Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, December 2, 2019
Online - via Zoom

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

Program

Host: University of Chicago
Wednesday, December 2, 2020
Online Conference

8:30 a.m.	**Sign-in and Member Visitation Time**
9:00 a.m.	**Welcome & Introduction** *David Mann, MD - CDS President*
9:05 a.m. - 9:40 a.m.	**Guest Lecture #1** "Inpatient Dermatology: Cases that have taught me dermatology – Part 1" *Lindy P. Fox, MD*
9:40 a.m. - 9:50 a.m.	**Questions & Answers**
9:50 a.m. - 10:35 a.m.	**Resident Case Presentations & Discussion** *University of Chicago Residents*
10:35 a.m. - 10:50 a.m.	**Guest Lecture #2** "Inpatient Dermatology: Cases that have taught me dermatology – Part 2" *Lindy P. Fox, MD*
10:50 a.m. - 11:00 a.m.	**Questions & Answers**
11:00 a.m.	**Closing Remarks and Introduction of Discussion Breakout Rooms** *David Mann, MD*
11:00 a.m. - 12:00 p.m.	**Breakout Rooms*** • Medical Students • Case Discussions • Practice Challenges • Residents Forum
12:00 p.m.	**Meeting adjourns**

* Four breakout sessions will commence at the conclusion of the second guest lecture. They are scheduled for approximately one hour (ending by 12 noon) and are intended to be open discussion with a moderator to facilitate the conversation. Meeting attendees were asked to indicate their choice of breakout session when first registering for the Zoom meeting.

Mark the Date!

Next CDS clinical meeting will be on Wednesday, April 7 – Co-hosted by the Stroger Hospital of Cook County. The next "CDS Connections" will be on Wednesday, December 15. *Note...* This is a slight variation on the normal schedule.
Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

LINDY P. FOX, MD

Professor of Dermatology,
University of California - San Francisco
School of Medicine; San Francisco, CA

Lindy P. Fox, MD is a dermatologist who cares for patients in the hospital with complex skin conditions.

Dr. Fox's research focuses on the impact of dermatologists have in the hospital setting. Her work has helped define this subspecialty within dermatology. She studies continuity of care for hospitalized patients with skin conditions, and she looks at how emerging patterns or new associations of skin diseases are recognized, documented and defined.

Dr. Fox earned her medical degree at the University of Texas Southwestern Medical School. She completed her residency in dermatology at New York – Presbyterian/Columbia University Irving Medical Center. She is president of both the Medical Dermatology Society and Society for Dermatology Hospitalists, and is secretary-treasurer of the Pacific Dermatologic Association. She is a member of the American Academy of Dermatology and Dermatology Foundation.

CME Information

December 2, 2020

Overview

The Chicago Dermatological Society was established in 1901 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 typically schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. Two lectures are given by the guest speaker, and the residents of the host institution present cases which are offered for audience discussion. During the coronavirus pandemic, CDS has continued to organize our regular educational conferences, but in a half-day "virtual" online live setting.

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 2020/21 series of meetings, the participant should be able to:
1. Describe the types of dermatological cases a clinician typically would encounter in an in-patient hospital setting.
2. Discuss what can be learned by the clinician about dermatological conditions from hospitalized patients with other significant diseases.
3. List the five main "take-aways" that can be learned from practicing in-patient consultive dermatology.

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 2 *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 an online CME claim form after the completion of the conference. A link to this form along with the online evaluation form will be sent to each conference attendee after 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. None of the participants in this conference have disclosed relevant potential conflicts of interest. The guest speaker, Dr. Lindy Fox, may discuss off-label or investigative uses of certain medications or products. These items will be clearly identified during the lecture.

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

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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.

University of Chicago
Section of Dermatology

Dermatology Residents

Third Year
Julia Dai, MD
Arjun Dayal, MD
Esther Kim, MD

Second Year
Margaret Boyle, MD
Margaret Bruns, MD
Erin Dodd, MD
Erin Ibler, MD

First Year
Scott Blaszak, MD
Maria Estela Martinez-Escala MD, PhD
Jake Lazaroff, MD

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PRESENTERS
Margaret Bruns MD; Keyoumars Soltani MD; Christopher Shea MD; Oluwakemi Onajin MD

HISTORY OF PRESENT ILLNESS
A 66-year-old female presented to dermatology for evaluation of a blistering rash and oral sores. Two months prior to presentation the patient was started on sitravatinib and nivolumab for metastatic urothelial cancer. Four weeks later she developed painful oral sores and a pruritic rash with blisters on the legs. Rash spread to involve the dorsal feet, dorsal hands, arms, and upper chest. No ocular or genital lesions. Sitravatinib and nivolumab were held and she was treated with a course of oral prednisone by her oncologist with some improvement.

PAST MEDICAL HISTORY
Metastatic urothelial carcinoma

FAMILY HISTORY
No family history of autoimmune disease or malignancy

SOCIAL HISTORY
Denies alcohol and tobacco use

MEDICATIONS
Nivolumab
Sitravatinib
Prednisone

ALLERGIES
Ciprofloxacin
Codeine

REVIEW OF SYSTEMS
Positive for odynophagia and ocular pruritus. Negative for genital sores, dysuria, hematuria, or urinary frequency.

PHYSICAL EXAMINATION
Numerous pink-to-violaceous papules and plaques with central erosions and heme-crust on the bilateral dorsal hands, extensor elbows, extensor knees, anterior legs and upper central chest. Grouped violaceous papules coalescing into plaques with admixed thin-walled, deflated bullae on the dorsal, lateral, and medial feet. Erosions throughout the buccal mucosa, gingiva, hard palate, and lower mucosal lip. Large ulceration on the dorsal tongue. White reticulations on the tongue and buccal mucosa. Nails appear normal.

LABORATORY TESTS
- BP180 126 RU/mL (Ref <20 RU/mL)
- BP230 105 RU/mL (Ref <20 RU/mL)

- HSV and VZV PCR negative
- Oral fungal culture negative

DERMATOPATHOLOGY
Punch biopsy for routine histology from the left foot demonstrated lichenoid interface dermatitis with dyskeratotic keratinocytes and formation of a subepidermal bulla. Punch biopsy for DIF from the left foot demonstrated linear deposition of IgG and C3 and shaggy deposition of fibrinogen at the basement membrane zone.

DIAGNOSIS
Lichen Planus Pemphigoides

TREATMENT & COURSE
Our patient was initially treated with prednisone 60 mg daily, topical clobetasol 0.05% ointment BID to lesions on body and in mouth, dexamethasone oral solution swish and spit BID, clotrimazole troche 10 mg for prevention of candida infection, and magic mouthwash QID PRN.

