Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, December 8, 2021
Online - via Zoom
and in-person at the Gleacher Center

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

Program

Host: University of Chicago
Wednesday, December 8, 2021
"Hybrid" Conference - In-person and Online

8:30 a.m.	**Sign-in and Member Visitation Time**
9:00 a.m.	**Welcome & Introduction** *Jordan Carqueville, MD - CDS President*
9:05 a.m. - 9:50 a.m.	***Guest Lecture*** " Update on Vitiligo" *Iltefat Hamzavi, MD*
9:50 a.m. - 10:00 a.m.	**Questions & Answers**
10:00 a.m. - 10:15 a.m.	Break
10:15 a.m. - 11:15 a.m.	**Resident Case Presentations & Discussion** *University of Chicago Residents*
11:15 a.m. - 12:00 p.m.	***Guest Lecture*** "The Latest on Hidradenitis Suppurativa" *Iltefat Hamzavi, MD*
11:00 p.m. - 12:10 p.m.	**Questions & Answers**
12:10 p.m.	**Closing Remarks and Announcements** *Jordan Carqueville, MD*
12:10 p.m. - 12:30 p.m.	**Discussion and questions regarding resident case presentations**
12:30 p.m.	**Meeting adjourns**

Mark the Dates!

Next CDS meeting will be on Wednesday, April 13th – Co-hosted by Stroger/Cook County Hospital
Watch for details on the CDS website: www.ChicagoDerm.org

The Illinois Dermatological Society annual Practice Management Conference will take place on Saturday morning, January 8 at the Stephens Convention Center in Rosemont. Get full details and register (*no fee*!) at www.IllinoisDermSociety.org

Guest Speaker

ILTEFAT HAMZAVI, MD

Private practice - Hamzavi/Dermatology Specialists; Fort Gratiot and Canton, Michigan
Clinical Associate Professor, Wayne State University School of Medicine; Henry Ford Hospital, Department of Dermatology; Photomedicine and Photobiology Unit

Dr. Iltefat Hamzavi, M.D., has practiced general dermatology in private practice since 2001 with a special focus on pigmentary disorders and hidradenitis suppurativa. Dr. Hamzavi earned his Bachelor of Arts degree, with honors, in Sociology from the University of Michigan, Ann Arbor. Dr. Hamzavi received his medical degree from the University of Michigan Medical School and graduated in 1996 with academic honors in a variety of specialty rotations. . Dr. Hamzavi completed his dermatology residency in 2000 at Wayne State University and then spent time in Europe training at some of the world's leading skin care centers. In 2001, Dr. Hamzavi completed an advanced one-year laser and photo-medicine fellowship at the University of British Columbia in Vancouver. Dr. Hamzavi is an active clinic researcher and investigates causes and treatments for vitiligo, hidradenitis suppurativa, photomedicine, and other conditions.

CME Information

December 8, 2021

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 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 regular educational conferences in a virtual setting, and with the December 2021 meeting, an in-person option has been offered for attendees, as well.

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 this meeting, the participant should be able to:
1. Describe the primary causes of vitiligo.
2. Outline treatment options for patients with vitiligo and discuss new advances for treating this condition.
3. List the main risk factors and causes for hidradenitis suppurativa.
4. Describe the progression and possible complications for patients with hidradenitis suppurativa.
5. Discuss new approaches to managing patients with hidradenitis suppurativa.

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 3 *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 in order to receive credit. Each attendee eligible for CME credit will receive a link to an online claim for and an evaluation form. 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 any relevant potential conflicts of interest.

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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.

University of Chicago
Section of Dermatology

Dermatology Residents

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

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

First Year
Brooke Cui, MD
Ekene Ezenwa, MD
Umar Sheikh, MD

AT THE FOREFRONT
UChicago Medicine

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CASE 1

PRESENTERS

Erin Dodd, MD; Angad Chadha, MD; Oluwakemi Onajin, MD; Arlene Ruiz de Luzuriaga, MD, MPH, MBA; Christopher Shea, MD; Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS

A 66-year-old male with metastatic high grade gastric neuroendocrine carcinoma (NEC) on nivolumab and ipilimumab was admitted to the hospital with subjective fevers and concern for bilateral lower extremity cellulitis. Dermatology was consulted for evaluation.

The patient reported an eight-week history of acute onset lower leg swelling, pain and redness. He had been treated for presumed stasis dermatitis with compression, topical mometasone, and furosemide without improvement. He was prescribed doxycycline for presumed cellulitis two days prior to admission, but the rash continued to worsen with development of subjective fevers. He was admitted directly from oncology clinic for broad spectrum intravenous antibiotics, but the rash had progressed despite nearly two days of vancomycin, cefepime, and metronidazole. He denied any significant lower extremity edema prior to starting immunotherapy with nivolumab and ipilimumab three months earlier. He denied abdominal pain, nausea, vomiting, diarrhea, hematuria, hemoptysis, chest pain, headache, and blurry vision.

PAST MEDICAL HISTORY

Metastatic high grade gastric neuroendocrine carcinoma (NEC)

- disease progression after 3 cycles of carboplatin and etoposide
- s/p palliative radiation
- nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) IV every 3 weeks, now s/p third cycle

Coronary artery disease and myocardial infarction s/p drug-eluting stent placement
Hypertension
Insulin-dependent type II diabetes mellitus
Hyperlipidemia
Obstructive sleep apnea
Severe obesity s/p Roux-en-Y gastric bypass
Osteoarthritis
Iron deficiency anemia

MEDICATIONS

Vancomycin 1750 mg intravenously every 12 hours
Cefepime 1g intravenously every 8 hours
Metronidazole 500 mg intravenously every 8 hours
Furosemide 40 mg intravenously as needed
Hydrochlorothiazide 25 mg by mouth daily
Valsartan 80 mg by mouth twice daily
Carvedilol 6.25 mg by mouth twice daily
Atorvastatin 40 mg by mouth at night
Aspirin 81 mg by mouth daily
Insulin aspart 5-10 units subcutaneously before meals and at night
Insulin glargine 6 units subcutaneously every morning
Enoxaparin 40 mg subcutaneously every morning
Morphine 15 mg ER by mouth twice daily
Gabapentin 100 mg by mouth three times daily
Ondansetron 4 mg by mouth every 12 hours as needed
Hydrocodone-acetaminophen 5-325 mg every 6 hours as needed

ALLERGIES
Metformin - difficulty urinating
Enalapril - pruritus

FAMILY HISTORY
Paternal grandfather with colon cancer (age 60s)
Cousin with esophageal cancer (age 68)

SOCIAL HISTORY
Lives at home with wife in Indiana. No recent travel. Former cigar smoker, quit 5 years prior. Rare alcohol use.

PHYSICAL EXAM
Physical exam revealed ill-defined warm, tender erythematous indurated plaques with focal areas of nodularity on bilateral lower legs. There were also several scattered slightly tender firm erythematous nodules on the left leg and right inner thigh.

DERMATOPATHOLOGY
Histopathology of punch biopsies from nodules on the left lower leg and left popliteal fossa showed a predominantly lobular panniculitis with necrotic lipocytes in the subcutis. There was a neutrophilic infiltrate with basophilic deposits at the margins of the fat necrosis that was highlighted with Von Kossa staining. GMS and Gram stains were negative for fungal and bacteria organisms in both specimens, respectively.

LABORATORY DATA
Based on the pathology findings, serum lipase was obtained and measured >3000 U/L (range 11-65 U/L). Erythrocyte Sedimentation Rate (53 mm/Hr) and C-Reactive Protein (86 mg/L) were elevated, and he had mild leukopenia (WBC 3.4 x $10^3/\mu L$).

The remaining lab workup–including basic metabolic panel and liver function tests–was otherwise unremarkable. All blood and tissue cultures were negative for fungus, bacteria and acid-fast bacilli.

IMAGING DATA
Computed Tomography (CT) Chest/Abdomen/Pelvis – with contrast
1. No radiographic evidence of pancreatic necrosis or peripancreatic fluid collections.
2. Worsening interval progression of metastatic disease with multiple new and enlarging masses within the mesentery and adjacent to the spleen in the upper abdomen. Small to moderate degree of ascites. Marked new and increased size of multiple hepatic metastases.

DIAGNOSIS
Pancreatic panniculitis in the setting of asymptomatic hyperlipasemia

TREATMENT AND COURSE
The patient continued to deny abdominal pain, back pain, nausea, vomiting, and diarrhea, and there was no abdominal tenderness, distention, or jaundice on exam. The possibility of immune checkpoint inhibitor (ICI)-related pancreatitis was considered given the onset of panniculitis a few weeks after starting nivolumab and ipilimumab. Rheumatology was consulted to evaluate for possible Immune-Related Adverse Event (IRAE). Antibiotics were discontinued, and he appeared to clinically stabilize on prednisone 60 mg twice daily. He was discharged with close outpatient follow up.

The patient was readmitted to the hospital one week later with hypoxic respiratory failure and worsening

panniculitis, now with focal ulcerations and oily yellow-brown drainage and further extension proximally up the legs and thighs. His lipase remained elevated at >3000 U/L, and repeat CT showed further progression of his metastatic disease. Given lack of improvement on high-dose steroids and unknown cause of hyperlipasemia, magnetic resonance cholangiopancreatography (MRCP) was recommended to more closely evaluate the pancreas. Unfortunately, the patient went into cardiac arrest and was unable to be resuscitated. To our knowledge, a post-mortem examination was not performed.

DISCUSSION

Pancreatic panniculitis (PP) is a form of fat necrosis that classically presents with erythematous, edematous plaques or nodules on the lower extremities. Lesions are often tender and may ulcerate or exude an oily brown substance.[1] PP may be accompanied by systemic symptoms including fever, polyarthritis, serositis, or abdominal pain.[1] While it is important to differentiate from other infectious and non-infectious panniculitides, the diagnosis can be made based on histopathology showing a predominantly lobular panniculitis with characteristic anucleate "ghost cells" and deposition of stippled basophilic material due to calcification.[1,2] Effective management of PP is dependent upon treatment of the underlying etiology, but supportive measures such as compression and elevation may offer some benefit.

While PP is well-documented, it remains a rare complication of pancreatic disease with an incidence ranging from 0.3 to 3 percent.[1,3,4] It is most commonly associated with pancreatitis and pancreatic neoplasms.[2,5] Acinar cell carcinoma is the most commonly implicated neoplasm,[1] but there have been 14 cases associated with neuroendocrine carcinomas (NECs) involving the pancreas.[3,6] PP has also been seen with pancreatic pseudocysts, congenital pancreatic abnormalities, and rarely in the setting of autoimmune connective tissue disease.[1] Importantly, PP may be the first manifestation of an underlying disorder, preceding clinical detection by days to months.[2,7]

To date, the pathogenesis of PP has yet to be thoroughly elucidated.[1,4,5] It is hypothesized that elevated levels of pancreatic enzymes extravasate from circulation causing saponification in susceptible peripheral tissue.[8] This is supported by elevated pancreas-specific lipase levels in blood, urine and skin lesions of patients with PP, and identification of anti-lipase antibodies have been found within necrotic adipocytes.[8] However, the rarity of PP compared with the incidence of pancreatic disease suggests that the pathogenesis is actually more complex. Indeed, *in vitro* studies have shown lack of fat necrosis in normal skin when incubated with exceedingly high pancreatic enzyme levels.[5] There are also rare cases in which PP has been reported in the absence of pancreatic enzyme elevation.[5,9] Vascular damage–due to inflammation or trauma–and immunological mechanisms have been proposed as additional factors that may promote fat necrosis.[1,4]

While the clinicopathological diagnosis of PP is not in question, the underlying cause of our patient's hyperlipasemia and resultant fat necrosis is less straightforward. Regarding pancreatic disease, he did not meet classic criteria for pancreatitis,[10] and the pancreas appeared normal on CT imaging. Non-pancreatic causes of significant hyperlipasemia include renal insufficiency, malignancy (specifically metastatic gastric or bowel cancer and hepatocellular carcinoma), critical illness, trauma, diabetes, drugs, and infections.[11] In our patient, we speculate the underlying etiology was either malignancy-related (as a result of his metastatic gastric cancer or perhaps an occult metastasis to the pancreas) or medication-induced due to ICI therapy.

Asymptomatic hyperlipasemia during ICI therapy is not uncommon and has been documented in up to six percent of patients treated with combination nivolumab and ipilimumab.[12,13] While most elevations are of unclear clinical significance, ICI-related pancreatitis is a documented but rare IRAE.[14,15,16,17] Early diagnosis is a clinical challenge as patients may have hyperlipasemia but tend to be asymptomatic and/or have normal imaging.[14,17,18,19] The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grades ICI-related pancreatitis based on severity, with the most mild disease requiring

one of the following: 1) pancreatic enzyme elevation; or 2) radiologic findings of pancreatitis.[20] Under these guidelines, a diagnosis of grade 2 ICI-related pancreatitis could be considered in our patient. Similarly, the National Comprehensive Cancer Network (NCCN) criteria for grade 2 disease are met based on elevated enzymes alone.[21] The classification, clinical significance, and management of equivocal or mild cases remains a matter of debate.[14,16,22]

Without further studies or postmortem examination, the ultimate existence and nature of pancreatic pathology in our patient cannot be determined. Regardless of the underlying etiology, this case emphasizes the importance of recognizing PP as a presenting sign of potentially serious internal disease and that, while rare, ICI-related pancreatitis should be considered in the appropriate clinical setting.

