarcoidal granulomas are not specific to this disease, as they can be found in reactions to foreign body material as well as other granulomatous conditions.

When sarcoidosis has cutaneous involvement, the pathology generally shows sarcoidal granulomas within the skin. Their depth varies according to the clinical subtype; however, most are located within the superficial or deep dermis and sometimes may extend into the subcutis. Sarcoidal granulomas rarely extend peri-neurally or peri-adnexally, and even more rarely involve the blood vessels. According to a recently published comprehensive literature review, there have only been 17 previously reported cases of cutaneous sarcoidal vasculitis. Cutaneous sarcoidal vasculitis most often affects small to medium sized blood vessels, predominately on the lower extremities. Manifestations include papules or nodules, plaques, macules or patches, ulcers and livedo. Most often, the sarcoidal vasculitis occurs at the same time as the onset of systemic sarcoidosis; however, 24% of cases of sarcoidal vasculitis occurred after the onset of systemic sarcoidosis.

There are no specific guidelines for the treatment cutaneous sarcoidal vasculitis; in fact, the treatment of sarcoidosis in general remains a mixture of evidence-based recommendations and clinical judgment. The approach to treatment of sarcoidosis depends upon the extent of the disease as well as the organ system most affected. Oral glucocorticoids are the mainstay for pulmonary sarcoidosis as well as many manifestations of extra-pulmonary disease. The antimetabolites, such as methotrexate, azathioprine, and mycophenolate, as well as anti-malarials, are often used in addition to or as alternatives to steroids. TNF inhibitors, namely infliximab, have been used in patients not amenable or responsive to more traditional therapies.

The TNFα inhibitor infliximab was first reported to be useful in refractory cutaneous and pulmonary sarcoidosis in 2001. Since then, other TNF inhibitors including etanercept and adalimumab have also been studied. The use infliximab in sarcoidosis is the most well studied, however, there are several reports about adalimumab with promising data as well. Etanercept has not been found to be as effective in sarcoidosis, possibly because infliximab and adalimumab achieve greater tissue penetration and cell mediated lysis of TNF-secreting cells.

There are no published cases of cutaneous sarcoidal vasculitis treated with infliximab to date. Other patients with this rare condition were treated with corticosteroids and some with an additional antimetabolite. Due to her severe neuropsychiatric symptoms secondary to corticosteroids, and her

previous intolerance to mycophenolate, the decision was made to initiate infliximab which patient has fortunately done very well on.

Unfortunately, there is a under recognized paradoxical response that can arise with anti-TNF alpha treatment called sarcoid-like granulomatosis. It is most widely reported with the receptor antagonist etanercept, however, it has been reported with the other TNF inhibitors as well. Therefore, physicians prescribing these drugs should be well aware of the possibility of a paradoxical effect, and consider discontinuation in case of suspicion.

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10. Weeden's Skin Pathology

CASE #7

PRESENTERS
Stephanie M. Kazantsev, MD; Christopher R. Shea, MD; Diana Bolotin, MD, PhD

HISTORY OF PRESENT ILLNESS
A 59-year-old woman with history of recurrent supraglottic squamous cell carcinoma presented from oncology clinic for evaluation of new skin lesions, six weeks after commencing therapy with nivolumab, ipilimumab, and lirilumab. The patient reported a 2 day history of redness surrounding the bilateral eyelids and "fluid-filled bumps" scattered across the body. The lesions were not pruritic or painful. She has not had a similar rash in the past. Review of systems was negative for fevers or chills.

PAST MEDICAL HISTORY
Supraglottic squamous cell carcinoma (diagnosed in 2015) complicated by multiple recurrences despite total laryngectomy, chemotherapy, and radiation therapy

MEDICATIONS
Aspirin
Ciprofloxacin
Famotidine
Gabapentin
Labetalol
Levothyroxine
Oxycodone
Polyethylene glycol
Sennosides-docusate-sodium

ALLERGIES
No known drug allergies

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
Former smoker (60 pack year history)

PHYSICAL EXAM
Examination revealed a slender woman with aphonia and laryngectomy tube in place. Cutaneous examination revealed purpura and edema on the superior and inferior eyelids bilaterally. Scattered erythematous edematous papules and plaques were noted on the bilateral arms and legs.