She initially saw some improvement but when prednisone was tapered her cutaneous and oral lesions flared. Given the progression of her lesions despite low-dose oral prednisone and elevated BP180/230 serologies, she was started on rituximab IV 375 mg/m^2 (lymphoma dosing) once weekly for 4 weeks. At follow-up visit four weeks after completion of rituximab she reported improvement in skin rash and oral erosions with minimal development of new lesions. She was tapered off prednisone with plans to repeat rituximab in 6 months if disease recurs. Oncology plans to continue treatment holiday given stable disease on last CT scan.

DISCUSSION
Lichen planus pemphigoides (LPP) is a rare autoimmune subepidermal blistering disorder characterized by the presence of both lichenoid lesions and bullae and autoantibodies to type XVII collagen (BPAG2, BP180). The true prevalence is not known but estimated to be 1 per 1,000,000. The average age of onset is approximately 46 years old. LPP is generally idiopathic but has been reported in association with various drugs, internal malignancies, and infections.[1]

The lichenoid lesions in LPP consist of pruritic violaceous, flat-topped, polygonal papules and plaques with white scale. Lace-like reticulated white patches may be seen on the buccal mucosa and external genital mucosa. The blisters typically appear de novo after the lichenoid lesions on previously unaffected skin. LPP affecting only the mucous membranes has been reported.[1]

Autoantibodies in LPP are most commonly found against the NC16A domain of BPAG2, and less frequently found against BPAG1, the C-terminal portion of BPAG2, and desmoglein 1. It has been proposed that the inflammatory basal cell infiltrate of lichenoid lesions may expose antigens and lead to subsequent autoantibody production. This theory is supported by the fact that blisters almost exclusively follow the lichenoid lesions. The heterogeneity of clinical presentations may relate to the variability in autoantigens detected.[1]

Histopathology of a bullous lesion in LPP shows the typical features of bullous pemphigoid (BP), including subepidermal separation with an eosinophilic infiltrate, whereas histopathology

of a lichenoid lesion shows the typical features of lichen planus (LP) with hyperkeratosis, hypergranulosis, subepidermal band-like lymphocytic infiltrate, and vacuolar interface dermatitis. IgG and C3 deposition at the dermal-epidermal junction zone can be detected via DIF of perilesional skin. Circulating autoantibodies to BP180 or desmogleins may be found using IIF on monkey esophagus or human neonatal foreskin or via ELISA.[1]

LPP must be distinguished clinically and histologically from several similar conditions, most notably bullous lichen planus. Bullous LP presents with vesicles or bullae within pre-existing LP lesions. Bullous LP is thought to be due to severe degeneration of basal layer cells and lacks autoantibodies to structural proteins of the epidermis. Histopathology of bullous LP demonstrates an extensive inflammatory infiltrate with formation of large Max-Joseph spaces and alteration of the dermoepidermal junction, which manifests clinically as tense bullae.[1]

Immune checkpoint inhibitors (ICI) have significantly improved the prognosis for patients with a variety of advanced malignancies. It is estimated that about 20% of patients treated with anti-PD-1 therapy will develop skin toxicity, including frequent reports of bullous pemphigoid and lichenoid eruptions.[2,3] LPP has been reported in associated with anti-PD-1 therapy, including pembrolizumab, nivolumab, and the recently FDA approved anti-PD-L1 agent, atezolizumab.[4 5] Interestingly, LPP has been described after combination therapy with the novel PD-1 inhibitor tisleizumab and sitravatinib.[6] Sitravatinib is a receptor tyrosine kinase inhibitor currently being studied for combination therapy with PD-1 inhibitors. Sitravatinib targets the tumor microenvironment and is thought to augment immune checkpoint inhibition for patients with incomplete treatment respose.[7] Reported cutaneous side effects of sitravatinib include hand–foot skin reactions and acneiform pustules, with no reports of bullous or lichenoid reactions.[6]

Treatment options for LPP most frequently reported in the literature include oral corticosteroids, topical corticosteroids, dapsone, and acitretin. Alternative agents include tetracycline in combination with nicotinamide, mycophenolate mofetil, cyclosporine, and methotrexate.[1] Rituximab, an anti-CD20 monoclonal antibody, was FDA-approved in 2018 as a front-line treatment for pemphigus vulgaris. Rituximab has recently been reported as a successful off-label treatment option for therapy-resistant BP, typically with the rheumatoid arthritis protocol (1g repeated in 2 weeks), and rarely with the lymphoma protocol (375 mg/m^2 weekly for 4 weeks).[8] However, a recent retrospective cohort study of 112 patients with pemphigus vulgaris found that patients who received lymphoma dosing were 2.7 times more likely to achieve complete remission off therapy compared to patients who received rheumatoid arthritis dosing, suggesting that lymphoma dosing may be preferred for immunobullous disorders.[9] Two reports highlight successful use of rituximab in nivolumab□induced BP. The authors propose that PD-1 blockade may dysregulate B-cell regulatory T-cells leading to enhanced antibody formation by B-cells.[10,11] Therefore depleting B-cells with rituximab is a logical, targeted treatment for BP and possibly LPP. To date there have been no reports of LPP treated with rituximab.

We present this case to highlight a rare autoimmune blistering disease presenting as a toxicity to checkpoint inhibitor immunotherapy, and review treatment options.

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11. Ridpath, A. V. *et al.* Novel use of combination therapeutic plasma exchange and rituximab in the treatment of nivolumab-induced bullous pemphigoid. *Int. J. Dermatol.* 57, 1372–1374 (2018).

CASE #2

PRESENTERS
Erin Dodd MD; Christopher Shea MD; Sarah Stein MD; Adena Rosenblatt MD PhD

HISTORY OF PRESENT ILLNESS
A two-year-old boy presented to dermatology clinic for evaluation of a life-long history of desquamative erythroderma involving the body and face. Previous treatments included topical hydrocortisone and triamcinolone ointments which they used with minimal improvement. He also had dry, thin hair and thickening of the palms and soles. In addition, he had global developmental delay, failure to thrive requiring enteral feeding via gastrostomy tube, hepatomegaly, short stature and sleep apnea. He had not identifiable odontic, visual, or auditory abnormalities.

PAST MEDICAL HISTORY
Global developmental delays
Hepatomegaly (resolving)
Short stature
Failure to thrive s/p gastrostomy tube placement
Sleep apnea s/p adenoidectomy

MEDICATIONS
Fluticasone nasal spray
Hydrocortisone 2.5% ointment
Triamcinolone 0.1% ointment
Hydroxyzine 2 mg/ml oral solution

ALLERGIES
No known allergies

FAMILY HISTORY
In foster care, family history unknown.

SOCIAL HISTORY
Lives at home with foster mother and four foster siblings. No pets or tobacco exposure at home.