REFERENCES

1. Cutlan RT, Wesche WA, Jenkins JJ 3rd, Chesney TM. A fatal case of pancreatic panniculitis presenting in a young patient with systemic lupus. *J Cutan Pathol*. 2000 Oct;27(9):466-71. PMID: 11028818.
2. Dahl PR, Su WP, Cullimore KC, Dicken CH. Pancreatic panniculitis. *J Am Acad Dermatol.* 1995 Sep;33(3):413-7. PMID: 7657863.
3. Preiss JC, Faiss S, Loddenkemper C, Zeitz M, Duchmann R. Pancreatic panniculitis in an 88-year-old man with neuroendocrine carcinoma. *Digestion*. 2002;66(3):193-6. PMID: 12481166.
4. Zellman GL. Pancreatic panniculitis. *J Am Acad Dermatol*. 1996 Aug;35(2 Pt 1):282-3. PMID: 8708043.
5. Berman B, Conteas C, Smith B, et al. Fatal pancreatitis presenting with subcutaneous fat necrosis. Evidence that lipase and amylase alone do not induce lipocyte necrosis. *J Am Acad Dermatol*. 1987 Aug;17(2 Pt 2):359-64. PMID: 2442210.
6. Kasamatsu H, Oyama N, Hasegawa M, et al. Fatal case of pancreatic panniculitis caused by occult neuroendocrine tumor in the corresponding organ: A case report and review of the published work. *J Dermatol*. 2021 Feb;48(2):237-241. PMID: 33073392.
7. Menzies S, McMenamin M, Barnes L, O'Toole D. Pancreatic panniculitis preceding acute pancreatitis and subsequent detection of an intraductal papillary mucinous neoplasm: A case report. JAAD Case Rep. 2016 Jun 24;2(3):244-6. PMID: 27408933
8. Dhawan SS, Jimenez-Acosta F, Poppiti RJ Jr, Barkin JS. Subcutaneous fat necrosis associated with pancreatitis: histochemical and electron microscopic findings. *Am J Gastroenterol*. 1990 Aug;85(8):1025-8. PMID: 2375312.
9. Jacobson-Dunlop E, Takiguchi R, White CR Jr, White KP. Fatal pancreatitis presenting as pancreatic panniculitis without enzyme elevation. *J Cutan Pathol*. 2011 Jun;38(6):455-7. PMID: 21521354.
10. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
11. Hameed AM, Lam VW, Pleass HC. Significant elevations of serum lipase not caused by pancreatitis: a systematic review. *HPB (Oxford)*. 2015 Feb;17(2):99-112. PMID: 24888393.
12. Michot JM, Ragou P, Carbonnel F, et al. Significance of Immune-related Lipase Increase Induced by Antiprogrammed Death-1 or Death Ligand-1 Antibodies: A Brief Communication. J *Immunother*. 2018 Feb/Mar;41(2):84-85. PMID: 29252914.
13. Su Q, Zhang XC, Zhang CG, Hou YL, Yao YX, Cao BW. Risk of Immune-Related Pancreatitis in Patients with Solid Tumors Treated with Immune Checkpoint Inhibitors: Systematic Assessment with Meta-Analysis. *J Immunol Res*. 2018 Jun 3;2018:1027323. PMID: 29971244
14. Abu-Sbeih H, Tang T, Lu Y, et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. *J Immunother Cancer*. 2019 Feb 6;7(1):31. PMID: 30728076.
15. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016 Jun;60:190-209. PMID: 27085692.

16. Kohlmann J, Wagenknecht D, Simon JC, Ziemer M. Immune-related pancreatitis associated with checkpoint blockade in melanoma. *Melanoma Res*. 2019 Oct;29(5):549-552. PMID: 30964768.
17. Alabed YZ, Aghayev A, Sakellis C, Van den Abbeele AD. Pancreatitis Secondary to Anti-Programmed Death Receptor 1 Immunotherapy Diagnosed by FDG PET/CT. *Clin Nucl Med*. 2015 Nov;40(11):e528-9. PMID: 26284765.
18. Ikeuchi K, Okuma Y, Tabata T. Immune-related pancreatitis secondary to nivolumab in a patient with recurrent lung adenocarcinoma: A case report. Lung Cancer. 2016 Sep;99:148-50. PMID: 27565931.
19. Yamamoto K, Oka K, Son R, et al. Acute pancreatitis without abdominal pain induced by administration of nivolumab and ipilimumab. *Mod Rheumatol Case Rep*. 2021 Jul;5(2):425-430. PMID: 33821775.
20. National Cancer Institute. (2017). *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 5.0. Retrieved from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
21. National Comprehensive Cancer Network. (2021). *NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities*. V4.2021. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
22. Rogers BB, Cuddahy T, Zawislak C. Management of Acute Pancreatitis Associated With Checkpoint Inhibitors. *J Adv Pract Oncol*. 2020 Jan-Feb;11(1):49-62. PMID: 33542849.

CASE 2

PRESENTERS
Margaret Bruns MD; Arlene Ruiz de Luzuriaga MD; Angad Chadha MD

HISTORY OF PRESENT ILLNESS
A 41-year-old male with a past medical history of paraplegia secondary to gunshot wound, chronic UTIs, and nephrolithiasis was admitted to UCMC urology service for management of nephrolithiasis with percutaneous nephrolithotomy. Dermatology was consulted for evaluation of rash that was noted in the perioperative period.

Patient reported a one-year history of a progressive rash that started on the lower legs and spread to involve the trunk, arms and face. Affected areas were pruritic on the upper half of the body but patient lacked sensation from the waist down. He was previously seen by an outside dermatologist and treated with antifungal creams with no improvement. He did not wash the legs regularly due to concern about "spreading the fungal infection". Patient denied starting any new medications prior to rash onset. He denied pain or stiffness of the joints or changes of the nails.

PAST MEDICAL HISTORY
Paraplegia secondary to gunshot wound, Chronic UTIs, Nephrolithiasis

FAMILY HISTORY
No family history of psoriasis

SOCIAL HISTORY
Resides in assisted living facility

MEDICATIONS
Amlodipine, Tamulosin

ALLERGIES
Latex

PHYSICAL EXAMINATION
On the face, arms chest, back and buttocks were numerous well-demarcated erythematous thin plaques ranging in size from 1-10cm with white to grey scale, some confluent forming extensive plaques and some annular. On the lower legs were extensive plaques with overlying thick, adherent brown scale and a rim of erythema. Rash spared the elbows, retroauricular areas and occipital scalp. No pitting, oil spots or subungual hyperkeratosis of the nails. No involvement of the palms and soles. No mucosal involvement.

LABORATORY RESULTS
Hemoglobin: 11.4 g/dL (ref 13.5 – 17.5 g/dL)

Comprehensive metabolic panel and complete blood count were otherwise unremarkable.
HIV Ab/Ag and Syphilis IgG/IgM were nonreactive.

DERMATOPATHOLOGY
Histopathologic analysis of punch biopsy specimens from the left abdomen and left knee both showed epidermal acanthosis with parakeratosis and neutrophils within the stratum corneum. There was a superficial perivascular lymphocytic infiltrate. Prominent, thin-walled dermal blood vessels approached close to the epidermis. GMS stain was negative for fungi.

DIAGNOSIS
Ostraceous psoriasis

TREATMENT & COURSE
The patient was started on triamcinolone 0.1% ointment BID for the body and hydrocortisone 2.5% cream BID for the face. He was also prescribed urea 40% cream BID for the hyperkeratotic lesions on the legs. At his follow-up appointment with dermatology one month after discharge he reported some improvement in the lesions with his topical regimen. However, he had persistent hyperkeratotic lesions on the legs and was advised to manually remove the plaques to assist with triamcinolone penetration. Unfortunately, the patient was out of network so long term systemic therapy could not be considered until he established routine care with a dermatologist in network.

DISCUSSION
Psoriasis is a chronic, relapsing inflammatory skin disease with variable clinical features. The typical variants are plaque, guttate, pustular, erythrodermic, and nail psoriasis. More unusual presentations include inverse, ostraceous, rupioid, elephantine, congenital, and photosensitive psoriasis. Ostraceous, rupioid, and elephantine are forms of hyperkeratotic psoriasis.

The term ostraceous psoriasis was first published in 1898 by Deutsch as 'atypical psoriasis'. In this form, the lesions demonstrate firmly adherent thick scales and varying color with a surface resembling an oyster shell.[1] In 1948 rupioid and ostraceous psoriasis were grouped together as "psoriasis exuditiva" by Grzybowski. This is in line with the current hypothesis that the crust is the result of voluminous serosanguineous exudate that hardens in combination with increased keratinocyte proliferation and inflammation. Rupioid stems from the Greek word *rhupos*, which means dirt or filth. It is now generally accepted that rupioid psoriasis (RupP) is characterized by hyperkeratotic, concentric, circular cone or limpet shaped layers.[2] Due to their rare incidence, only a few case reports of ostraceous and rupioid psoriasis have been published and the distinction between the two entities in the literature is poorly defined. There is variable overlap reported and some authors consider the terms interchangeable.[3] The elephantile form has very rarely been reported in the literature and is characterized by large thick simple chronic plaques.[4]

Compared to thin plaque psoriasis, hyperkeratotic or thick plaque psoriasis has been associated with male gender, increased incidence of nail psoriasis and psoriatic arthritis[5], as well as a greater body surface area affected.[6] Rupioid and ostraceous psoriasis can occur in isolation or can be triggered by medications, including oral and intravenous corticosteroids, nonsteroidal anti-inflammatory drugs, lithium, β-blockers, hydroxychloroquine, pembrolizumab, valproic acid, antibiotics, and antihypertensives.[789] Medication-induced RupP has been reported in pharmacologically unrelated drugs, suggesting multiple pathogenic mechanisms for development of lesions. Recently a case was reported of drug-induced RupP in a patient 12 months after initiating a strong vasodilatory drug regimen for pulmonary arterial hypertension (treprostinil, macitentan, tadalafil). The authors hypothesize that the immunopathogenic, hyperproliferative, and vasodilatory properties of the patient's pulmonary artery hypertension drug regimen synergistically contributed to her presentation.[9]

Hyperkeratotic psoriasis indicates extensive cutaneous inflammation and may be suggestive of immunosuppression, such as HIV infection. Psoriasis vulgaris in HIV patients tends to be more severe, extensive and atypical, with reports of ostraceous and rupioid psoriasis presenting in HIV-positive patients.[10]

Differential diagnoses that may manifest with skin lesions of similar morphology include secondary syphilis, hyperkeratotic scabies, reactive arthritis, disseminated histoplasmosis, and photosensitive skin

lesions in association with aminoaciduria. Malignant or rupioid syphilis refers to the stage in which papulopustules of pustular syphilis undergo central necrosis due to endarteritis obliterans and intravascular thrombosis.[6]

Typical psoriasis pathological findings are the same for both rupioid and ostraceous psoriasis, and show features similar to psoriasis vulgaris. These similarities include parakeratosis with neutrophil infiltration in the stratum corneum, acanthosis with elongation of rete ridges, hypogranulosis, and dilatation of blood vessels in the dermis.[11]

Rupioid and ostraceous psoriasis are typically considered resistant to topical treatment due to the hyperkeratosis impeding drug penetration. Most cases have been treated with combined systemic and topical therapy. Treatment successes have been reported with systemic agents, including acitretin, cyclosporine, methotrexate, adalimumab, and ustekinumab, many with remarkable improvement.[3]

All patients presenting with hyperkeratotic plaques should have syphilis and HIV testing since similar lesions can be observed in secondary syphilis and HIV. Additionally, patients should have a careful drug history taken. The diagnosis of hyperkeratotic psoriasis can be made with a biopsy demonstrating the typical features of psoriasis. Our patient had negative syphilis and HIV testing and no obvious culprit medications, though studies have suggested a possible role of calcium channel blockers as a precipitating or exacerbating factor in patients with psoriasis.[12]

We present this case to highlight a rare presentation of a common disease.