DERMATOPATHOLOGY
A punch biopsy from a characteristic lesion on the right thigh demonstrated superficial perivascular and interstitial infiltrates composed predominantly of neutrophils. The subcutaneous tissue contained histiocytes centered around adipocytes, forming foci of granulomatous inflammation. The colloidal iron stain demonstrated a focal increase in mucin within the dermis and subcutis. There was no evidence of marked papillary dermal edema, spongiotic changes in the epidermis, or vasculitis. Periodic acid-Schiff, methenamine silver, Gram, and Fite stains were negative for organisms.

LABORATORY DATA
Complete blood count notable for neutrophils 6.99 (1.12-6.72 x 10^3/μL), lymphocytes 0.39 (0.9-3.30 x

10^3/µL), monocytes 1.00 (0.16-0.92 x 10^3/µL)
HSV and VZV PCR negative

DIAGNOSIS
Superficial neutrophilic dermatosis and granulomatous panniculitis resulting from nivolumab/ipilimumab/lirilumab triple immunotherapy

TREATMENT AND COURSE
The patient was started on mometasone ointment twice daily to non-facial lesions. She reported improvement to her skin lesions within days of initiation of therapy.

One month after this visit, the patient was admitted for recurrent oropharyngeal bleeding, and was ultimately discharged to home hospice in the setting of imminent carotid blowout. She passed away at home later that week.

DISCUSSION
Recent advances in the understanding of the molecular pathogenesis and immunology of cancer have led to the development of novel therapies for advanced and refractory malignancies. Programmed cell death (PD)1 receptors are immune checkpoint regulators expressed by activated T-cells, B-cells and natural killer (NK) cells. When bound by their ligands, PD1 receptors down-regulate T-cell activation, thereby acting as a natural brake to the immune system. Nivolumab is a humanized IgG monoclonal antibody that blocks the interaction between PD1 receptor and its ligand, which is frequently expressed on tumor cells. This in turn disrupts negative signaling from the tumor cell, and allows for enhanced immune response [1-2].

Ipilimumab is a humanized IgG monoclonal antibody that targets CTLA4 on T-cells. When bound to B7 (CD80 and CD86) on antigen presenting cells (APC), CTLA4 receptors signal T-cell inhibition. Therefore, CTLA4 primarily counteracts the activity of its co-stimulatory T-cell receptor, CD28. When the same B7 from APC interacts with CD28, on the T-cell in the setting of antigen presentation by MHC molecules, it leads to T-cell activation. Thus, by blocking the interaction CTLA4 and B7, ipilimumab releases this negative regulatory checkpoint in tumor antigen recognition and allows for T-cell potentiation, activation, and anti-tumor activity [2-3].

Lirilumab is a human monoclonal antibody against killer cell immunoglobulin-like receptors (KIR). KIRs are found on the surface of natural killer (NK) cells, and function to suppress the cytotoxic activity of NK cells when bound to HLA-C class I molecules. Addition of lirilumab to cancer regimens blocks the KIR and HLA-C interaction, and thereby enhances the cytotoxic activity of NK cells against tumor cells [2, 4].

Nivolumab and ipilimumab act as a double immune checkpoint blockade, amplifying T-cell activation. Single blockade of CTLA4 or PD1 pathways in preclinical models led to upregulation of the other unblocked pathway, which is thought to be a mechanism of treatment failure. Subsequent clinical trials have shown higher response rates with the combination of nivolumab and ipilimumab over single-agent therapy. Furthermore, the addition of a third agent with anti-KIR activity leads to NK cell activation, thus potentiating the anti-tumor response. This combination therapy targets the multiple mechanisms by which tumor cells avoid immune response, thereby leading to improved immune-mediated destructionof cancer cells. [5,6]

Given the mechanisms of action of these checkpoint inhibitors, immune-related adverse events have been reported with these therapies. The most common cutaneous reactions to PD1 inhibitors include lichenoid reactions, eczema, vitiligo, and more rarely sarcoid-like reactions [1]. Granulomatous panniculitis

developing in patients on PD1 inhibitors has only recently been described [7-8]. This has been proposed to be a subset of sarcoid-like granulomatous reactions to anti-PD1 therapy, likely related to Th1 cell activation [7-8].