PHYSICAL EXAM
Physical exam revealed patchy ill-defined thin pink to erythematous plaques with fine scale on the face, trunk and extremities. Palms and soles had confluent keratoderma with a stippled morphology but no evidence of transgriedens. Scalp hair was thin with soft and curly texture. Hair mount demonstrated pili torti. There were no identifiable odontic, visual or auditory abnormalities.

This constellation of findings raised concern for a syndromic disorder of keratinization versus immunodeficiency syndrome. In addition to skin biopsy, we recommended evaluations by genetics and immunology.

DERMATOPATHOLOGY

Histopathology from punch biopsy of the back demonstrated basket-weave stratum corneum with focal compact orthokeratosis and parakeratosis. The basilar half of the epidermis was markedly spongiotic with a mild superficial perivascular lymphocytic infiltrate.

LABORATORY DATA

Immunological workup was unremarkable with normal lymphocyte subsets and naïve T cells, immunoglobulins, and humoral function without eosinophilia.

Whole exome sequencing revealed a novel monoallelic DNA sequence change, c.1756C>T in exon 14 of the *DSP* gene resulting in the amino acid change, p.His586Tyr.

DIAGNOSIS

Stippled palmoplantar keratoderma, diffuse ichthyotic dermatitis, and pili torti associated with novel *DSP* gene mutation

TREATMENT AND COURSE

The patient was subsequently referred to cardiology due to known risk of cardiomyopathy and arrhythmias associated with *DSP* mutations. Electrocardiogram and echocardiography did not reveal any concerning findings, and he will continue to follow up with cardiology on an annual basis.

His dermatitis and palmoplantar keratoderma are managed supportively to improve quality of life and shorten duration of severe flares. He has had variable improvement with topical corticosteroids, urea cream, ammonium lactate cream, salicylic acid 3% shampoo, and bleach baths 1-2 times per week.

DISCUSSION

Desmoplakin is a protein that plays a critical role in maintaining the structural integrity of epidermal cells and cardiomyocytes. To date, more than 120 *DSP* gene mutations have been described with variable inheritance and phenotypic features[1]. Classic findings include palmoplantar keratoderma and woolly hair, but the spectrum has been expanded to include alopecia, nail dystrophy, leukonychia, skin fragility, oligodontia, and dental enamel defects.[1,2] Importantly, it is well-established that *DSP* gene mutations confer an increased risk of cardiomyopathy and life-threatening arrhythmias.[3] Carvajal syndrome is an example of a rare genodermatosis due to *DSP* gene mutations that is characterized by palmoplantar keratoderma, woolly hair, and cardiac abnormalities.[2,4]

To our knowledge, the specific *DSP* sequence change found in our patient (c.1756C>T, p.His586Tyr) has never been previously described. There have only been two patients reported with a mutation at the same position, but it resulted in a different amino acid substitution (p.His586Pro). Interestingly, these patients' findings were similar to our patient and included desquamative erythroderma, palmoplantar keratoderma, nail dystrophy, woolly hair, and failure to thrive.[5,6] Cardiac abnormalities were not reported in either of these patients. This case presents

a previously undescribed pathogenic desmoplakin mutation and further emphasizes the extensive phenotypic heterogeneity amongst *DSP* gene mutations.

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CASE #3

PRESENTERS
Scott Blaszak MD; Esther Kim MD; Dennis Whiting PA; Oluwakemi Onajin MD

HISTORY OF PRESENT ILLNESS
A 77-year old Caucasian male presented to the dermatology clinic with a six-year history of an intermittently pruritic rash on the right buttock. A skin biopsy performed at an outside clinic was interpreted as subacute spongiotic dermatitis. Prior treatments included several topical corticosteroids and antifungal cream with no improvement. He discontinued all topical treatments several weeks prior to his clinic visit.

PAST MEDICAL HISTORY
Coronary artery disease, hypertension, and GERD

MEDICATIONS
Aspirin, Famotidine, Lisinopril, Metoprolol, and Pravastatin

ALLERGIES
Penicillin – Rash
Sulfa (sulfonamide antibiotics) – Rash

FAMILY HISTORY
Mother – CVA
No known personal or family history of skin disease

REVIEW OF SYSTEMS
Pertinent negatives include fevers, chills, weight loss, and lymphadenopathy

PHYSICAL EXAMINATION
Pink-violaceous indurated plaque with overlying faint white scale on the right buttock extending to the intergluteal cleft

HISTOPATHOLOGY
Skin biopsy demonstrated irregular epidermal acanthosis with hyperkeratosis and mild spongiosis. Few scattered necrotic keratinocytes were present at the basal epidermis. A diffuse proliferation of small-caliber capillary sized vessels without significant atypia occupied the upper to mid-dermis, with associated edema and a band-like inflammatory infiltrate composed predominantly of lymphocytes.

LABORATORY AND IMAGING DATA
No additional work-up

DIAGNOSIS
Prurigiform angiomatosis

TREATMENT AND COURSE

The patient was advised to continue avoidance of topical steroids. He was instructed to apply petroleum jelly and cover with a hydrocolloid dressing to help off-load pressure from the area. At follow-up, the patient reported minimal improvement with persistent pruritus.

DISCUSSION

Prurigiform angiomatosis is a newly described entity which is thought to be a benign reactive angioproliferation to chronic mechanical stress or inflammation. The term was first proposed by Ortins-Pina et al in 2020, who reported similar clinical and histologic findings in thirty-eight patients.[1] Prurigiform angiomatosis is a novel entity with unknown prevalence. It is most often seen in elderly, male patients with a mean age of 76 years.[1] The clinical features include an asymptomatic or pruritic red-brown or pink-violaceous, slightly hyperkeratotic patch and plaque that is typically resistant to multiple topical treatments. Common locations of these characteristic lesions are on pressure areas including the buttock and/or intergluteal folds of elderly patients though lesions on the knees, hips, and inguinal region have been previously reported. Upon initial clinical evaluation, these benign cutaneous angioproliferations may present a diagnostic challenge and raise suspicion for cutaneous neoplasms such as squamous cell carcinoma and lymphoma.