REFERENCES

1. Nascimento BAM do, Carvalho AH, Dias CM, Lage TL, Carneiro CMO, Bittencourt M de JS. A case of generalized ostraceous psoriasis mimicking dermatitisneglecta. *An Bras Dermatol*. 2015;90(3 Suppl 1):197. doi:10.1590/ABD1806-4841.20153858
2. S ML, J S, FM P, S ML, R F, SF S. Case for diagnosis. *An Bras Dermatol*. 2014;89(5):841-842. doi:10.1590/ABD1806-4841.20143195
3. Ip KH-K, Cheng HS, Oliver FG. Rupioid Psoriasis. *JAMA Dermatology*. 2021;157(7):859-859. doi:10.1001/JAMADERMATOL.2021.0451
4. Tafazzoli Z, Meibodi NT, Torabi S. Solitary ostraceous psoriasis treatment: A rare presentation of a common disease. *Dermatol Ther*. 2021;34(1):e14567. doi:10.1111/DTH.14567
5. R M. Ostraceous psoriasis presenting over distal extremities. *Int J Dermatol*. 2011;50(9):1115-1116. doi:10.1111/J.1365-4632.2011.04873.X
6. Jin Chung H, Marley-Kemp D, Keller M, St C. Case Report Rupioid Psoriasis and Other Skin Diseases With Rupioid Manifestations Practice Points. *Cutis*. 2014;94:119-121.
7. Bonciani D, Bonciolini V, Antiga E, Verdelli A, Caproni M, Senetta R. A case of rupioid psoriasis exacerbated by systemic glucocorticosteroids. *Int J Dermatol*. 2015;54(4):e100-e102. doi:10.1111/IJD.12755
8. Jesús Gómez-Arias P, José A, García-Nieto V. Queirós N, Torres T. HIV-associated psoriasis. *J Clin Aesthet Dermatol*. 2014;94:32-40. doi:10.1503/cmaj.200517
9. U R, M T, S G, LS W, JC F, AL K. Onset of rupioid psoriasis after vasodilatory regimen initiation in a patient with pulmonary arterial hypertension. *JAAD case reports*. 2021;12:77-80. doi:10.1016/J.JDCR.2021.03.031
10. RL C, GZ R, FD R. Ostraceous and inverse psoriasis with psoriatic arthritis as the presenting features of advanced HIV infection. *Singapore Med J*. 2014;55(4). doi:10.11622/SMEDJ.2014062
11. Gilang RR, Oki D, Hartati S, et al. A Successful Treatment of Ostraceous Psoriasis Associated with Psoriatic Arthritis in Children: A Case Report. Published online 2020. doi:10.2147/PTT.S285832
12. Cohen AD, Kagen M, Friger M, Halevy S. Calcium channel blockers intake and psoriasis: A case-control study. *Acta Derm Venereol*. 2001;81(5):347-349. doi:10.1080/000155501317140061

PRESENTERS
Ekene Ezenwa MD; Eduardo Moioli, MD; Christopher Shea MD; Oluwakemi Onajin MD

CASE 1

HISTORY OF PRESENT ILLNESS
A 53-year-old African American female with a history of systemic lupus erythematosus presented with a 4-year history of pruritic nodules within a on the right lateral lower leg that was placed 25 years ago. Prior treatments included intralesional triamcinolone, with mild improvement, as well as topical clobetasol 0.05% ointment without benefit.

PAST MEDICAL HISTORY
Systemic lupus erythematosus, hypertension, type 2 diabetes mellitus, osteoarthritis, carpal tunnel syndrome

FAMILY HISTORY
Mother with sarcoidosis

MEDICATIONS
Hydroxychloroquine, pioglitazone, losartan, aspirin

ALLERGIES
Metformin, penicillin

PHYSICAL EXAMINATION
Two 2-4 cm, firm, erythematous to hyperpigmented nodules within a tattoo on the right lower lateral leg localized to areas with red pigment.

LABORATORY RESULTS
CBC, CMP were within normal limits
ESR elevated at 55 mm/Hr (ref range 1 – 41 mm/Hr)

DERMATOPATHOLOGY
A punch biopsy from a nodule on the right lateral lower leg demonstrated irregular epidermal acanthosis and spongiosis with exocytosis of lymphocytes. There was a diffuse dermal infiltrate within a fibrotic dermis, extending to the subcutis. The infiltrate was predominantly composed of small CD3+ T-cells and a few CD20 B-cells with admixed plasma cells, histiocytes and foamy giant cells. Methenamine silver and Fite stains were negative for infectious organisms.

DIAGNOSIS
Nodular T-cell pseudolymphoma arising within a tattoo

TREATMENT & COURSE
The patient was referred to plastic surgery and underwent excision of the nodules with split-thickness skin graft from the right thigh. At her most recent follow-up visit, there was no evidence of recurrence.

CASE 2

HISTORY OF PRESENT ILLNESS

A 36-year-old African American female presented with a 1-month history of papules within a tattoo on the left chest that was placed 8 years ago. The tattoo was repigmented for color enhancement 6 months prior to presentation. The papules started focally and over time, extended along lines of the tattoo, and were intermittently tender to palpation. Prior treatments included 1% hydrocortisone and over-the-counter antibiotic ointments.

PAST MEDICAL HISTORY
Hypertension, genital herpes

FAMILY HISTORY
Noncontributory

SOCIAL HISTORY
Denies any recreational drug use.
History of tattoo 8 years ago

MEDICATIONS
None

ALLERGIES
None

PHYSICAL EXAMINATION
Erythematous papules distributed along part of a tattoo, predominantly within areas of red ink, and extending along black-inked portion laterally on the left chest.

LABORATORY RESULTS
None available

IMAGING
None

DERMATOPATHOLOGY
A punch biopsy of a papule on the left chest demonstrated a diffuse superficial to deep dermal infiltrate composed of small lymphocytes and histiocytes with macrophages containing red and black granules. The lymphocytes expressed CD3, CD4, and CD8. A few CD20+ B-cells were present. Ki67 demonstrated increased proliferation index throughout the infiltrate.

DIAGNOSIS
Nodular T-cell pseudolymphoma arising within a tattoo

TREATMENT AND COURSE
The patient was initially treated with topical triamcinolone 0.1% ointment pending biopsy results. Intralesional triamcinolone injections were planned but patient was lost to follow up.

DISCUSSION
In this case series, we present two patients with nodular T-cell pseudolymphoma arising within tattoos. Cutaneous pseudolymphomas (PSL) or cutaneous lymphoid hyperplasia are reactive lymphoid infiltrates in the skin that clinically and/or histopathologically mimic lymphomas. Cutaneous PSL have been associated with various causative agents[1] including drugs, trauma, arthropod bite, infection, and exogenous contactants such as tattoo dyes. Cutaneous PSL may present with solitary or multiple nodules,

papules, and plaques. These lesions may be asymptomatic or present with pruritus, pain, or swelling[2].

Histopathologic findings of pseudolymphomas include nodular, epidermotropic or diffuse dermal lymphocytic infiltrates with variable plasma cells, histiocytes, eosinophils and neutrophils. Immunophenotypic studies further characterize the infiltrates as T- vs B-cell, CD4+ vs CD8+, CD30+. Molecular studies for clonality may be helpful, but should be interpreted only in the clinical context. Clonal T- and B-cells are not specific for lymphoma, and can also occur in inflammatory diseases, infections, and PSL[3].

Reactions to tattoo simulate various inflammatory dermatoses and cutaneous neoplasms. Different subsets of inflammatory tattoo reactions include fibrosing, lichenoid, granulomatous, pseudoepitheliomatous hyperplasia, and spongiotic[4]. Historically, lichenoid reactions were found to be the most common subtype of inflammatory tattoo reactions[5].

Previous studies have shown that tattoos account for 26% of pseudolymphoma cases[1]. Onset can be from within months of tattooing to up to several decades; our first case presented after approximately 20 years of tattoo administration[1]. Although the full mechanism of action has yet to be elucidated, studies have suggested a pathogenesis of delayed hypersensitivity to a metal component of the ink. Red dyes are often the target of the lymphocytic infiltrate, secondary to historically-used metal compounds and more recently reported synthetic azo-dyes [6].

Diagnosis of cutaneous PSL requires clinicopathologic correlation. Typical histopathologic and immunophenotypic features in addition to absence of T-cell or B-cell clonality and absence of monotypic expression of immunoglobulin heavy chains favor a diagnosis of cutaneous PSL[7].

There is no gold standard of care for cutaneous pseudolymphoma arising within tattoos; several treatment modalities have been reported with variable outcomes[1]. Topical corticosteroids as monotherapy have a response range from no response to complete resolution [1]. One case reported improvement with combination treatment of topical corticosteroids and hydroxychloroquine. Spontaneous regression has been reported[6,8]. Surgical removal, when feasible, has been shown to be the most effective treatment method [9]. Lastly, Q-switched ND:YaG and CO2 laser therapies have shown notable improvement as monotherapies or with adjuvant intralesional corticosteroid therapy[9,10].

Although pseudolymphomas are considered benign lymphocytic infiltrates, patients should be monitored longitudinally. The natural history of pseudolymphomas is varied as some have been shown to regress spontaneously while others persist for several years[6].
Progression to malignancy has been previously reported in pseudolymphoma[11]. Close follow-up of patients diagnosed with PSL is recommended, with one study recommending up to five years to monitor for the progression to cutaneous lymphoma[6,12].

REFERENCES

1. Marchesi A, Parodi PC, Brioschi M, et al. Tattoo ink-related cutaneous pseudolymphoma: a rare but significant complication. Case report and review of the literature. Aesthetic Plast Surg. 2014;38(2):471-478.
2. Kluger N, Vermeulen C, Moguelet P, et al. Cutaneous lymphoid hyperplasia (pseudolymphoma) in tattoos: a case series of seven patients. J Eur Acad Dermatol Venereol. 2010;24(2):208-213.
3. Mitteldorf C, Kempf W. Cutaneous pseudolymphoma-A review on the spectrum and a proposal for a new classification. J Cutan Pathol. 2020;47(1):76-97.
4. Forbat E, Al-Niaimi F. Patterns of Reactions to Red Pigment Tattoo and Treatment Methods. Dermatol Ther (Heidelb). 2016;6(1):13-23.

5. Litak J, Ke MS, Gutierrez MA, Soriano T, Lask GP. Generalized lichenoid reaction from tattoo. Dermatol Surg. 2007;33(6):736-740.
6. Gutermuth J, Hein R, Fend F, Ring J, Jakob T. Cutaneous pseudolymphoma arising after tattoo placement. J Eur Acad Dermatol Venereol. 2007;21(4):566-567.
7. Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. J Am Acad Dermatol. 1998;38(6 Pt 1):877-895; quiz 896-877.
8. Mendez Diaz Y, García-Arpa M, Parra Cubillos A, De Lara Simón IM, García Rodriguez R, Gómez Torrijos E. Cutaneous Pseudolymphoma Secondary to Exogenous Pigment in a Polychrome Tattoo. J Investig Allergol Clin Immunol. 2018;28(3):199-201.
9. Miguel D, Peckruhn M, Elsner P. Treatment of Cutaneous Pseudolymphoma: A Systematic Review. Acta Derm Venereol. 2018;98(3):310-317.
10. Tan LS, Lucinda TS, Oon HH, et al. Successful Treatment of Tattoo-Induced Pseudolymphoma with Sequential Ablative Fractional Resurfacing Followed by Q-Switched Nd: YAG 532 nm Laser. J Cutan Aesthet Surg. 2013;6(4):226-228.
11. Anandasabapathy N, Pulitzer M, Epstein W, Rosenman K, Latkowski JA. Pseudolymphoma evolving into diffuse large B-cell lymphoma. Dermatol Online J. 2008;14(5):22.
12. Prabhu V, Shivani A, Pawar VR. Idiopathic cutaneous pseudolymphoma: An enigma. Indian Dermatol Online J. 2014;5(2):224-226.

CASE 4

PRESENTERS

Jake Lazaroff MD, Diana Bolotin MD PhD

HISTORY OF PRESENT ILLNESS

91-year-old man with history of atrial fibrillation on warfarin and multiple non-melanoma skin cancers presented to Dermatology clinic with a pink scaly papule on the right medial nasolabial cheek and an eroded pink papule on the right frontal scalp. Shave biopsies were performed, and both showed keratinocytes with severe cytologic atypia extending from the epidermis into the dermis, consistent with invasive squamous cell carcinomas (SCCs). The patient was referred for Mohs micrographic surgery.

The patient returned for the procedures 4 weeks later. A pre-procedure INR was found to be 2.5, which was within his therapeutic goal range (INR 2.0-3.0). The right medial nasolabial cheek SCC was completely excised in 2 stages and resulted in a surgical defect measuring 1.0 cm x 0.5 cm, and the right frontal scalp was excised in 1 stage and had a final post-operative size of 1.7 cm x 0.9 cm. Both sites were repaired with linear layered closures. The procedure was uncomplicated and the wounds were subsequently dressed with petrolatum, a non-adherent bandage, and a compression dressing.