Multiple case reports highlight the development of neutrophilic dermatoses in patients being treated with CTLA4 inhibitors. Rudolph et al described a patient who developed pyoderma gangrenosum and colitis while on ipilimumab [9]. Three cases of Sweet syndrome developing in patients receiving ipilimumab have been reported [10-12]. Additionally, a case of ipilimumab-induced acute generalized exanthematous pustulosis was previously reported [13]. Although the exact etiology of these neutrophilic eruptions is unclear, it has been proposed that CTLA4 inhibition causes cytokine dysregulation leading to neutrophil homing, accumulation, and activation [13, 14]. Another proposed etiology is that CTLA4 inhibition alters the skin flora, leading to a neutrophilic infiltrate [13].

To our knowledge, the combination of a superficial neutrophilic dermatosis with concurrent granulomatous panniculitis while on treatment with a combination of PD1 and CTLA4 inhibitors has not been previously reported. We propose that this unique histopathological finding may be a result of ipilimumab-induced neutrophilic dermatosis and nivolumab-induced granulomatous panniculitis. Dermatologists and oncologists should be aware of the unique morphological appearance of these adverse events related to the newer immune therapies for cancer treatment.

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CASE #8

PRESENTERS
Kathleen Kelley, MD; Aisha Sethi, MD; Juliana Basko-Plluska, MD; Christopher Shea, MD

UNKNOWN CASE
A 29 year old man presented to the Dermatology clinic in the fall of 2016 for evaluation of several chronic, purulent ulcers on his right ankle.

CASE #9

PRESENTERS
Clifford Hsieh MD; Sarah Stein MD

HISTORY OF PRESENT ILLNESS
The patient is a 14-year-old African American female who presented for routine follow up of congenital erythropoietic porphyria (CEP). The patient noted occasional development of small erosions on the arms, hands, lower legs, and feet when experiencing unintended sun exposure. In general, the patient reported avoiding sun exposure, and using sunscreen with SPF 100 to the face and exposed skin daily. However, she and her mother admit that in recent years, they have become somewhat less diligent with sun protection. The family was interested in discussing hair removal options for excessive hair growth on the face. The patient is less concerned about hair growth on her arms and legs. She shaves her facial hairs several times a week. Eflornithine (Vaniqa) cream was used previously, but family reported minimal benefit, and the patient has stopped using this agent.

PAST MEDICAL HISTORY
Premature birth at 32 weeks
Congenital erythropoietic porphyria diagnosed in the newborn period after demonstration of significant blistering following phototherapy for hyperbilirubinemia

PAST SURGICAL HISTORY
Z-plasty contracture release

MEDICATIONS
Calcium and vitamin D supplement daily.

ALLERGIES
No known drug allergies

FAMILY HISTORY
No family history of CEP or other photosensitive disorders.

SOCIAL HISTORY
Lives at home with mother and father
Home schooled and in 10^{th} grade
No smoking, alcohol, or illicit drug use

PHYSICAL EXAM
Examination revealed a teenage female with Fitzpatrick type V skin. Dark red-staining of her teeth with corrective braces was noted, as was right-sided strabismus without nystagmus. Increased dark terminal hairs densely involved her lateral chin, cheeks, and temples. Hyperpigmented and minimally hypertrophic scars extended outward from the bilateral oral commissures to laterally involve the cheeks. There were multiple hypertrophic and dyspigmented scars involving the trunk with evidence of contractures in flexural areas. The volar aspect of bilateral upper arms had hypertrophic Z shaped surgical scars. Her dorsal hands demonstrated a few hyper and hypo-pigmented macules and mildly atrophic plaques. Her skin exam revealed no active vesicles or erosions. Her abdominal examination was negative for evidence of splenomegaly.

LABORATORY DATA
Complete blood count and comprehensive metabolic panel were within normal limits.