Histopathologic features of prurigiform angiomatosis consist of acanthosis and hyperkeratosis, similar to lichen simplex chronicus or prurigo, with prominent proliferation of dilated capillaries and postcapillary venules in the underlying dermis. One-third of cases may present with a subepidermal lymphocytic infiltrate. It is important to note that these findings within the dermis are not observed in area beyond the overlying epidermal changes.[1]

Immunostaining with vascular endothelial growth factor (VEGF) demonstrates strong and diffuse positivity in the upper portions of the epidermis with sparing of the basal layer and adnexa in lesional epidermis. VEGF positivity in peri-lesional normal skin is limited to the stratum granulosum. Additionally, tyrosine kinase receptor, VEGFR-2, highlights the endothelia of the post-capillary venules and capillaries, which is absent in endothelia of non-lesional skin. Additional immunostaining demonstrates CD31 positive and podoplanin negative endothelia.[1]

Currently, there is no specific treatment for prurigiform angiomatosis. Given the nature of prurigiform angiomatosis being a reactive angioproliferative process, redistribution of the chronic mechanical stress should be pursued. Prurigiform angiomatosis is known to persist despite multiple topical therapies. In Ortins-Pina et al (2020), surgical excision was performed on 18 cases without evidence of recurrence to date.[1]

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CASE #4

PRESENTERS
Jake Lazaroff MD; Arjun Dayal MD; John Fox MD; Mark D. Hoffman MD

Patient A
HISTORY OF PRESENT ILLNESS
69-year-old woman with history of multiple myeloma who was referred from hematology/oncology for an asymptomatic growth on the scalp that was present for 4 months. She denies any bleeding or discharge from the lesion. Patient had a PET scan prior to presentation which demonstrated small mild cutaneous activity in the right frontal scalp without osseous lesions.

A 3mm punch biopsy demonstrated scar with sparse inflammation but no evidence of cyst or malignancy. At follow up 7 months later, the patient reported that the lesion was growing in size, but remained asymptomatic. In the interim she had repeat PET that demonstrated a mildly hypermetabolic right frontal scalp focus, likely inflammatory in origin.

REVIEW OF SYSTEMS
No headache, vision changes, weight loss, night sweats, fevers, chills, myalgias.

PAST MEDICAL HISTORY
Hypertension, migraines, asthma, GERD, multiple myeloma s/p autologous stem cell transplant.

MEDICATIONS
Daratumumab, lenalidomide, acyclovir, albuterol, aspirin, baclofen, dexamethasone, furosemide, lisinopril, lorazepam, esomeprazole.

FAMILY HISTORY
None pertinent

PHYSICAL EXAM
Right frontal scalp with a firm non-tender non-mobile indurated ~3 cm subcutaneous nodule with overlying central whitish scar

LABORATORY AND IMAGING DATA
Serum IgG lambda of 5.4 g/dl and 280mg of paraprotein in 24-hour urine collection
Bone marrow biopsy: borderline hypercellular marrow with 30-40% plasma cells

PET 10/15/2019
Small mild activity along the right frontal scalp cutaneously, likely inflammatory.

PET 5/11/2020
Small mildly hypermetabolic focus in the right frontal scalp that has increased in size from prior imaging; favored inflammatory although a tumor could not be excluded.

HISTOPATHOLOGY
Subcutaneous tissue with neoplastic proliferation of atypical cells with enlarged round to oval eccentric nuclei, coarse chromatin, prominent nucleoli and abundant amphophilic cytoplasm, reminiscent of a plasmacytoid morphology. Numerous mitotic and apoptotic bodies are noted. The neoplastic cells are CD138+. Findings consistent with cutaneous involvement of an atypical plasma cell neoplasm.

DIAGNOSIS
Cutaneous Multiple Myeloma

TREATMENT AND COURSE
Her oncologist referred the patient to radiation oncology. She received low dose XRT therapy and reported significant improvement and near resolution of the scalp lesion.

Patient B
HISTORY OF PRESENT ILLNESS
57-year-old man with a history of two heart transplants and a kidney transplant presented to clinic reporting changes to his orbital skin. The patient reports crusting and discoloration of this skin for several years. He attributes this to trauma related to tape removal and frequent manipulation of the skin in the area, but denied symptoms such as itching or pain.

REVIEW OF SYSTEMS
No fatigue, dyspnea on exertion, neuropathic symptoms or dysphagia.

PAST MEDICAL HISTORY
Cardiac transplant due to viral cardiomyopathy followed by a second transplant due to rejection and a kidney transplant from immunosuppressive-related end-stage renal disease; hypothyroidism.

MEDICATIONS
Amlodipine, buspirone, esomeprazole, levothyroxine, lisinopril, mycophenolate mofetil, prednisone, ranitidine, sertraline, ketoconazole shampoo

FAMILY HISTORY
None pertinent

PHYSICAL EXAM
Orange to brown, purpuric patches and waxy papules on the eyelids and a few white dome shaped papules.

LABORATORY AND IMAGING DATA
Serum protein electrophoresis and immunofixation notable for the presence of monoclonal IgG lambda at a concentration of 0.15 g/dL.

Serum free light chain assay was notable for an elevated kappa light chain of 3.68 (0.33 – 1.94 mg/dL) and lambda light chain of 57.0 (0.57 – 2.63 mg/dL), with a kappa to lambda ratio of 0.0646 (0.26 – 1.65 mg/dL).

Bone marrow biopsy demonstrated 3-4% plasma cells.

Cardiac MRI showed normal LV function and no evidence of infiltrative process.

Calcium level 10.1 (8.4 - 10.2mg/dL).

HISTOPATHOLOGY

A 5 mm fat pad biopsy was performed. There was no evidence of amyloid deposition and the congo red stain was negative. Congo red stain was retroactively performed on liver biopsy and was also negative.

Skin biopsy of right upper eyelid demonstrated elastotic hemorrhage. There were amorphous eosinophilic deposits at the dermoepidermal junction, superficial blood vessels, and within the mid-reticular dermis that were highlighted by Congo red stain. Consistent with cutaneous amyloidosis.

DIAGNOSIS

Cutaneous Amyloidosis consistent with AL Amyloidosis

TREATMENT AND COURSE

Given his complex past medical history of immunosuppressive state it was decided not to pursue treatment for amyloidosis. However, the patient began endorsing weight loss and dysphagia. He underwent and upper and lower endoscopy with biopsies showing amyloid in the rectum and duodenum. His oncology team is now considering treatment with daratumumab, bortezomib, and dexamethasone.

DISCUSSION

Plasma cell dyscrasias are a group of disorders characterized by clonal expansion of plasma cells that secrete monoclonal immunoglobulins.[1] These conditions range from monoclonal gammopathy of undetermined significance (MGUS), to AL amyloidosis, to smoldering multiple myeloma (SMM) to multiple myeloma (MM).