The next day, during the routine post-operative call, the patient reported continued bleeding from the wound on the right medial nasolabial cheek. He was immediately seen for an evaluation. On examination, the right cheek had extensive ecchymosis with a focal area of hematogenous ooze centrally. The epidermal sutures and several dermal sutures were removed to allow for exploration of the wound which showed diffuse slow bleeding and a developing hematoma that was evacuated. Any visualized bleeding vessels were cauterized, the wound was observed for 15 minutes and subsequently closed with 4-0 Maxon dermal and 4-0 Prolene running horizontal mattress sutures. The scalp incision also had a focal area of oozing that was controlled with an additional horizontal mattress suture of 2-0 Nylon. An additional INR was drawn at the same time which was found to be supra-therapeutic at 3.1. The result was communicated to the anti-coagulation service who held his Coumadin dose for two days then resumed at previous dosing.

Over the course of the next week, the patient returned to clinic every 2 days for wound checks and dressing changes where he was noted to have significant purpura and a firm, organized hematoma on the cheek, but no active bleeding. Approximately 1 week after the initial procedure the patient reported developing new active re-bleeding from the surgical site and through pressure bandages overnight on the cheek and went to an outside hospital emergency room where he had additional epidermal sutures placed. An INR re-checked at that time was found to be 4.5. He was again seen by the anti-coagulation service who advised to hold two doses of Coumadin and referred him to his PCP for further work up due to unexplained significant fluctuations in INR.

Two days later, the patient again noted bleeding through the pressure bandage and was seen at an outside emergency room where he was given vitamin K for reversal and observed with a new pressure bandage without further bleeding overnight. He returned to Mohs procedures clinic the next day at which time active oozing at the suture line was again noted. The area was re-opened and explored for additional bleeding vessels and was found to have diffuse oozing. Hemostasis was obtained by electrocoagulation and the wound was repaired with a layered closure. A pressure bandage was re-applied and he was started on PO Cephalexin given recurrent hematoma necessitating multiple evacuation procedures. He was seen two days later for a bandage change in the Procedures unit and was seen by his PCP who ordered another dose of vitamin K and performed additional lab work that included a complete blood count (CBC) which was notable for a platelet count of 26 x $10^3/\mu L$ [150-400 x $10^3/\mu L$]. The patient was admitted to an outside hospital for further treatment and workup for a bleeding diathesis.

PAST MEDICAL HISTORY
Atrial fibrillation, sinus node dysfunction s/p dual-chamber pacemaker, cervical spinal stenosis, cerebral vascular accident, hypertension, benign prostatic hypertrophy s/p TURP

MEDICATIONS
Warfarin, atorvastatin, enalipril, sertraline, tamsulosin, topical ivermectin, topical metronidazole, topical clotrimazole.

FAMILY HISTORY
None pertinent

PHYSICAL EXAM
Healing surgical wound on the right cheek with significant purpura on the cheeks and periorbital skin. Minimal bleeding at incision site.

LABORATORY DATA
Platelets of 26 x $10^3/\mu L$ [150-400 x $10^3/\mu L$]
PT of 20.8 seconds [9.7-11.8 seconds], PTT of 39 seconds [22-32 seconds], INR of 2.1
D Dimer >35.2 μ /mL [<0.57 μ /mL]
Fibrinogen of 54 mg/dL [190-425 mg/dL], Haptoglobin of <6 mg/dL [36-195 mg/dL]
Factor V Assay 38% [75-137%], Factor VII Assay 69% [71-147%], Factor VIII Assay 89% [57-152%]
ADAMTS 13 Functional 90% [60-130%], ADAMTS 13 inhibitor < 0.5 [<0.5]

DIAGNOSIS
Disseminated intravascular coagulopathy

TREATMENT AND COURSE
Upon admission, the patient was found to have significantly decreased fibrinogen as well as thrombocytopenia and an elevated D-dimer and was diagnosed with disseminated intravascular coagulation (DIC). Work up for the underlying cause of DIC was performed and was notable for CT Chest/Abdomen/Pelvis with soft tissue lesions within the medullary canals of bilateral proximal femurs and lymphadenopathy within the upper abdomen and lower posterior mediastinum concerning for metastatic disease. PET scan showed several foci of increased uptake in multiple ribs and the bilaterally proximal to mid femurs all consistent with diffuse bony metastasis. Malignancy work up revealed a PSA of 378 [<4.01 ng/mL]. The patient was diagnosed with DIC resulting from new diagnosis of Stage IV metastatic prostate cancer. The MMS sites remained stable with no further bleeding during his admission. He subsequently established care with oncology. The patient was treated with bicalutamide, leuprorelin, abiraterone-prednisone, enzalutamide, and radium 223, however his disease continued to progress and he passed away less than 1 year later.

DISCUSSION
Mohs micrographic surgery (MMS) is a common procedure implemented in dermatology to treat cutaneous malignancies. MMS offers excellent cure rates, preserves local function and cosmesis, and is well tolerated. In a large multicenter study that evaluated postoperative complications of MMS, the overall rate of adverse events was low at 0.72% of cases. And of those, bleeding and hematomas were reported 15.4% of the time [1].

Studies have shown that patients taking anticoagulant or antiplatelet medications have a higher risk of peri-operative bleeding in MMS. This is of particular concern, as approximately 46% of patients undergoing MMS are on at least one anticoagulant or antiplatelet medication [2]. Patients taking warfarin have an odds ratio of having moderate to severe bleeding of 6.69 compared to control [3]. Similarly,

novel oral anticoagulants (nOAC), which includes rivaroxaban, dabigatran, and apixaban, confer a comparably elevated risk of perioperative bleeding [2].

Even though anti-coagulant and anti-platelet agents increase the risk of perioperative bleeding complications the absolute risk remains low. Current guidelines suggest that clinicians should evaluate each patient on a case by case basis and perform appropriate risk-benefit analysis. In general, as was the case in the patient presented above, warfarin can be continued as long as an INR is checked preoperatively and is below 3.5 [4].

In addition to the medications, the size of the operative defect and subsequent surgical repair is associated with a higher risk of post-operative bleeding. Furthermore, the risk of bleeding has been shown to be elevated in complex repairs, graft repairs, flap repairs, and partial repairs when compared to intermediate closures [5]. Factors such as type of malignancy, location, or number of Mohs stages were not correlated with an increased risk of bleeding [2]. While medications contribute to a large proportion of bleeding complications following MMS, particularly in refractory cases, it is important to keep in mind and evaluate patients for other rare conditions contributing to post-operative bleeding risk.

DIC is a consumptive coagulopathy and results from an imbalance between coagulation and fibrinolysis [6]. There is a spectrum of clinical manifestations ranging from life threatening bleeding to rather mild symptoms. Laboratory findings depend on the chronicity and underlying cause, but include thrombocytopenia, increased prothrombin time (PT), increased partial thromboplastin time (PTT), and an elevated D-dimer are present [6]. Furthermore, decreased fibrinogen and antithrombin are seen as a result of consumption [7].

Several societies have put forth diagnostic scoring systems that incorporate these laboratory values including the International Society on Thrombosis and Hemostasis and Japanese Association for Thrombosis and Hemostasis [7]. Given the variabilities and implementation of these scoring systems a true prevalence is challenging to calculate. However, some studies have shown DIC to occur of 1% of hospitalized patients and up to 10-30% of ICU patients [8]. True incidence and prevalence of DIC in the ambulatory population are unknown.

Common causes of DIC include infection, burns, pregnancy, and cancer. The mechanism by which cancer causes DIC is incompletely understood. However, it has been proposed that malignant cells express procoagulants, such as tissue factor, and fibrinolytic inhibitors, such as plasminogen activator inhibitor type 1 [10].

DIC can be subdivided into predominately procoagulant, predominately fibrinolytic, and balanced subtypes [6]. The fibrinolytic subtype, which results in hypofibrinogenemia, is often marked by more severe bleeding and has been linked to prostate cancer. This may result from overproduction of urinary-type plasminogen activators by prostatic cancer cells [10]. Studies have found that most patients with prostate cancer who develop DIC have a high-grade malignancy, and the increased fibrinolysis can actually promote metastatic spread of the cancer [10]. Even though 13-30% of patients with prostate cancer develop DIC, the vast majority of these are subclinical with only about 1% having clinical manifestations [6]. In rare instances DIC and bleeding has been reported to be the presenting manifestation of prostate cancer, as was the case in our patient [11, 12, 13]. Surgical procedures, including MMS, have been reported to unmask the underlying compensated coagulation disorder in such patients [13].

Treatment of DIC is complicated and tailored to the patient and underlying cause. In the case of DIC associated with malignancy, careful coordination between hematology and oncology is required to provide supportive care to control the abnormal coagulation while also treating the cancer [12].

REFERENCES

[1] Alam M, Ibrahim O, Nodzenski M, Strasswimmer JM, et al. Adverse events associated with mohs micrographic surgery: multicenter prospective cohort study of 20 821 cases at 23 centers. JAMA Dermatol 2013;149:1378–85.

[2] Eilers RE Jr, Goldenberg A, Cowan NL, Basu P, Brian Jiang SI. A Retrospective Assessment of Postoperative Bleeding Complications in Anticoagulated Patients Following Mohs Micrographic Surgery. Dermatol Surg. 2018 Apr;44(4):504-511

[3] Lewis KG, Dufresne RG. A meta-analysis of complications attributed to anticoagulation among patients following cutaneous surgery. Dermatol Surg 2008;34:160–4; discussion 64–5.

[4] Iyengar S, Yeager DG, Cohen JL, Ozog DM. Update and Review of Bleeding Considerations in Dermatologic Surgery: Anticoagulants and Antiplatelets. Dermatol Surg. 2020 Feb;46(2):192-201.

[5] Bordeaux JS, Martires KJ, Goldberg D, Pattee SF, et al. Prospective evaluation of dermatologic surgery complications including patients on multiple antiplatelet and anticoagulant medications. J Am Acad Dermatol 2011;65:576–83.

[6] Palma Anselmo M, Nobre de Jesus G, Lopes JM, Victorino RM, Meneses Santos J. Massive Bleeding as the First Clinical Manifestation of Metastatic Prostate Cancer due to Disseminated Intravascular Coagulation with Enhanced Fibrinolysis. Case Rep Hematol. 2016;2016:7217915.

[7] Kitchens CS. Thrombocytopenia and thrombosis in disseminated intravascular coagulation (DIC). Hematology Am Soc Hematol Educ Program. 2009:240-6. doi: 10.1182/asheducation-2009.1.240.

[8] Adelborg K, Larsen JB, Hvas AM. Disseminated intravascular coagulation: epidemiology, biomarkers, and management. Br J Haematol. 2021 Mar;192(5):803-818.

[9] Sivula M, Tallgren M, Pettila V. Modified score for disseminated intravascular coagulation in the critically ill. Intensive Care Med. 2005;31:1209–14.

[10] Hyman DM, Soff GA, Kampel LJ. Disseminated intravascular coagulation with excessive fibrinolysis in prostate cancer: a case series and review of the literature. Oncology. 2011;81(2):119-25.

[11] Navarro M, Ruiz I, Martín G, Cruz JJ. Patient with disseminated intravascular coagulation as the first manifestation of adenocarcinoma of the prostate. Risks of prostatic biopsy. Prostate Cancer Prostatic Dis. 2006;9(2):190-1. doi: 10.1038/sj.pcan.4500854.29107338

[12] Duran I, Tannock IF. Disseminated intravascular coagulation as the presenting sign of metastatic prostate cancer. J Gen Intern Med. 2006;21(11):C6-C8.

[13] Guldbakke KK, Schanbacher CF. Disseminated intravascular coagulation unmasked by Mohs micrographic surgery. Dermatol Surg. 2006; 32(5): 760- 764.

CASE 5

PRESENTERS
Erin Ibler, MD; Angad Chadha, MD; Arlene Ruiz de Luzuriaga, MD, MPH, MBA

HISTORY OF PRESENT ILLNESS
A 17 year-old G1P0 female at 29 weeks gestation was transferred to the University of Chicago for coordination of dermatological and obstetric care. She presented with erythematous annular plaques with central scale/crust, peripherally studded with pustules, which involved ~70% body surface area (BSA). The lesions were itched, burned, and were painful. Prior to admission, she endorsed feeling dizzy and nauseated. On admission, she was afebrile but tachycardic to the 130's-140's, mildly hypotensive to the 90's/50's, and had a white count of 18.

Her medical history was notable for previously mild (<5% BSA) plaque psoriasis, which had progressively worsened throughout her pregnancy. A skin biopsy performed by her local dermatologist prior to admission was consistent with pustular psoriasis. Prior treatments included triamcinolone 0.1% ointment (body), hydrocortisone 1% cream (face), clobetasol 0.05% cream (body), mometasone solution (scalp), and copious Vaseline.

Given the extensive BSA involved, the concern for superinfection/sepsis, and the need for fetal monitoring, the patient was admitted for management.

PAST MEDICAL HISTORY
Plaque psoriasis (previously mild, estimated less than or equal to 5% BSA)

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
Non-contributory

MEDICATIONS
None

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Multiple erythematous annular plaques with central scale/crust, peripherally studded with pinpoint pustules and pustular lakes, of the upper extremities, groin, axillae, lower extremities, and to a lesser extent involving the face and scalp. Abdomen with near-confluent erythematous thin plaques with yellow-white scale and pustules coalescing at periphery. Scalp with thick silver scale throughout. Erythematous plaques around the nailfolds, no nail pitting, oil spots or onycholysis. No oral involvement.