Neonatal period (2002) and age 5 years old (2007):

24 hour urine studies			
	Neonatal	Age 5	Reference ranges
Aminolevulinic acid	0.4	0.33	0- 0.66 µmol/L
Porphobilinogen	<0.1	0.3	0- 0.5 µg/24hr
Uroporphyrin	417	1839	3- 25 µg/24hr
Coproporphyrin	144	2129	8- 110 µg/24hr

Isomers chromatography of urine revealed uroporphyrin I and coproporphyrin I were the predominant isomers present.

24 hour fecal studies			
	Neonatal	Age 5	Reference ranges
Uroporphyrin I		22	< 120 µg/24hr
Coproporphyrin I	632	25616	< 500 µg/24hr
Protoporphyrin		21	< 1500 µg/24hr

Total porphyrin levels in plasma in the neonatal period and age 5 were elevated. Isomers chromatography showed increased levels of uroporphyrin I and coproporphyrin I.

Total porphyrin levels in erythrocytes in the neonatal period and age 5 were elevated. Porphyrin fractionation showed increased uroporphyrin and coproporphyrin.

DIAGNOSIS

Congenital erythropoietic porphyria

TREATMENT AND COURSE

The patient was diagnosed with congenital erythropoietic porphyria in infancy when she presented with extensive blistering after exposure to phototherapy for hyperbilirubinemia. The early blistering led to extensive hypertrophic scarring. Her subsequent course has been relatively uncomplicated, without evidence of ongoing mutilating scarring, excessive photosensitivity, or hemolytic anemia. The patient and her family have continued to be relatively attentive to photoprotection which limits their choice of activities. Recent case reports of improved phototolerance in patients with erythropoietic protoporphyria treated with cimetidine was shared with the family. The family was interested in pursuing similar treatment in hopes of further alleviating the risks associated with unintended exposure to ultraviolet light, thus a trial of cimetidine 800 mg twice a day was initiated.

The patient expresses that the hypertrichosis associated with her disease significantly impacts her quality of life. Laser hair removal was discussed. The risks of laser hair removal in the setting of CEP and in the setting of the patient's baseline skin pigmentation was reviewed. The patient has elected to pursue laser hair removal. At her first laser hair removal session, test spots will be done to assess tolerance to this treatment.

DISCUSSION

Congenital erythropoietic porphyria (CEP) is a rare metabolic disorder of the porphyrin-heme biosynthetic pathway, with approximately 200 reported cases [1]. It is an autosomal recessively inherited disorder, with known mutations at locus 10q25.2-q26.3, leading to markedly deficient catalytic activity of uroporphyrinogen III synthase (UROS), the fourth enzyme in the heme biosynthetic pathway [2]. The decreased enzymatic activity of UROS leads to non-enzymatic conversion of hydroxymethylbilane to

uroporphyrinogen I. Uroporphyrinogen I is subsequently metabolized to coproporphyrinogen I, which is oxidized to uroporphyrin I and coproporphyrin I [1,3]. These porphyrin end-products accumulate in erythrocytes, bone marrow cells, plasma, urine, and feces. Approximately 50 loss of function mutations in UROS have been identified as causative for CEP. The severity of the disease is variable based on the amount of residual UROS activity as determined by which alleles are mutated [1].

Congenital erythropoietic porphyria typically presents in infancy or in the first decade of life. Patients exhibit severe cutaneous photosensitivity, presenting with vesicles, bullae, erosions, and ulcerations, and later with hyperpigmentation and mutilating scarring in sun exposed (or other UV-exposed) regions. Staining of diapers with pink-red colored urine may be the initial presentation. Uroporphyrin I and coproporphyrin I deposition in the skin reacts to the 400-410 nm range of visible light (Soret band), causing photoexcitation and production of oxygen-dependent free radicals that cause local tissue damage [1,3]. Mutilation of cartilaginous structures and excessive scarring and deformation of body sites can occur. Porphyrin deposition causes red-brown discoloration of the teeth (erythrodontia), corneal ulcerations, other ocular abnormalities, and bone marrow hyperplasia leading to bone fragility. Hemolytic anemia, hepatosplenomegaly, and hypertrichosis are also complications of CEP [1,2,4]. The mechanism of the hypertrichosis has not been determined.