The annual incidence of multiple myeloma is 5 cases per 100,00 person years.[2] The vast majority of patients are diagnosed later in life, with 90% occurring after age 50 and a median age of 70 years.[2] Even though MGUS is also a disease that primarily effects the elderly with an average age of diagnosis of 72, MGUS is considerably more prevalent with 169 people per 100,000 carrying a diagnosis.[3] Because there is no recommended screening, it has been widely estimated that as many as 80% of individuals with MGUS go clinically unrecognized, and most of these diagnoses are made by incidental findings.[3] The annual risk of progression from MGUS to MM is only around 1% where the yearly risk of progression for SMM is around 10%.[4]

Classically MM presents with symptoms represented by the mnemonic CRAB: Hypercalcemia, renal dysfunction, anemia, and bone lesions. These findings help distinguish multiple myeloma from monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma.[5] MM is distinguished from MGUS and SMM through the clinical presentation and through a battery of laboratory testing. The international myeloma working group recommends that initial work up includes the following tests: biochemical studies (creatinine, calcium, beta2-microglobulin, LDH, albumin), protein studies (SPEP, UPEP, serum light chain measurement, and immunofixation), bone marrow biopsy, and skeletal survey.[5] Based on these results clinicians can appropriately diagnose and risk stratify patients. MGUS has serum M protein > 3g/dL and less than a 10% burden of plasma cells in the bone marrow and SMM has a serum M protein >3g/dL and 10-60% of the bone marrow infiltrated by plasma cells; in both of these entities CRAB symptoms are not present.[4]

As MM progresses, patients can develop extramedullary spread out of the bone marrow and into other organs, which occurs in approximately 4% of patients.[2] This can occur in nearly every organ system, and cutaneous involvement in particular was found to occur in just over 1% of MM patients. Extramedullary spread of multiple myeloma is thought to be, most commonly, the result of direct extension of the disease from a neighboring neoplastic lesion. However, skin involvement can also occur secondary to lymphatic or hematologic spread.[7]

Clinically, a range of dermatologic findings have been observed in cutaneous MM, commonly these lesions are characterized as being pink to violaceous papules, nodules, or plaques.[2] These occurrences do not seem to have a predilection for any part of the body. Histologically, plasma cells are characterized by an eccentric nucleus and basophilic cytoplasm. However, in MM these plasma cells show a range of atypia. One way to recognize these atypical cells is immunophenotypically in which the plasma cells are positive for CD138 and MUM1 and negative for B cell markers such as CD20 and Pax-5.[8]

On average cutaneous metastases from the MM develop 16 months after the initial diagnosis of MM.[9] Nevertheless, they can arise at any time during the disease course and a retrospective study found that at the time of diagnosis 21% of patients presented with 'non-CRAB' symptoms, and more specifically 4% of patients presented with symptoms related to extramedullary spread.[5] Extramedullary spread of MM to the skin is an important entity to understand and properly characterize as it portends a worse prognosis. A study conducted by Woo et al., found that when comparing MM patients with cutaneous involvement to those who do not, the median survival was 28 months compared to 57 months respectively.[9]

Another complication of plasma cell dyscrasias is AL amyloidosis, where the plasma cells produce misfolded immunoglobulin light chains that can deposit in organs around the body.[10] The amyloid may deposit in the skin leading to the characteristic cutaneous findings, but may also deposit in vital organs leading to dysfunction. Of patients with AL amyloidosis approximately 15% have underlying MM, whereas 5-15% of patients with MM go on to develop AL amyloidosis.[15]

Skin involvement is present in approximately 30-40% of AL amyloidosis patients.[12] The most common skin findings are waxy papules, plaques and nodules. Additionally, bruising is a common feature that can sometimes be induced by valsalva or friction, which is the result of vascular

amyloid deposition and in some instances an acquired Factor X deficiency that leads to the characteristic "raccoon eyes".[11,14]

Definitive diagnosis of amyloidosis is made through tissue biopsy. Biopsies can be obtained from either clinically uninvolved sites, such as subcutaneous fat or from affected organs, however the sensitivity might be limited. For AL Amyloidosis in particular fat pad biopsies had a sensitivity of 70-80% and the sensitivity increases with biopsy size.[6] It is important for dermatologists to recognize the cutaneous manifestations of plasma cell dyscrasias and also to keep them on the differential even if histologic studies do not support the diagnosis, given their variable sensitivities.

Patients with plasma cell dyscrasias should be properly evaluated and managed by hematology/oncology. For MGUS the standard of care is for no treatment and continued clinical monitoring, even though specific guidelines are not established. On the opposite end of the spectrum, various treatment modalities exist for MM. Regarding the entity of cutaneous multiple myeloma in particular there is no uniform treatment or standard of care. However, since it is associated with reduced survival, prompt and aggressive therapy is likely warranted and managed by hematology/oncology. There are reports of using bortezomib and autologous stem cell transplant with varying degrees success.[13]

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CASE #5

PRESENTERS

Maria Estela Martinez Escala MD PhD; Esther Kim MD; Julia Dai MD; Sarah Stein MD; Oluwakemi Onajin, MD.

HISTORY OF PRESENT ILLNESS

A 19-year-old Hispanic female presented to dermatology clinic with a two-month history of a generalized itchy blistering rash. She reported first developing a discolored rash on her back, abdomen and arms. As the rash spread, blisters began to emerge. The rash was itchy, but not tender or painful. She denied blisters or erosions on the genitalia, but she did endorse a tender ulcer on the right lateral side of her tongue that interfered with eating. She had not noticed worsening of the rash with sun exposure. She had gone twice to the emergency room and was prescribed methylprednisolone, which she took briefly then discontinued, and triamcinolone ointment, which was not helpful.

Three months prior to the onset of the rash, the patient presented to her primary care physician for one-year history joint pain and stiffness. She was subsequently diagnosed with systemic lupus erythematosus. No treatments had yet been implemented.

REVIEW OF SYSTEMS

Review of systems was notable for bilateral eyelid edema, right eye vision changes, shortness of breath and chest pain, unintentional 30 pounds weight loss over six months, loss of appetite, and one-year-history of joint pain and swelling.

Pertinent negatives included fevers, night sweats, chills, cough, nausea, vomiting, abdominal pain, diarrhea, blood in urine, lower extremity edema, or neurological deficits.

PAST MEDICAL HISTORY

Subclinical hypothyroidism since age of 8
Dysmenorrhea

FAMILY HISTORY

Mother with diabetes mellitus
Paternal aunt and several cousins with “lupus”

MEDICATIONS

None

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

Skin exam demonstrated widespread involvement of the trunk and extremities with tense bullae and hemorrhagic crusts arranged in serpiginous, arcuate and annular plaques with erythema and

hypopigmentation centrally and hyperpigmentation peripherally. Face had several scattered bullae and crusted erosions.

Lips were crusted at the vermilion border. On the right lateral tongue there was a 1cm ulcerated plaque. On the buccal mucosa there were ill defined erosions. Genitalia was spared.

LABORATORY RESULTS

Hemoglobin:10.9 mg/dl (N: 11.5 – 15.5)
Erythrocyte Sedimentation Rate (ESR): 73 mm/hr (N<5)
Antinuclear antibodies (ANA): 1:640, speckled pattern
Double-stranded DNA (ds-DNA): 222 IU/ml (N<30)
Complement 3 (C3): 31 mg/dl (N: 83 – 188)
Ribonucleoprotein (RNP) antibody: 1.5 IU/ml (N< 1.0)
Urinalysis was remarkable for mild proteinuria and moderate hematuria

Comprehensive metabolic panel, rheumatoid factor, C4, SSA, SSB, anti-Smith and Antiphospholipid panel were normal.