LABORATORY RESULTS
White blood cell count: 18.0 x 10^3/μL (ref 3.5 - 11.0 10^3/μL)
Total protein: 5 g/dL (ref 6-8.3 g/dL)
Albumin: 2.7 g/dL (ref 3.5-5 g/dL)
Skin culture (swab) grew methicillin susceptible *Staphylococcus aureus* and *Streptococcus agalactiae*

CBC WNL (aside from iron deficiency anemia)
CMP WNL
Blood cultures were negative x4
HSV/VZV PCR negative

IMAGING
CT-PE: No CT evidence of pulmonary embolism or other acute cardiopulmonary abnormality

DERMATOPATHOLOGY
Biopsy of a representative lesion on the right arm demonstrated neutrophilic crust with surrounding parakeratosis, irregular acanthosis, spongiosis, and dilated capillary loops. Intracorneal neutrophilic microabscesses and subcorneal pustules were noted.

DIAGNOSIS
Pustular psoriasis of pregnancy

TREATMENT & COURSE
The patient was initiated on prednisone 1mg/kg daily, wet wrap therapy with triamcinolone 0.1% ointment for the body BID, and hydrocortisone 2.5% cream for the face BID. She was also initiated on broad spectrum antibiotics (vancomycin, cefepime, clindamycin, and metronidazole) and started on IV fluids. Bacterial cultures (skin swab) grew MSSA and Strep agalactiae, and antibiotics were subsequently tapered to cephalexin. Skin stabilized, and tachycardia, hypotension, and systemic symptoms improved.

As the patient stabilized, an attempt was made to begin tapering the dose of prednisone. Although her skin remained stable, she again reported malaise, had increased tachycardia, and developed intermittent fevers of unclear etiology (cultures remained negative). At that time, cyclosporine was initiated (at 3 mg/kg/day gravid weight). Vitals again stabilized, the patient reported feeling improved, and remained afebrile for 48h. She was discharged with close outpatient follow up with her primary dermatologist.

While outpatient, another attempt was made to decrease her prednisone. She again experienced malaise and significant worsening in her skin, despite resuming the higher dose. The patient was re-admitted due to progression, at which time she was erythrodermic with >80% BSA involvement. Her cyclosporine was subsequently increased to 5mg/kg/day, and she was transitioned from prednisone to IV dexamethasone (both for the flare and for fetal lung maturity). Skin and hemodynamics again stabilized, and patient was subsequently discharged. She was maintained on high dose oral dexamethasone and cyclosporine until induction at 36 weeks. She had an uncomplicated delivery, and the baby is doing well. The patient's psoriasis also flared severely after delivery, at which time she was transitioned from dexamethasone/cyclosporine to IV infliximab as an outpatient.

DISCUSSION
Pustular psoriasis of pregnancy (PPP; also known as impetigo herpetiformis) is commonly regarded as a dermatosis of pregnancy. However, it is suggested that the condition is a variant of generalized pustular psoriasis, and is commonly seen in women with a personal or family history of psoriasis.

Classically, sterile micropustules studded on the periphery of annular erythematous patches are seen within the intertriginous areas. The pustules rapidly coalesce to form large desquamative plaques, which spread centrifugally to the extremities. The oral mucosa may be involved but the face, palms, and soles are typically spared. Histologic findings mirror those of psoriasis and include psoriasiform acanthosis, confluent parakeratosis, hypogranulosis, thinning of suprapapillary plates, and dilated vessels in dermal papillae, as well as sub- and intracorneal neutrophilic abscesses.

The molecular pathogenesis of PPP or generalized pustular psoriasis is thought to differ from that of traditional plaque psoriasis, given differences in treatment response between the two conditions. Studies have identified that the expression of IL-1 and IL-36 are more prominent in pustular psoriasis. Some patients with pustular psoriasis also have an IL-36 receptor antagonist deficiency, and respond to treatment IL-1, IL-1 receptor, or a novel anti-IL-36 receptor monocolonal antibody. Therefore, IL-36 is thought to play a critical role in the pathogenesis of the condition.

PPP is most typically seen during the early portion of third trimester, although presentation ranges from the first trimester through the immediate post-partum period. PPP has also been associated with changes in menstrual cycle and oral contraceptive use. The condition frequently recurs with subsequent pregnancies, often at an earlier stage and with more severe presentation. PPP generally resolves rapidly after delivery.

PPP may be life-threatening for both the mother and fetus if untreated. Systemic manifestations may include fatigue, fever, malaise, arthralgias, and tachycardia, as well as nausea, diarrhea, delirium, and seizures. Markers of inflammation (including white blood cell counts) may be elevated and erythroderma with electrolyte imbalances (particularly hypocalcemia), impaired thermoregulation, or sepsis from secondary infection may be seen. Fetal complications include placental insufficiency, with subsequent intrauterine growth restriction or fetal demise. Therefore, close monitoring of the mother's hemodynamic status, laboratory parameters, and fetal monitoring are imperative for severe cases of PPP.

Prompt recognition and treatment of PPP is essential. In milder cases, low doses (30mg/day) of systemic corticosteroids may be sufficient. In more severe cases, higher doses of steroids or cyclosporine are both considered first line. The standard dose of cyclosporine in PPP is 2-3mg/kg/ body weight/day, as this dose has been shown to be safe in pregnant transplant patients. There are also reports utilizing narrow-band UVB, infliximab (although use is generally limited to first 30 weeks of pregnancy), systemic antibiotics, and granulocyte and monocyte adsorptive apheresis. A single case report documents the use of Ustekinumab in the treatment of recalcitrant PPP, with good outcome for mother and infant. For post-partum flares, treatments options are less constrained. Of note, cyclosporine is more controversial in breastfeeding patients, as the effect/exposure through breast milk is not clear. If our patient continued to flare on dexamethasone and cyclosporine, approval was obtained for ixekizumab. IL-17 agents have been shown to have a faster onset of action in comparison to other biologics, and have been shown to be safe and effective in treating in pustular psoriasis. There is limited safety data for these agents in pregnancy, though existing data is promising.

We present this case of severe pustular psoriasis of pregnancy necessitating multiple high-dose immunosuppressants for academic interest, and to review management options for the treatment of this challenging condition.

REFERENCES

1. Andrulonis R., Ferris L. K. Treatment of severe psoriasis with ustekinumab during pregnancy. *Journal of Drugs in Dermatology (JDD)* 2012;11(10):1240–1241
2. Egeberg A, Iversen L, Kimball AB, Kelly S, Grace E, Patel H, Xu W, Gallo G, Riedl E, Feldman SR. Pregnancy outcomes in patients with psoriasis, psoriatic arthritis, or axial spondyloarthritis receiving ixekizumab. J Dermatolog Treat. 2021 Sep 21:1-7. doi: 10.1080/09546634.2021.1976375. Epub ahead of print. PMID: 34547967
3. Falto-Aizpurua LA, Martin-Garcia RF, Carrasquillo OY, Nevares-Pomales OW, Sánchez-Flores X, Lorenzo-Rios D. Biological therapy for pustular psoriasis: a systematic review. Int J Dermatol. 2020 Mar;59(3):284-296. doi: 10.1111/ijd.14671. Epub 2019 Oct 15. PMID: 31612467
4. Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, Kahlenberg JM, Harms PW, Gudjonsson JE. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy

Clin Immunol. 2017 Jul;140(1):109-120. doi: 10.1016/j.jaci.2016.08.056. Epub 2016 Dec 31. PMID: 28043870; PMCID: PMC5494022.
5. Namazi N, Dadkhahfar S. Impetigo Herpetiformis: Review of Pathogenesis, Complication, and Treatment. *Dermatol Res Pract*. 2018;2018:5801280. Published 2018 Apr 4. doi:10.1155/2018/5801280
6. Trivedi MK, Vaughn AR, Murase JE. Pustular psoriasis of pregnancy: current perspectives. *Int J Womens Health*. 2018;10:109-115. Published 2018 Feb 26. doi:10.2147/IJWH.S125784
7. Wang WM, Jin HZ. Biologics in the treatment of pustular psoriasis. Expert Opin Drug Saf. 2020 Aug;19(8):969-980. doi: 10.1080/14740338.2020.1785427. Epub 2020 Jul 2. PMID: 32615817.

CASE 6

PRESENTERS
Brooke Cui MD; Victoria Barbosa MD, MPH; Oluwakemi Onajin MD

HISTORY OF PRESENT ILLNESS
A 58-year-old African American female presented to the dermatology clinic with a 6-year history of hair loss involving the frontal hairline and vertex scalp, sparing the eyelashes and eyebrows. She endorsed scalp pruritus and scaling. Her last braided hairstyle was approximately 20 years ago. Previous treatments included topical corticosteroid and minoxidil with no significant improvement.

PAST MEDICAL HISTORY
Psoriasis, depression, migraines

FAMILY HISTORY
No family history of hair loss

SOCIAL HISTORY
Denies history of smoking and recreational drug use.

MEDICATIONS
Alprazolam 0.5mg
Betamethasone 0.05% ointment BID prn
Cetirizine 10mg daily
Estradiol vaginal tablet twice weekly
Fluticasone 50mcg
Naproxen 500mg BID prn
Olopatadine 0.1% ophthalmic solution 1 drop to both eyes BID
Pantoprazole 40mg BID
Phentermine 37.5mg 0.5 tablet BID
Topiramate 100mg daily

ALLERGIES
Erythromycin, rash
Oxycodone, pruritus

PHYSICAL EXAMINATION
Well demarcated, erythematous patches diffusely distributed on the scalp with decreased hair density and follicle density of the frontal hairline, temporal and vertex scalp

LABORATORY RESULTS
Complete blood count with differential, basic metabolic panel, iron, ferritin, thyroid stimulating hormone and vitamin D were within normal limits. Scalp dermatophyte culture grew *Trichophyton tonsurans*

IMAGING
None

DERMATOPATHOLOGY
Histopathologic analysis of punch biopsy specimens from the scalp demonstrated decreased number of follicles and sebaceous lobules and dermal fibrosis. On vertical section, fungal spores were present within the hair shaft in endothrix pattern.

DIAGNOSIS

T. Tonsurans Tinea capitis (endothrix)

TREATMENT & COURSE

The patient was started on Terbinafine 250mg daily for 6 weeks. At her follow up appointment she endorsed continued scalp pruritus and hair loss, despite completing therapy. Her scalp exam demonstrated persistent erythematous plaques and scale at the frontal hairline and vertex scalp. Given the residual scale, the patient was prescribed a second 6-week course of Terbinafine. She reported resolution of her scalp itching with no hair regrowth upon follow up. The patient declined repeat scalp biopsy. Due to concern for an underlying second diagnosis of cicatricial alopecia, the patient was started on Doxycycline 100mg twice daily for 4 months and topical Fluocinonide 0.05% ointment daily. The patient was lost to follow up.

DISCUSSION

Tinea capitis is a dermatophyte infection of the scalp, hair follicles and hair shafts. It is a common disorder in school-age children and is rare in adults. Its prevalence varies geographically and demographically. Data from 1995 to 2004 reports the prevalence of tinea capitis in the US as about 15%, however it is thought to be higher. Only 3-5% of tinea capitis occur in adults older than 20 years old with a preference for women. It is hypothesized that menopausal women may be more at risk of contracting tinea capitis due to sebaceous involution due to decreased serum estrogen levels during menopause. Other groups that are more susceptible are patients with diabetes, anemia and immunosuppression.

Dermatophytes are filamentous fungi in the genera of *Microsporum* and *Trichophyton* that infect keratinized tissue. Dermatophytes are divided into anthrophilic (human), zoophilic (animal) and geophilic (soil) fungi. The leading dermatophyte that causes tinea capitis varies geographically. The most frequent fungal species in tinea capitis in the US is *T tonsurans*.

Tinea capitis is spread by direct contact of the scalp with the dermatophyte. The dermatophytes invade the hair shaft in three ways which determines clinical presentation: endothrix (fungal spores are within the hair shaft), ectothrix (spores are outside the hair shaft) and Favus (hyphae and air spores are within the hair shaft). The endothrix type of infection is be caused by *T. tonsurans* species. This type of infection is non-fluorescent under Wood's light. Hairs often break at scalp level leaving swollen hair stubs within the follicles.

A review of the relevant literature discloses cases of adult patients with tinea capitis mimicking scarring alopecia. Ages ranged from 19 to 56-years old, some presented with two months to several years of symptoms. Clinical presentation ranged from lichen planus to tufted hair folliculitis to dissecting folliculitis. Fungal cultures were positive for *T. tonsurans*, *T. rubrum*, *M. canis* and *T. schoenleinii.* After treatment, most patients had full hair regrowth, however one case had residual cicatricial areas.