The mainstay of management of congenital erythropoietic porphyria is photoprotection from wavelengths <410 nm by using broad-spectrum sunscreens, wearing UV protective clothing, and avoiding sunlight exposure, including protection from light through window glass. As a result, adequate vitamin D supplementation must be maintained. Splenectomy may be indicated to reduce hemolysis and platelet consumption. Frequent blood transfusions can suppress erythropoiesis, leading to decreased porphyrin production. Bone marrow or hematopoietic stem cell transplantation can be considered in those with severe hematologic involvement and can be curative, though erythrodontia will persist [1,2,5]. Management of the associated hypertrichosis includes all of the techniques available for hair removal in general, such as manual removal, topical treatments, and/or laser hair removal [1].

There are currently no FDA approved treatments for CEP or the associated photosensitivity. In the European Union, afamelanotide (Scenesse) has been approved to prevent phototoxicity in adult patients with erythropoietic protoporphyria (EPP). Afamelanotide is a synthetic α-melanocyte stimulating hormone analogue and melanocortin-1 receptor agonist, increasing melanin production in melanocytes and thus skin pigmentation [6,7]. It is administered subcutaneously as a resorbable implant.[6] Studies have shown improved light tolerance, ability to spend more time in sunlight without pain and symptoms of phototoxicity, and improved quality of life with few side effects (headache, nausea, and implant-site reactions) in patients with EPP [6,7,8]. A case report of CEP from Australia documented darkening of the patient's skin and improved tolerance to sunlight with a trial of afamelanotide.[3] A small number of case reports have shown that cimetidine improved symptoms in a variety of porphyrias, including acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria [9,10,11]. Cimetidine is an H2 receptor antagonist and inhibitor of cytochrome P-450, a heme containing enzyme. Cimetidine has been shown to inhibit heme biosynthesis by inhibiting δ-aminolevulinic acid synthase, the first enzyme in the heme biosynthetic pathway [11]. A recent pediatric case series of three erythropoietic protoporphyria cases reported rapid reduction in photosensitivity, improvement of skin photodamage, and ability to spend more time in the sun with initiation of oral cimetidine (30-40 mg/kg/day divided twice daily, with maximum of 800mg twice a day) without any adverse effects.

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CASE #10

PRESENTERS
Larry A. Napolitano Jr, MD, Vesna Petronic-Rosic MD, MSc, Christopher R. Shea MD

HISTORY OF PRESENT ILLNESS
A 43-year-old African American female presented with well-demarcated, hyper-keratotic, hypo-pigmented, verruciform plaques located on bilateral palms and the medial arch of right foot. The patient has had recurrent similar lesion for approximately 5 years that have, at different times affected the bilateral palms and plantar feet. The lesions have been treated with multiple modalities including cryotherapy and multiple surgical excisions and grafting by plastic surgery. The patient presented to dermatology requesting a second opinion for non-surgical treatment options. Patient admitted to "digging at the sites with a nail file," using the same nail file to each site. Her current lesions had been present for 6 months and are asymptomatic.

PAST MEDICAL HISTORY
Chronic back pain
Atopic dermatitis

FAMILY HISTORY
Unknown

MEDICATIONS
Clobetasol proprionate 0.05% ointment twice daily for atopic dermatitis flares

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Examination revealed three well-demarcated, hyperkeratotic, exophytic, hypopigmented verruciform plaques located on both palms and the medial arch of right foot. The lesions ranged in diameter from 3-9 cm.

LABORATORY DATA
HIV, Hep B, Hep C negative
CBC, CMP within normal limits
Immunoglobulin profile was within normal limits

DERMATOPATHOLOGY
Three punch biopsy specimens, taken from lesions of each palm and from the arch of right foot, all showed similar findings, consistent with verruca vulgaris. Prominent papillomatosis, compact hyperkeratosis with focal hemorrhage, hypergranulosis, and acanthosis were present.