Pulmonary function test, X-rays of bilateral hands were normal and a transthoracic echocardiogram is still pending.

DERMATOPATHOLOGY

Skin biopsy showed subepidermal bullae with signs of re-epithelization. A brisk neutrophilic infiltrate and karyorrhexis were predominantly seen in the dermal papilla. Within the epidermis, dyskeratoses and focal acantholysis were identified.

Direct immunofluorescence (DIF) showed linear deposition of immunoglobulin G (IgG), IgA, IgM and C3 at the epidermal basement membrane zone (BMZ) as well as fibrinogen in the dermis.

DIAGNOSIS

Bullous systemic lupus erythematosus (SLE).

TREATMENT & COURSE

Treatment was initiated with clobetasol and hydrocortisone ointments while awaiting results of laboratory investigations and input from rheumatology, nephrology, and ophthalmology. Oral prednisone (20 mg daily) and hydroxychloroquine (300 mg daily) were initiated 10 days later. Due to persistent rash and blisters, the patient was started on dapsone (50mg daily) which led to significant improvement. Methotrexate (20 mg weekly) was added for management of class 1 lupus nephritis (mesangial proliferative lupus nephritis) diagnosed via renal biopsy.. She was started on artificial tears for keratoconjuntivitis sicca.

Due to worsening anemia, dapsone was decreased to 25mg daily which caused recurrence of the rash. Once anemia improved, dapsone was increased to 50mg daily resulting in rapid improvement of the rash.

DISCUSSION

Bullous SLE is an immunobullous disorder associated with SLE. Bullous SLE manifests among young adults between the second and third decade of life (median age of 27), but cases within an age range of 8 to 77 years have been described. It is more common in women, and it has been reported in all races.[1–3]

Bullous SLE pathogenesis has been associated with the presence of antibodies against type VII collagen with a similar antigenic profile as epidermolysis bullosa acquisita (EBA).[5-7] However, antibodies against other proteins of the BMZ have also been reported, though it is thought to be due to an epitope spreading phenomenon.[8]

Bullous SLE has an acute onset, typically generalized, yet with predominance of the upper trunk, and upper extremities. Vesicles and bullae appear on sun-exposed and non-sun-exposed areas. Oral and genital mucosa are involved in most of the cases. Tense vesicles and bullae, are typically identified over both inflammatory plaques and normal appearing skin. Vesicles and bullae tend to heal without forming milia or scarring, but post-inflammatory hypopigmentation is typical.[1–3,5]

Considering that 76% of SLE patients present with dermatologic manifestations, only 5% will have vesiculobullous morphology.[1,2] Bullous SLE as initial presentation of SLE is observed in 36% of the cases.[3,4] Of note, not all vesiculobullous eruptions in patients with SLE are equivalent to bullous SLE. There are four possible alternative scenarios to consider: 1) SLE with severe interface dermatitis inducing dermal-epidermal cleavage, manifesting clinically as bullae, 2) toxic epidermal necrolysis-like SLE, 3) SLE with other concomitant immunobullous disease including dermatitis herpetiformis (DH), EBA or bullous pemphigoid, all reported in the literature, and 4) *bona fide* bullous SLE.[2,9]

Extracutaneous manifestations associated with bullous SLE are arthralgias/arthritis (74%), hematologic manifestations (58%), lupus nephritis (50%), serositis (20%), and neuropsychiatric lupus (12%). Bullous SLE flares may appear independently of extracutaneous flares.[3]

Skin biopsies of patients with bullous SLE are characterized by subepidermal blisters with a predominantly neutrophilic infiltrate either focused in the dermal papilla (as observed in DH skin biopsies), and/or distributed with a band-like pattern along the BMZ (as seen in inflammatory EBA skin biopsies). Subepidermal blisters may contain fibrin and neutrophils. There is a perivascular lymphocytic infiltrate, but neutrophils and eosinophils may be seen. Secondary leukocytoclastic vasculitis and karyorrhexis may be present. While vacuolization of the BMZ and epidermal atrophy are features observed in other variants of cutaneous lupus, deposition of mucin in the reticular dermis is considered a distinguishing feature of bullous SLE.[1,2,5]

DIF or immunoelectron microscopy (IEM) of bullous SLE skin biopsies may show deposition of IgG, IgM, IgA, and C3, with a granular or linear pattern at the BMZ. Deposition in the upper dermis and around blood vessels may also be present.[1,2,5]

Indirect immunofluorescence (IIF) on salt-split skin (SSS) may show deposition of antibodies most commonly on the dermal side, much less frequently on the epidermal side or it can even be

negative.[5] Enzyme-linked immunosorbent assay may detect circulating antibodies against type VII collagen in 69% of the cases.[2,3,5,7]

The diagnostic criteria first established by Camisa and Sharma et al. in 1983, and revised by Camisa and Grimwood in 1986 continue to be used for the diagnosis of bullous SLE today (Table 1).[10]

Table 1. Diagnostic criteria of bullous SLE by Camisa and Grimwood.[11,12]

1. Diagnosis of SLE based on the European League Against Rheumatism/American College of Rheumatology classification criteria
2. Vesicles and bullae arising upon but not limited to sun-exposed skin
3. Histopathology compatible with DH.
4. Negative indirect immunofluorescence for circulating basement membrane zone (BMZ) antibodies.
5. DIF of lesional and nonlesional skin revealing linear or granular IgG and/or IgM and often IgA at the BMZ; if there is a linear pattern of immunoglobulin deposition, immunoelectron microscopy should be done to demonstrate the immune reactants below the basal lamina.

The majority of patients with bullous SLE have shown a significant response to dapsone (93%), with cessation of blister formation reported within 48 hours of treatment initiation, even at a low dose (25 – 50 mg). Treatment withdrawal can cause rapid relapse (as seen in our case). When refractory, systemic glucocorticoids and other immunosuppressant agents may be necessary. If the patient is already on systemic glucocorticoids and immunosuppressant agents to manage pre-existing SLE, consideration may be given to increasing dose of these treatments with or without addition of dapsone. Recent reports support the use of rituximab (1000 mg/m^2 dosed two weeks apart) in cases refractory to dapsone, systemic glucocorticoids, and immunosuppressant agents.[2,3,5]

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CASE #6

PRESENTERS
Erin Ibler MD; Mark D. Hoffman MD

HISTORY OF PRESENT ILLNESS
A 42 year old woman presented to the dermatology clinic for further management of longstanding and severe hidradenitis suppurativa (HS). She had multiple erythematous papules and nodules, with interconnected sinus tracts, significant scarring, and foci of purulent drainage, affecting the bilateral axilla, inframammary folds, groin, and buttock.