We present this case for clinical interest, expanding upon the differential diagnosis for an adult patient presenting with a clinical picture of scarring alopecia.

REFERENCES

1. Abdel-Rahman SM, Farrand N, Schuenemann E, et al. The prevalence of infections with Trichophyton tonsurans in schoolchildren: the CAPITIS study. *Pediatrics*. 2010;125(5):966-973. doi:10.1542/peds.2009-2522

2. Mirmirani P, Tucker L-Y. Epidemiologic trends in pediatric tinea capitis: a population-based study from Kaiser Permanente Northern California. *J Am Acad Dermatol*. 2013;69(6):916-921. doi:10.1016/j.jaad.2013.08.031
3. Panackal AA, Halpern EF, Watson AJ. Cutaneous fungal infections in the United States: Analysis of the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), 1995-2004. *Int J Dermatol*. 2009;48(7):704-712. doi:10.1111/j.1365-4632.2009.04025.x
4. Leung AKC, Hon KL, Leong KF, Barankin B, Lam JM. Tinea Capitis: An Updated Review. *Recent Pat Inflamm Allergy Drug Discov*. 2020;14(1):58-68. doi:10.2174/1872213X14666200106145624
5. John AM, Schwartz RA, Janniger CK. The kerion: an angry tinea capitis. *Int J Dermatol*. 2018;57(1):3-9. doi:10.1111/ijd.13423
6. Nenoff P, Krüger C, Ginter-Hanselmayer G, Tietz H-J. Mycology - an update. Part 1: Dermatomycoses: causative agents, epidemiology and pathogenesis. *J Dtsch Dermatol Ges J Ger Soc Dermatol JDDG*. 2014;12(3):188-209; quiz 210, 188-211; 212. doi:10.1111/ddg.12245
7. Hay RJ. Tinea Capitis: Current Status. *Mycopathologia*. 2017;182(1-2):87-93. doi:10.1007/s11046-016-0058-8
8. Daadaa N, Ben Tanfous A. Favus. In: *StatPearls*. StatPearls Publishing; 2021. Accessed October 15, 2021. http://www.ncbi.nlm.nih.gov/books/NBK559024/
9. Auchus IC, Ward KM, Brodell RT, Brents MJ, Jackson JD. Tinea capitis in adults. *Dermatol Online J*. 2016;22(3):13030/qt4dm9s3fh.
10. 1Gupta AK, Summerbell RC. Tinea capitis. *Med Mycol*. 2000;38(4):255-287. doi:10.1080/mmy.38.4.255.287
11. Castelo-Soccio L. Diagnosis and Management of Alopecia in Children. *Pediatr Clin North Am*. 2014;61(2):427-442. doi:10.1016/j.pcl.2013.12.002
12. Cremer G, Bournerias I, Vandemeleubroucke E, Houin R, Revuz J. Tinea capitis in adults: misdiagnosis or reappearance? *Dermatol Basel Switz*. 1997;194(1):8-11. doi:10.1159/000246048
13. Bolognia J, Jorizzo J, Schaffer J, et al. *Dermatology, 3rd Edition*. Elsevier; 2012.
14. Fuller LC, Barton RC, Mohd Mustapa MF, et al. British A ssociation of D ermatologists' guidelines for the management of tinea capitis 2014. *Br J Dermatol*. 2014;171(3):454-463. doi:10.1111/bjd.13196
15. Baroni A, Ruocco E, Aiello FS, et al. Tinea capitis mimicking tufted hair folliculitis. *Clin Exp Dermatol*. 2009;34(8):e699-e701. doi:10.1111/j.1365-2230.2009.03435.x
16. Stein LL, Adams EG, Holcomb KZ. Inflammatory tinea capitis mimicking dissecting cellulitis in a postpubertal male: a case report and review of the literature. *Mycoses*. 2013;56(5):596-600. doi:10.1111/myc.12082
17. Tangjaturonrusamee C, Piraccini BM, Vincenzi C, Starace M, Tosti A. Tinea capitis mimicking folliculitis decalvans. *Mycoses*. 2011;54(1):87-88. doi:10.1111/j.1439-0507.2009.01761.x
18. Black dot tinea capitis caused by trichophyton rubrum in an adult female presenting with cicatricial alopecia. Indian Journal of Dermatology, Venereology and Leprology. Published February 28, 2015. Accessed October 20, 2021. https://ijdvl.com/black-dot-tinea-capitis-caused-by-trichophyton-rubrum-in-an-adult-female-presenting-with-cicatricial-alopecia/
19. Poppe H, Kolb-Mäurer A, Wobser M, Trautmann A. Pitfall scarring alopecia: favus closely mimicking lichen planus. *Mycoses*. 2013;56(3):382-384. doi:10.1111/myc.12035

PRESENTERS

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CASE 1

HISTORY OF PRESENT ILLNESS

Dermatology was called to evaluate skin changes in a hospitalized 18 year-old Palestinian male with a complex medical history, including bleeding diathesis due to thrombomodulin coagulopathy (*THBD* gene mutation) and chronic kidney disease secondary to atypical hemolytic uremic syndrome (aHUS), who was day 4 post-op from a deceased donor kidney transplant. The patient's chronic medical conditions were stable at the time of transplantation. Surgery was complicated by intraoperative bleeding causing hemorrhagic shock, requiring resuscitation with multiple blood products (including fresh frozen plasma, platelets, cryoprecipitates, desmopressin and tranexamic acid). The post-operative course was complicated by immediate kidney graft failure, requiring continuous veno-venous hemodialysis (CVVHD), and deep venous thrombosis of the right iliac vein managed with inferior vena cava (IVC) filter. On day 4 post-transplant, bluish discoloration of the fingertips and toes was noted, as well as purplish discoloration of the dorsum of the nose. There were no other significant changes to his general status such as fever or respiratory distress. Recurrent aHUS was suspected and eculizumab 1200 mg had been administered.

REVIEW OF SYSTEMS

Abdominal pain and distention post-surgery, decreased urine output, easy bruising/bleeding.

Pertinent negatives included: absence of fever, chills, visual or hearing problems, seizures, dyspnea, cough, leg swelling, muscle weakness, joint pain.

PAST MEDICAL HISTORY

Thrombomodulin coagulopathy (*THBD* gene mutation) causing bleeding diathesis with prolonged prothrombin time (PT) and prothrombin thromboplastin time (PTT)–resultant complications included intracranial bleed at 4 years-old from ground level fall, and hemorrhagic shock from epistaxis at 17 years-old.
Atypical hemolytic uremic syndrome (aHUS) initial presentation 10 months ago
Chronic kidney disease, stage IV, secondary to aHUS
Acute deep vein thrombosis of iliac vein and left femoral vein s/p IVC 10 months ago
Acute pancreatitis of unclear etiology 10 months ago, currently resolved

MEDICATIONS

Eculizumab 1200 mg every other week
Penicillin V potassium 500 mg twice a day
Benzapril 10 mg daily
Ergocalciferol 1,250 mg every other week
Sevelamer carbonate 800 mg three times a day
Sodium bicarbonate 650 mg daily
Pantoprazole 40 mg daily
Folic acid/vitamin B complex and C 800 mg daily
Basiliximab 20 mg (on day 0 and 4 post-op)
Mycophenolate mofetil 1 gr twice a day
Trimethoprim-sulfamethoxazole 400 – 800 mg three times a week
Fluconazole 100 mg daily
Valganciclovir 450 mg twice a day

ALLERGIES
No known allergies

FAMILY HISTORY
Parents are both Palestinian, moved to Chicago
Mother and father are cousins
No history of bleeding diathesis or thrombosis in the family

PHYSICAL EXAM
Ill-appearing 18 year-old male in acute distress, but hemodynamically stable.
Breathing on room air. Tachycardic. Abdomen with mild distention. Anasarca present.
Significant findings on skin exam included dorsal nose with well-demarcated purpuric plaque symmetrically over almost the entire nose with no frank ulceration; cluster of petechiae with surrounding ill-defined erythema on mid-R cheek.
Distal bilateral fingers and toes with dusky bluish discoloration, cool to the touch; no evidence of frank purpura or ulceration; cap refill 2-3 seconds on fingers and toes; distal popliteal pulses intact bilaterally.

LABORATORY AND IMAGING DATA
Hemoglobin 5.8 g/dl (13.5 – 17.5)
White blood cells 11.8x10*3/µl (3.5 – 11)
Absolute neutrophils 10.71 10*3/µl (1.12 – 6.72)
Absolute lymphocytes 0.27 10*3/µl (0.9 – 3.30)
Platelets 31 10*3/µl (150 – 450 10*3)
Potassium 5.3 mmol/L (3.5 – 5.0)
Blood urea nitrogen (BUN) 58 mg/dl (7 – 20)
Creatinine 5.1 mg/dl (0.5 – 1.4)
Fibrinogen 124 mg/dl (180 – 409)
Prothrombin time (PT) 17.1s (12 – 14)
International National Ratio (INR) 1.4 (0.9 – 1.1)
Lactate dehydrogenase (LDH) 1398 U/L (116 – 245)
ADAM metallopeptidase with thrombospondin type 1 motif 13 (ADAMST-13) functional test: 65% (69 – 113), inhibitor test was within normal limits. A test with <10% activity confirms the diagnosis of Thrombocytopenic Thrombotic Purpura (TTP).
Complement 3 (C3) 69 mg/dl (83 – 188)
Complement 4 (C4) 14 mg/dl (18 – 45)
Total complement <3 U/ml (30 – 75)

Reminder of comprehensive chemical panel and coagulation studies were within normal limits.

Urinalysis and urine culture were negative for urine infection
Blood cultures did not grow any microorganism
Epstein-Bar Virus, Cytomegalovirus and Varicella Zoster serologies were negative
SARS-CoV-2 polymerase chain reaction was negative prior to admission

Chest-X-ray showed large pleural effusion with near complete atelectasis of the left lung, and new perihilar opacities.
Arterial duplex ultrasound upper extremities bilaterally: right with normal perfusion to the right upper extremity; left with normal perfusion to the left upper extremity; occlusion (100%) of the left mid/distal radial artery with evidence of intraluminal echoes consistent with arterial thrombus.

HISTOPATHOLOGY
Biopsy not performed due to increased risk of bleeding.

DIAGNOSIS
"Blue toe syndrome" affecting all digits and nose in the setting of recurrent aHUS induced by *THBD* gene mutation.

TREATMENT AND COURSE
The presence of hemolytic anemia, thrombocytopenia and worsening of kidney function was consistent with thrombotic microangiopathy due to the recurrence of aHUS, most likely triggered by transplant surgery. In addition to eculizumab (a monoclonal antibody that targets C5) every other week, plasmapheresis every other day and pulse dose methylprednisolone 1 mg/kg daily were added for the management of aHUS. An argatroban drip was started for anticoagulation. To optimize peripheral vasodilation, IV L-arginine 38 mEq twice daily and topical nitroglycerin 2% paste were added. Over the course of 2 weeks, the bluish discoloration of the fingers and toes resolved without evolving to digital necrosis, and the purpura of the dorsal nose regressed with minimal superficial necrosis. Patient was discharge on day 34 post-op and is currently on hemodialysis for chronic kidney disease.

CASE 2

HISTORY OF PRESENT ILLNESS
Dermatology was called to evaluate a hospitalized 15 year-old Black girl with a 1 week history of excruciating pain, tingling sensation and bluish discoloration of bilateral 4^{th} and 5^{th} fingertips and a 2 day history of similar symptoms involving the toes. The symptoms were not associated with cold exposure or any other skin or constitutional complaints. Past medical history was remarkable for hypercholesterolemia and asthma; the only medication was intramuscular medroxyprogesterone for dysmenorrhea. She denied use of any illicit substances.

Laboratory studies were notable for proteinuria and hematuria, but comprehensive work up, including autoimmune panel, coagulation studies, infectious work up, malignancy screening, and imaging tests did not reveal a unifying diagnosis. A kidney biopsy was pending.

Empirical treatments prior to dermatology evaluation included: intravenous methylprednisolone 0.5 mg/kg every 6 hours for presumed systemic vasculitis; one dose of aspirin 325 mg followed by enoxaparin 0.5 mg/kg/dose every 12h for presumed thrombotic disorders; to promote peripheral vasodilation, sildenafil 20mg three times a day, topical nitroglycerin 2% twice a day and one session of botulinum toxin type A injections to hands had been administered.

REVIEW OF SYSTEMS
Notable for one episode of nausea and vomiting.

Pertinent negatives included: absence of fevers, night sweats, chills, weight loss, fatigue, lymphadenopathy, vision changes, mouth sores, shortness of breath, cough, abdominal pain or diarrhea, photosensitivity, morning joint pain or stiffness, muscle weakness or bilateral lower leg swelling.

PAST MEDICAL HISTORY
Obesity, hypercholesterolemia, asthma, dysmenorrhea.