DIAGNOSIS
Verrucae Vulgares

TREATMENT AND COURSE
Patient refused both cryotherapy and injectable medications, and requested topical therapy. Lesions were recalcitrant to topical imiquimod titrated up to twice daily with nightly occlusion, 5 days per week for 4 months. The risks, benefits, and side effects of IV cidovofir, intralesional bleomycin, topical 5-

fluorouricil, and topical cidofovir were discussed, and patient opted for topical cidofovir. Topical cidofovir 3 % cream was prescribed for twice daily use.

At 8 weeks follow-up, the verrucous lesions were reduced to pink granulated plaques. Cidofovir was stopped and the patient was instructed to apply Vaseline to area twice daily. At 15 weeks off treatment, the patient's skin demonstrated gross re-epithelialization of the affected areas with focal areas of re-pigmentation.

DISCUSSION

Verrucae vulgares (common warts) are benign proliferations of the epidermis caused by several strains of Human Papilloma Virus (HPV) [1]. Most common warts, as well as those found on the palmar and/or plantar regions, are caused by HPV types 1, 2, and 4. Warts can be found throughout the body, but are most commonly seen on the hands, feet, face, and anogential region. Verruca vulgaris is a common cutaneous entity affecting 7-10% of the population [2]. Warts typically present as hyperkeratotic, exophytic, endophytic, or dome-shaped verruciform papules or plaques with punctate black dots (thrombosed capillaries) that disrupt the normal contour of dermatoglyphs. Histologically, warts show papillomatosis, hyperkeratosis, columns of parakeratosis overlying papillomatous projections, often with small hemorrhages in columns, hypergranulosis in "valleys," and acanthosis [3].

Most warts are painless and of only minor cosmetic significance. They can, however, become cosmetically distressing or cause enough pain to interfere with normal daily activities [1]. Typical examples of painful warts include those on the nail folds and those on the soles. In otherwise healthy individuals, 20% of all warts will resolve spontaneously within a 3-month period [4]. The remaining lesions can be difficult to treat because of their unpredictable response and high relapse rates [1]. Multiple treatment options are currently available, such as topical chemical agents, surgical excision, immunotherapy, cryotherapy, intra-lesional bleomycin, and laser therapy.

Cidofovir, a broad-spectrum antiviral agent, acts as a potent nucleoside analog of deoxycytidine monophosphate with activity against several DNA viruses [5]. When incorporated into the host cell, cidofovir undergoes two stages of phosphorylation to form the active intracellular metabolite cidofovir diphosphate. Once incorporated into growing viral DNA, it blocks further viral DNA synthesis and replication. Cidofovir was approved in 1997, for intravenous use only, in the treatment of cytomegalovirus retinitis resistant to ganciclovir and foscarnet in AIDS patients [6]. Topical cidofovir is an off-label treatment modality that has been shown effective in resistant HSV infections, molluscum contagiosum, and human papillomavirus infections [5-9]. Whereas systemic cidofovir has numerous side effects, including nephritis, myositis, and GI upset, topical cidofovir is generally well tolerated, although local erythema and burning at the site of application are reported in up to 50% of patients [6,8,9]. A search of the literature revealed two case reports of acute kidney injury in association with topical cidofovir in the treatment of resistant herpes simplex virus infections [10]. Of note, both cases had multiple confounding factors including concomitant use of medications well known to induce kidney injury.

A review of the literature identified a number of larger studies of recalcitrant warts treated with topical cidofovir. For the purpose of the review, we defined recalcitrant as having failed at least two treatment modalities over a minimum of a one year period. Cohorts were comprised of healthy adults, with two exceptions – one studying an immunocompromised cohort and the other a pediatric cohort [13,14]. Study sizes ranged from 4-41 patients [11-17]. In all but one study, twice daily application was instituted, with the two largest studies applying for 5 consecutive days out of 7 for eleven weeks. Duration of application varied greatly from 1 to 11 weeks. Response rates ranged from 47% - 92%, with a weighted response rate of ~84%. The majority of outcomes were maintained over time, even in the notoriously difficult to treat warts of the periungual and plantar skin.

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