Her medical history was notable for systemic lupus erythematosus diagnosed at the age of 8 **(**complicated by end stage renal disease, for which she is on hemodialysis), calciphylaxis, deep venous thrombosis, and a latex allergy (hives). Her lupus is currently quiescent, but she remains on hydroxychloroquine as maintenance to help prevent future flares.

Given the patient's multiple open, draining lesions and extensive skin involvement, the transplant service was concerned about increased potential for infection if she were to undergo renal transplant. They deemed her ineligible for transplantation unless her HS was better controlled. She has been assessed by surgery, who recommended optimizing medical management prior to surgical intervention to help with wound healing post-procedure.

The patient's prior treatments for HS include intralesional triamcinolone, several courses of doxycycline (lasting at least 3 months), and rifampin/clindamycin for 10 weeks, without improvement. In addition, she has also made lifestyle modifications and lost 20-30 pounds, without apparent change in HS flares or severity.

Rheumatology recommended avoidance anti-TNF agents due to the potential for drug-induced lupus. Additionally, her history of latex allergy conditions use of other injectable biologics, such as secukinumab or ustekinumab.

PAST MEDICAL HISTORY
HS x ~17 years; SLE c/b ESRD (on HD x 17 years), calciphylaxis, DVT, latex allergy (hives). No h/o IBD.

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
Non-smoker

MEDICATIONS
Hydroxychloroquine 200mg daily, cholecalciferol, cinacalcet

ALLERGIES
Latex, vancomycin

PHYSICAL EXAMINATION
Multiple erythematous papules and nodules, with interconnected sinus tracts, significant scarring, and foci of purulent drainage, affecting the bilateral axilla, inframammary folds, groin, and buttock.

LABORATORY RESULTS

• ESR	100 mm/Hr	(0-20)
• dsDNA	38 iU/mL	(<30.0)
• Crithidia IgG	Negative	
• C3	126 mg/dL	(83-188)
• C4	31 mg/dL	(18-45)
• Quantiferon Gold TB	Indeterminate	

IMAGING
Chest X-Ray unremarkable

DIAGNOSIS
Hidradenitis suppurativa

TREATMENT &COURSE
Management with ertapenem was discussed with the patient and she was referred to infectious disease for evaluation and possible initiation. The ID service was initially hesitant, due to limited data and concern for carbapenem resistant organisms if the patient were to be transplanted in the future. However, they ultimately agreed to a trial, and the patient completed a course of ertapenem 1g three times weekly (with hemodialysis) for 7 weeks total.

Post-treatment, she noticed significant improvement in her disease, estimating about 70% improvement from her baseline. At a clinical follow up visit (delayed due to the COVID pandemic), she reported that over the past 3 months (post-treatment), she had no drainage from the axillary, inframammary, or groin lesions. However, the buttock lesions were not significantly changed and continued to drain. At that time, she underwent an additional 6 weeks of antibiotic consolidation with clindamycin/rifampin/metronidazole.

After additional discussion with patient, the decision then was made to start infliximab, with close monitoring for evidence of TNF-induced lupus.

DISCUSSION
The pathogenesis of HS is still not clearly defined. The condition is thought to involve follicular abnormalities, heightened immune/inflammatory activity, alterations in the skin microbiome, an interplay between hormonal and genetic factors, and behavioral influences. While no specific microbe has been implicated, chronic lesions may demonstrate polymicrobial anaerobic flora including Prevotella and Actinomycetes, as well as coagulase negative staph and *milleri* group strep. Studies using prolonged culture methods have also linked disease severity to increases in anaerobic bacteria or more resistant species. Although true infections are rarely seen, it has been speculated that HS could involve an aberrant immune response to commensal skin flora.

Also supporting the role of an underlying bacterial etiology is the successful use of antibiotics in the treatment of HS. Recently, ertapenem has been investigated as another treatment option for severe HS. Ertapenem is a carbapenem class antibiotic which is used for complicated skin and soft tissue infections. It has broad-spectrum antibacterial activity against aerobic and anaerobic gram-positive and gram-negative organisms, without apparent intrinsic anti-inflammatory activity.

The primary evidence supporting the use of ertapenem in HS is derived from a single retrospective study by Join-Lambert et al (2016). Thirty consecutive patients with severe HS were included, who received an initial 6-week course of intravenous ertapenem (1g daily) followed by a 12-week consolidation phase: a 6-week course of rifampicin 10mg/kg once daily/moxifloxacin 400mg once daily/metronidazole 500mg TID, then a final 6-weeks of rifampicin and moxifloxacin without metronidazole. Patients were followed for a total of 6 months, and underwent repeated clinical consolidation with several different antibiotic regimens as needed, based on the severity of subsequent flares. After 6 months, clinical remission was reported in 100% of Hurley stage I lesions, 96% of Hurley stage II lesions, and 27% of Hurley stage III lesions (in compliant patients).

Since this study, Braunberger et al. conducted a retrospective chart review and phone interview of 36 patients with Hurley stage II or III HS treated with ertapenem. In this study, 71.4% of patients reported satisfaction with IV ertapenem therapy, with 89.3% of patients reporting improvement in the amount of drainage from HS lesions, and 85.7% of patients reporting improvement in quality of life after treatment. However, data regarding ertapenem in HS remains very limited overall. The responses seen in treatment with ertapenem suggest avenues for further investigation relating to HS pathogenesis and/or disease maintenance.

Another important consideration in treating with ertapenem is the potential for bacterial resistance. Antibiotic resistance in gram-negative bacteria is increasing, and β-lactamase-mediated carbapenem resistance is a serious clinical issue and public health concern. Therefore, use of this agent should be determined in conjunction with infectious disease specialists, on a case by case basis.

Ertapenem is typically used as a bridge to surgery or another therapeutic modality. In our patient, we plan on consolidation/maintenance therapy with infliximab. Although drug-induced lupus may develop with TNF-inhibitors, this side effect is relatively uncommon, having been estimated at a cumulative incidence of 0.5-1%. The frequency may depend on the specific anti-TNF agent administered. TNF-induced lupus usually involves skin or musculoskeletal manifestations, much less commonly visceral manifestations, and generally resolves with cessation of the inciting agent. Varada et al have described their experience treating patients with coexistent psoriasis and lupus with anti-TNF agents, and found only a 0.92% incidence of lupus flare events per patient-year of treatment. While concern for drug-induced or exacerbated lupus is valid, the use of anti-TNF agents in individuals with pre-existing connective tissue disease is not necessarily precluded.

We present this case to highlight an alternative therapeutic option for consideration in patients with refractory hidradenitis, in particular, those who have exhausted or are not candidates for other more standard treatment options.