MEDICATIONS
Medroxyprogesterone intramuscular every three months (last dose received 3 months before presentation).

ALLERGIES
No known drug allergies.

FAMILY HISTORY
Maternal aunt with history of pulmonary embolism at 24 years-old.
Maternal great uncle with history of thrombosis at the age of 40 years-old.

PHYSICAL EXAM
Weight: 250 pounds, blood pressure: 160/110
Well-developed 15 year-old girl in visible pain.
Mucous membranes within normal limits. Skin exam was significant for the digits with findings as follows: Fingers and toes felt warm but were diffusely tender to light touch.
Right and left second to fourth fingers and all ten toes showed diffuse distal bluish discoloration. Distal splinter hemorrhages were present within bilateral thumbnails. Left lateral thumbnail fold had a focal well-demarcated purple plaque consistent with subcorneal hemorrhage. Pulp of the bilateral 4th and 5th of fingers demonstrated a well-demarcated purple plaque. At the base of the toes, a purplish reticular network extending to the forefoot was noted.
Bilateral plantar feet had patchy blanchable erythema. No erosions or ulcerations were present. No hypertrophy of the cuticle or loop capillaries were noted on proximal nailfolds.
Ears, nose and other acral areas were unaffected.
No other skin rash was present.

LABORATORY AND IMAGING DATA
General:
Erythrocyte sedimentation rate: 120 mm/Hr (1-44)
C-reactive protein: 14 mg/L (<5)
Haptoglobin: 206 mg/dl (51 – 192)
LDH: 424 U/L (116 – 245)
Urinalysis with +1 proteinuria and +3 hematuria
Cell blood count, Comprehensive metabolic panel, ferritin, IgG, IgM and IgA levels within normal limits.

Coagulation studies:
Fibrinogen: 440 mg/dl (180 – 409)
D-Dimer: 0.7 µg/ml (< 0.40)
Antiphospholipid syndrome (APLS) panel 1: **positive** lupus anticoagulant; **negative** cardiolipin immunoglobulin (Ig) G and IgM and beta-2 glycoprotein IgG and IgM

APLS panel 2: **negative** cardiolipin and beta 2-glycoprotein IgA, and anti-phosphatidylserine/prothrombin IgG and IgM.

The following were within normal limits: Partial Thromboplastin Time (PTT), PT, INR, homocysteine, factor VIII, anti-thrombin levels, APC resistance, protein C/S, von Willebrand factor

Rheumatology studies:
Negative: ANA, SS-A, SS-B, SM, RNP, SmRNP, double-stranded DNA, A-Jo-1, PM/SCI, SS-A 52KD, U1-RNP, U3/RNP, U2-SNRNP, KU, MDA-5, Mi-2, NXP-2, OJ, PL12-, PL-7, TIF-1, SRP, p-ANCA, c-ANCA, SCL70, anti-centromere antibodies.

Negative: Cryoglobulin, cold agglutinins and cryofibrinogen.

Infectious disease:
Negative: Respiratory virus panel, parvovirus B19 and SARS-CoV-2 polymerase chain reaction.
Negative: Serologies for Hepatitis A, B and C, syphilis, SARS-CoV-2 and antistreptolysin.
No microorganisms were detected in bacterial or fungal blood cultures.

Tests to rule out specific entities associated with thrombotic microangiopathy:
ADAMST-13 functional test: 33% (69 – 113), inhibitor test was within normal limits.
aHUS panel showed activation of both classic and alternative pathway of complement, which can be seen in several inflammatory/infectious reactions. (An activation of only alternative complement pathway would be suggestive of aHUS.)

Hematology/Oncology:
Flow cytometry did not detect a decreased expression of glycosylphosphatidylinositol-linked proteins in red blood cells ruling out paroxysmal nocturnal hemoglobinuria.
Serum protein electrophoresis showed elevated levels of globulin, alpha 1 globulin, and alpha 2 globulin. Elevation of these can be seen in acute processes. No paraproteinemia or monoclonal gammopathy detected.

Toxicologic screening:
Ethanol, barbiturates, opioids, amphetamines, cocaine, acetaminophen, salicylates, benzodiazepines, phencyclidine and cannabinoid metabolites were not detected.

Imaging studies:
Transthoracic echocardiography showed no valvular vegetations or dysfunction or cardiac shunts.
Computed tomography angiography of chest, abdomen and pelvis showed normal vasculature.
Arterial duplex ultrasound of upper and lower extremities showed normal perfusion and no evidence of occlusion of arteries.
Renal ultrasonography and renal artery duplex ultrasound showed normal kidneys without evidence of artery occlusion.

Pathology:
Kidney biopsy: Mild mesangial proliferative glomerulonephritis suggestive of infection-related glomerulonephritis or C3 glomerulonephritis.

HISTOPATHOLOGY
Skin biopsy from the base of the left great toe showed orthohyperkeratosis with full thickness necrosis in the epidermis. In the dermal papillae there was nuclear dust fragments, neutrophils, lymphocytes and histiocytes. Occlusive thrombi were present in superficial and deep blood vessels. There was no significant inflammation surrounding the blood vessels. The periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening. The Gram stain was negative for bacteria.

Direct immunoflorescence showed deposition of IgM and fibrinogen on and inside some dermal vessels as well as scant C3 in the areas.

DIAGNOSIS
Primary antiphospholipid syndrome presenting as “blue toe syndrome”

TREATMENT AND COURSE
Initial management in the acute setting was directed toward a diagnosis of aHUS vs APLS. The patient was treated with Eculizumab (loading dose of 900 mg/weekly per 4 weeks and maintenance dose of 1200 mg

every other week), heparin drip (with a target of PTT of 63 – 90s), and IV L-arginine 38 mEq twice daily. Digital pain was managed with acetaminophen, ketamine drip, hydromorphone drip, lidocaine patches and musical therapy. The heparin drip was ultimately bridged to warfarin, with INR goal of 2 – 3. The patient was discharged home on eculizumab 1200 mg infusion every other week, warfarin, pain management and wound care. Repeat APLS panel 12 weeks after the acute event was positive for lupus anticoagulant and eculizumab infusions were discontinued. The patient has significant disability due to complete necrosis of the majority of her toes and the 4th and 5th fingertips of bilateral hands.

DISCUSSION

Blue toe syndrome is characterized by the development of blue or violaceous discoloration of the digits, more commonly the toes, in the absence of obvious trauma or cold-induced injury or disorders that induce generalized cyanosis such hypoxemia or methemoglobinemia.[1] The affected digits may be painful. In the early stages, the discoloration may be blanchable with pressure or extremity elevation, indicating a sluggish flow of desaturated blood.[1] Ultimately blood flow may be completely blocked leading to purpura and necrosis. The differential diagnosis is extensive and overlaps that considered in the setting of retiform purpura (see table 1). Evaluation and management requires obtaining a comprehensive clinical history, performing a complete physical examination, and often performing skin biopsies for histological analysis and tissue cultures. [1]

Our first case involved the diagnosis of aHUS. aHUS is a subtype of thrombotic microangiopathy (TMA).[2] TMAs are rare multisystem diseases characterized by massive occlusion of small vessels by platelet-rich fibrin thrombi. They share phenotypic features such as consumptive thrombocytopenia, microangiopathic hemolytic anemia (characterized by elevated LDH, decreased haptoglobin and the presence of schistocytes on smear), and ischemic damage of several organs.[2] Thrombotic thrombocytopenic purpura (TTP) and aHUS are both types of TMA. TTP is characterized by the deficiency of ADAMST13 protease due to a genetic defect or as an acquired disorder. ADAMST13 is a protease that regulates vonWillebrand protein. aHUS results from a mutation causing deficit in regulatory or gain-of-function mediators, or acquired, due to inhibitory autoantibodies against various components of the alternative complement pathway, resulting in inappropriate activation of the pathway and excessive clotting. TTP and aHUS can be difficult to clinically differentiate, though they tend to target different organs. TTP typically affects the central nervous system and heart, while aHUS most frequently involves the kidney. The ADAMST13 assay is the laboratory method used to differentiate between the 2 conditions. Less than 10% of functionality is diagnostic of TTP, while >10% functionality suggest other etiologies of TMA.[2] A diagnosis of aHUS is confirmed by a complement assay, in which the alternative complement pathway will be abnormally activated. Next generation gene sequencing can be used for the detection of mutations that predispose to aHUS (*C3*, *CD46* (*MCP*), *CFB*, *CFH*, *CFHR1*, *CFHR3*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *THBD*, and *VTN*).[3] Patient 1 was found to have the THBD mutation which encodes thrombomodulin protein, a transmembrane protein involved in the generation of a protease that cleaves C3 and C5a.[4]

There are several pediatric case reports of digital ischemia associated with the small vessel vasculopathy that occurs in aHUS as a result of abnormal complement activation.[5–7] Eculizumab is a monoclonal antibody that blocks C5-activation and thus blocks activation of the clotting cascade. Treatment with this agent has been successful in improving digital ischemia in some cases.[4] aHUS has a 25% mortality rate; and about 50% of aHUS patients develop renal failure, These numbers have improved after the use of eculizumab for aHUS treatment. There is a significant incidence of recurrent renal failure after kidney transplant, as observed in our case.[4]

Our second case of blue toe syndrome was in the setting of antiphospholipid syndrome (APLS). APLS is an acquired systemic disorder characterized by arterial and/or venous thrombotic events. Pediatric APLS presents before the age of 18 years, most commonly between 9-14 years of age. There is no universally validated criteria for the diagnosis of pediatric APLS.[8] It has been observed that, in children, non-thrombotic

symptoms may precede overt thrombosis causing a delay in the diagnosis. The most frequent clinical presentation is lower limb thrombosis, while digital ischemia represents only 4% of the cases.[8] Initial therapy is with low-molecular-weight heparin or unfractionated heparin, followed by oral anticoagulation. Long-term anticoagulation is recommended if the lupus anticoagulant test is persistently positive.

Both of our patients received treatment with L-arginine and topical nitroglycerine paste to promote peripheral vasodilation. Both treatments increase the supply of nitric oxide, which promote relaxation of the vascular smooth muscle from small arteries.[9] Our second case also received botulinum toxin on her hands and feet. It is hypothesized that botulinum toxin block the production of reactive oxygen species preventing the activation of an opposed pathway of nitric oxide. It also increases the intracellular calcium inducing vasodilation of the arterioles.[10] L-arginine and botulinum toxin are currently treatments used for refractory Raynaud's syndrome.

We present two cases of blue toe syndrome to highlight the complexity of such cases and the need to urgently initiate aggressive therapy to avoid significant future disability, even if a final diagnosis has not yet been confirmed.

Table 1. Causes of blue to syndrome (obtained from Hirschmann JV et al).[1]

Causes of Blue toe syndrome		
Etiology		
Decreased arterial flow	Embolism	Atheroemboli Cardiac or aortic tumor Cardiac vegetations (infective endocarditis, Nonbacterial thrombotic endocarditis)
	Thrombosis	APLS Malignancy (paraneoplastic acral vascular syndrome) Thrombotic microangiopathy (thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome) Disseminated intravascular coagulation Warfarin skin necrosis
	Vasoconstrictive disorders	Acrocyanosis Perniosis Chilblains lupus erythematosus Medication-induced vasococnstriction
	Infectious and non-infectious inflammation	Syphilis Pyogenic infection Behçet's disease Other forms of vasculitis
	Other vascular obstruction	Calcific vasculopathy (Calcyphilaxis)
Impaired venous outflow	Extensive venous thrombosis	Phlegmasia cerulea dolens and venous gangrene
Abnormal circulating blood	Paraproteinemia with hyperviscosity	
	Myeloproliferative disorders	Polycythemia vera Essential thrombocytopenia
	Cryofibrinogenemia	
	Cryoglobulinemia	
	Cold agglutinins	