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CASE #7

PRESENTERS
Margaret Boyle MD; Mark D Hoffman MD

HISTORY OF PRESENT ILLNESS
A 79 year old man with a history of polycythemia vera was referred to the dermatology clinic for refractory clinically amyopathic dermatomyositis (CADM). His skin changes first developed 5 years ago, and he had been diagnosed with CADM 1.5 years earlier. He presented to the clinic with cutaneous signs and symptoms without muscular weakness.

PAST MEDICAL HISTORY
Dermatomyositis, polycythemia vera (JAK-2 mutation), chronic lower extremities wounds (in past variably managed as PG, venous, diabetic, pressure-induced, and/or hydroxyurea-induced ulcers), peripheral vascular disease, coronary artery disease, gout, Alzheimer's dementia.

MEDICATIONS
Hydroxychloroquine 200 mg BID
Hydroxyurea 500 mg TID (for 12 years)
Atorvastatin 10 mg daily (for 22 years)
Pentoxifylline-ER 400 mg TID
Aspirin 81 mg daily
Folic acid 1 mg daily
Metoprolol succinate ER 50 mg daily
Losartan 100 mg daily
Furosemide 20 mg daily
Allopurinol 100 mg daily
Donepezil 10 mg QHS
Duloxetine delayed-release 60 mg daily
Omeprazole 20 mg BID
Tamsulosin 0.4 mg daily
Clobetasol 0.05% ointment BID

PHYSICAL EXAMINATION
Violaceous thin scaly plaques accentuated over interphalangeal joints and metacarpal phalangeal joints and extensor surfaces of elbows. Erythematous patches overlying forehead, cheeks, and nape of neck. Periungual telangiectasias on nailfold capillary exam. Shallow ulceration at the base of left great toe.

LABORATORY DATA
The following were positive or abnormal:
ANA: 1:160 (speckled)
LDH: 533 (116-245 U/L)
Aldolase: 14.8 (2-8 U/L)
MCV: 109.3 (81-99 fL)

The following were negative or within normal limits:
CK, Myomarker 3 panel (Jo-1, U1-RNP, PM/Scl-70, SSA-52KD, U3/RNP, PL-7, PL-12, Mi-2, KU, EJ, OJ, SRP, MDA-5, TIF1-γ, U2 SNRNP, NXP-2), SSB, remainder of CBC/diff, CMP

DERMATOPATHOLOGY
Punch biopsy of the left forehead (2018) demonstrated vacuolar interface dermatitis consistent with connective tissue disease.

DIAGNOSIS
Hydroxyurea-induced dermatomyositis

TREATMENT & COURSE

Eighteen months prior to consultation, he presented to an outside rheumatologist with acral skin lesions, facial erythema, and Raynaud's, but without muscular weakness and was diagnosed with CADM. He presented to our clinic for management of refractory skin disease on hydroxychloroquine and topical clobetasol. He had been previously trialed on prednisone, mycophenolate mofetil, methotrexate, and IVIG but was intolerant of these medications. Of note, he had been on hydroxyurea for polycythemia vera for 12 years and atorvastatin for cardiovascular disease for 22 years.

When he was referred to our clinic, he was suspected to have drug-induced dermatomyositis secondary to hydroxyurea (or less likely atorvastatin). After discussing the possibility of drug-induced dermatomyositis secondary to hydroxyurea with his oncologist, he was started on ruxolitinib for both treatment for polycythemia vera and dermatomyositis and tapered off hydroxyurea. His cardiologist also discontinued atorvastatin. At his 6 month follow-up, he had significant improvement in his cutaneous findings. Moreover, he had resolution of his chronic lower extremity ulcers (which had been present for 2-4 years), supporting our initial impression that these were also secondary to chronic hydroxyurea. He has tolerated ruxolitinib well without adverse effects.

DISCUSSION

Drug-induced dermatomyositis-like eruptions have been associated with a number of drugs, including hydroxyurea, statins, penicillamine, BCG vaccine administration, immunostimulatory herbal supplements (e.g. *Spirulina, Alphanizomenon flos-aquae,* alfalfa) and several other drugs in the literature. More recently, cases of PD-1 inhibitor and CTLA-4 drug-induced DM have been described. Hydroxyurea is the most commonly reported drug associated with drug-induced DM-like eruptions. A review of cases reported in the literature by Siedler and Gottlieb in 2008 found that overall cases of DM-like eruptions associated with hydroxyurea were later in onset (30 to 60 months after start of hydroxyurea), more common in older patients (range 50 to 60 years old), had an absence of muscular weakness, and had a lower percentage of cases with ANA positivity compared to non-hydroxyurea reported cases. The patients on hydroxyurea also had a long-standing history of lymphoreticular malignancies compared to patients on other medications.

The mechanism of DM-like eruptions from hydroxyurea is poorly understood. It has been postulated that the cytotoxic effect from inhibiting both DNA repair and DNA synthesis may lead to DM-like eruptions. Another possible mechanism is that the effect of hydroxyurea blocking DNA site repair combined with UV irradiation synergistically results in DNA strand breaks which ultimately leads to DM manifestations.

Hydroxyurea is also associated with a number of other cutaneous adverse effects, with an incidence of 10-35% for patients on chronic hydroxyurea. Common adverse effects of hydroxyurea include facial erythema, hyperpigmentation, ichthyosis, alopecia, atrophy, acral erythema, palmo-plantar keratoderma, small vessel vasculitis, melanonychia, and leg ulcers. Rare adverse effects include aggressive nonmelanoma skin cancers and DM-like eruptions.

In this case, a JAK inhibitor was used as alternative treatment for polycythemia vera instead of hydroxyurea, while offering the potential to accelerate cutaneous improvement following hydroxyurea cessation. Ruxolitinib, a selective inhibitor of JAK1 and JAK2, was recommended since there have been numerous case reports in the literature demonstrating that JAK inhibitors including ruxolitinib, tofacitinib, and baricitinib can be helpful in treating refractory DM. Activation of interferon-regulated pro-inflammatory cytokines have been shown to play a role in the pathogenesis of dermatomyositis. JAK inhibitors have potent immunomodulating effects. They block interferon-beta-induced signal transducers and activators of transcription 1 (STAT1), which blocks the pathway of type I interferons. Blockade of the type I interferon pathway may reduce inflammation in dermatomyositis. JAK inhibitors have been shown to treat cutaneous (including stabilization of calcinosis cutis), muscular, and pulmonary symptoms in both juvenile and adult cases of refractory dermatomyositis as monotherapy and in combination therapy. Which if any of these JAK-targeted inflammatory pathways might be germane in hydroxyurea-induced skin disease is uncertain.

We present a case of hydroxyurea-induced dermatomyositis effectively treated by discontinuation of the culprit drug and initiation of ruxolitinib. This case provides additional evidence that a careful medication review is essential in the evaluation of patients with dermatomyositis, and that JAK inhibitors might represent an effective component of treatment for dermatomyositis.

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