REFERENCES

1. Hirschmann JV, Raugi GJ. Blue (or purple) toe syndrome. *Journal of the American Academy of Dermatology*. 2009;60(1):1-20. doi:10.1016/j.jaad.2008.09.038
2. Mannucci PM, Cugno M. The complex differential diagnosis between thrombotic thrombocytopenic purpura and the atypical hemolytic uremic syndrome: Laboratory weapons and their impact on treatment choice and monitoring. *Thrombosis Research*. 2015;136(5):851-854. doi:10.1016/j.thromres.2015.09.007
3. Noris M, Bresin E, Mele C. Genetic Atypical Hemolytic-Uremic Syndrome. :26.
4. Raina R, Krishnappa V, Blaha T, et al. Atypical Hemolytic-Uremic Syndrome: An Update on Pathophysiology, Diagnosis, and Treatment. *Therapeutic Apheresis and Dialysis*. 2019;23(1):4-21. doi:10.1111/1744-9987.12763
5. Rigothier C, Delmas Y, Roumenina LT, et al. Distal Angiopathy and Atypical Hemolytic Uremic Syndrome: Clinical and Functional Properties of an Anti–Factor H IgAλ Antibody. *American Journal of Kidney Diseases*. 2015;66(2):331-336. doi:10.1053/j.ajkd.2015.03.039
6. Malina M, Gulati A, Bagga A, Majid MA, Simkova E, Schaefer F. Peripheral Gangrene in Children With Atypical Hemolytic Uremic Syndrome. *Pediatrics*. 2013;131(1):e331-e335. doi:10.1542/peds.2012-0903
7. Sathe KP, Ohri A, Mishra A, Ali U. Digital gangrene in a child with atypical hemolytic uremic syndrome associated with anti-factor H antibodies. *Indian Journal of Nephrology*. 2016;26(3):231. doi:10.4103/0971-4065.169557
8. Rosina S, Chighizola CB, Ravelli A, Cimaz R. Pediatric Antiphospholipid Syndrome: from Pathogenesis to Clinical Management. *Curr Rheumatol Rep*. 2021;23(2):10. doi:10.1007/s11926-020-00976-7
9. Curtiss P, Schwager Z, Lo Sicco K, Franks Jr. A g. The clinical effects of l_arginine and asymmetric dimethylarginine: implications for treatment in secondary Raynaud's phenomenon. *Journal of the European Academy of Dermatology and Venereology*. 2019;33(3):497-503. doi:10.1111/jdv.15180
10. Neumeister MW. The Role of Botulinum Toxin in Vasospastic Disorders of the Hand. *Hand Clinics*. 2015;31(1):23-37. doi:10.1016/j.hcl.2014.09.003

CASE 8

PRESENTERS
Umar Sheikh MD; Sarah Stein MD

HISTORY OF PRESENT ILLNESS
A 10-month-old male presented to dermatology for evaluation of a diaper rash. The family reported ongoing waxing and waning rashes in the diaper area since 2 months of age. They identified that the most recent flare of red patches on the buttocks was likely triggered by diarrhea over the past few days. They were most concerned about persistent thick white plaques located focally in the inguinal creases that had been present since 5 months of age. They described a skin care regimen which included cleaning the skin with a moist cloth, then drying the diaper area with a cool hair dryer, followed by the application of thick layers of zinc oxide paste. Numerous topical medications had additionally been used at various times through infancy, including nystatin cream, ketoconazole cream, hydrocortisone cream and betamethasone-clotrimazole cream.

PAST MEDICAL HISTORY
Full term gestation; vaginal delivery complicated by meconium aspiration requiring management in the Neonatal Intensive Care Unit for 5 days

FAMILY HISTORY
Father with history of atopic dermatitis. No family history of autoimmune conditions or recurrent infections

SOCIAL HISTORY
Lives at home with father and mother.

MEDICATIONS
Cholecalciferol (vitamin D3) supplementation

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Well appearing 10-month old in no distress with normal vital signs.
Skin exam was significant for the bilateral deep inguinal creases with ill-defined light pink plaques with overlying white keratotic coalescing gritty papules. On the buttocks and posterior inner thighs there were ill-defined beefy red patches and plaques involving predominantly the convex surfaces with fine wrinkling. There were no pustules, satellite papules or erosions. The perianal skin was clear.

LABORATORY RESULTS
Not applicable

IMAGING
Not applicable

DERMATOPATHOLOGY
Not applicable

DIAGNOSIS
Granular parakeratosis of the diaper area and concomitant irritant contact dermatitis of buttocks

TREATMENT & COURSE

The patient was diagnosed with granular parakeratosis of the diaper area and concomitant irritant contact dermatitis of the buttocks in the setting of recent change in stooling pattern. The granular parakeratosis was felt to be secondary to long term consistent use of zinc oxide based products in the skin folds. The family was instructed to minimize use of zinc oxide pastes in the deep skin crease regions. For the irritant diaper dermatitis, the family was advised to use high absorbency disposable diapers to minimize contact of skin with feces and urine and minimize use of packaged diaper wipes. Zinc oxide paste was to be used as a barrier with every diaper change, but specifically avoiding the bilateral inguinal creases. Alclometasone 0.05% ointment was prescribed for use two to three times a day for 3-4 days until the erythema resolved.

One month after the visit, communications with the family confirmed that the inguinal rash completely resolved 2-3 days after stopping the use of zinc oxide paste. The irritant diaper rash had also cleared.

DISCUSSION

Granular parakeratosis, an acquired keratotic dermatosis, was originally reported in 1991 to occur in the axillae but is now recognized in other intertriginous sites such as the groin. It is most commonly observed in adult women. Granular parakeratosis was initially associated with the use of personal hygiene products such as deodorants, used in excess or in a susceptible individual. The primary lesions are keratotic, brownish red papules that coalesce into larger, well-demarcated plaques with varying degrees of maceration. Pruritus can be a common associated finding, and irritation can also be prevalent if there are erosions or fissures. Patients may experience a flare if there is an increase in ambient temperature and sweating.[1]

In 2002, Trowers et al.[2] reported the first infant with granular parakeratosis and Patrizi[3] reported four more infants with this finding. Trowers' original case was a nine month old male with hyperpigmented, scaly flat topped papules in both inguinal folds that did not improve with over the counter 1% hydrocortisone. The patient's skin care included Desitin ointment (40% zinc oxide, vitamins A and D, lanolin, and talc). The discontinuation of Desitin was recommended, but the patient was lost to follow-up.[3] Patrizi's four cases all presented with a napkin area dermatitis characterized by asymptomatic aggregated and non-confluent brownish-red papules, covered by thick glazed scales. All four cases had spontaneous resolution within 3 months to a year. Skin care regimen was not specifically mentioned, but two of the four cases were described to be unresponsive to topical steroids and emollients.[3]

A case series of three patients published by Chang[4] demonstrated two different clinical patterns for infantile granular parakeratosis including bilateral linear plaques in the inguinal folds, and erythematous geometric plaques underlying pressure points from the diaper. A thick, flake-like scale is present in both forms and is characteristic. These authors suggested that diaper wearing plays an important role. Two of three patients in the case series had spontaneous resolution of their lesions with continued use of petrolatum or zinc oxide paste while the third patient's eruption resolved with pimecrolimus 1% cream.[4]

Akkaya et al. published a case series of seven infants with granular parakeratosis (ages 4 months to 2 years) and reported that frequent application of zinc oxide pastes preceded the development of the eruption in the inguinal folds, intergluteal area, or neck in six of the seven infants. The remaining infant had a history of excess sweating and frequent emollient use. Cessation of zinc oxide paste led to a resolution of lesions within two weeks. Avoiding frequent application of emollient creams in the remaining infant also led to resolution within two weeks.[5]

While the exact etiology of granular parakeratosis is unknown, it is hypothesized that chemical and mechanical irritation, together with a humid environment, compromises the epidermal barrier and causes

proliferation and altered maturation in predisposed individuals.[5] Zinc oxide increases epidermal turnover and can lead to disproportionate thickening of the cornified layer. Mice studies have shown that zinc oxide increases the mitotic activity of epidermal basal cells. In addition to zinc oxide's proposed antimicrobial properties, the increased activity of basal cells may also explain the enhanced wound healing seen with topical application of zinc oxide pastes.[6] Molecular studies have shown that a basic defect exists in processing profilaggrin to filaggrin in granular parakeratosis. Profilaggrin is the main component of the keratohyalin granules in the granular layer and breaks down to filaggrin in the terminal differentiation of epidermis. Filaggrin degrades keratohyalin granules and is the key protein in the formation of the epidermal barrier by serving as an adhesive matrix for the keratin filaments. Filaggrin deficiency can lead to a failure in the barrier function of the skin. Atopic dermatitis is also associated with filaggrin deficiency.[5]

Pathological descriptions of granular parakeratosis are notable for a visible retention of basophilic keratohyalin granules in the granular layer that differentiates it from ordinary parakeratosis. It additionally consists of a distinctive thickened stratum corneum compacted with increased eosinophilic staining as well as retained nuclei throughout this keratin layer creating the parakeratosis. The clinical differential diagnosis includes common causes of intertrigo such as seborrheic dermatitis, candidiasis, inverse psoriasis and intertrigo as well as Hailey-Hailey disease, Darier disease, and pemphigus vegetans. Irritant or allergic contact dermatitis also needs to be considered in some patients. A biopsy can confirm the diagnosis of granular parakeratosis. Spontaneous resolution has been observed.[1] As mentioned above, cessation of use of zinc oxide paste has been reported to lead to resolution of granular parakeratosis in infants.[7] For persistent cases, therapeutic success has been reported with topical corticosteroids, vitamin D analogues, retinoids, ammonium lactate and antifungals. Cryotherapy, oral isotretinoin and oral antifungals have also been used.

REFERENCES

1. Bolognia J,Schaffer JV, Cerroni L. Granular Parakeratosis. *Dermatology*. 4th eds. [Philadelphia]: Elsevier Saunders, 2012. 173-174.
2. Trowers AB, Assaf R, Jaworksy C. Granular parakeratosis in a child. Pediatr Dermatol. Mar-Apr 2002;19(2):146-7.
3. Patrizi A, Neri I, Misciali C, et al. Granular parakeratosis: four paediatric cases. Br J Dermatol. 2002 Nov;147(5):1003-6.
4. Chang MW, Kaufmann JM, Orlow SJ, et al. Infantile granular parakeratosis: recognition of two clinical patterns. J Am Acad Dermatol. 2004 May;50(5 Supple):S93-6.
5. Akkaya AD, Oram Y, Aydin O. Infantile granular parakeratosis: cytologic examination of superficial scrapings as an aid to diagnosis. Pediatr Dermatol. 2015; 32: 392-6.
6. Woodhouse JG, Bergfield W. Granular parakeratosis. Pediatr Dermatol. Nov-Dec 2004;21(6):684.
7. Almeshal HM. Infantile granular parakeratosis: Case report and review of the literature. Journal of Dermatology & Dermatologic Surgery. 2020. Volume 24. Issue 2. Pages 135-136.

CASE 9

PRESENTERS
Scott Blaszak MD; Oluwakemi Onajin MD; Mark D. Hoffman MD

HISTORY OF PRESENT ILLNESS
A 71-year-old female with a history of stage IV non-small-cell lung cancer (NSCLC) with intracranial metastasis and recent pneumonitis, presented to the dermatology clinic with a 2-month history of a pruritic rash, which started on her neck with subsequent spread to her face, chest, and abdomen; she also had noticed that her hands had become thickened. Prior to the development of her eruption, she had been on pembrolizumab for approximately one and a half years, but had doubled her dose two weeks before developing these skin changes. At time of initial presentation, the patient had not tried any previous therapies.

PAST MEDICAL HISTORY
Non-small-cell lung cancer, pneumonitis (possibly checkpoint-therapy-induced, without evidence of interstitial lung disease), chronic hepatitis C virus infection, chronic obstructive pulmonary disease, chronic kidney disease, and hypertension.

FAMILY HISTORY
No known personal or family history of dermatologic or autoimmune conditions.

MEDICATIONS
Pembrolizumab, glecaprevir-pibrentasvir, amlodipine, gabapentin, albuterol sulfate, and budesonide-formoterol.

REVIEW OF SYSTEMS
Pertinent positive include arthralgia of right knee.
Pertinent negatives include fevers, chills, night sweats, shortness of breath, and Raynaud's phenomenon.

PHYSICAL EXAMINATION
Numerous brown macules and infiltrated papules with fine overlying scale on the face, neck, and upper chest.

Taught shiny-appearing induration of the bilateral dorsal hands.

Well-demarcated infiltrated light brown quasi-rectangular-shaped plaques over the abdomen

LABORATORY AND IMAGING DATA
ANA – 1:320 – Homogenous [< 1:80]
Anti-dsDNA antibody – 33.9 [< 30 iU/mL]; dsDNA negative by Crithidia
Rheumatoid factor – 42 [< 14 iU/mL]
Anti-CCP antibody – 16 [< 3 U/mL]

Cytokine panel:
10 months after onset
TNF – < 10.0 [< 10.0]
IL-6 – < 5.0 [< 5.0]

13 months after onset
TNF – 21.4 [< 7.2]
IL-6 – 3.3 [< 2.0]

CBC with differential [WNL]
CMP – chronically elevated, stable creatinine; otherwise unremarkable
Anti-Ro antibody – < 0.2 [WNL]
Anti-La antibody – < 0.2 [WNL]
Anti-RNP antibody – < 0.2 [WNL]
Anti-Sm antibody – < 0.2 [WNL]
Anti-RNA Polymerase III antibody – < 10 [WNL]

SPEP/Immunofixation – No monoclonal protein detected

DERMATOPATHOLOGY
Skin biopsy demonstrated vacuolar interface with pigment incontinence and dermal sclerosis. Dermis was remarkable for a homogenized sclerotic appearance with decreased hair follicles, peri-eccrine adipocytes, and eccrine trapping. A superficial to deep perivascular and peri-eccrine infiltrate composed of plasma cells and lymphocytes was present. Colloidal iron stain revealed increased mucin within the deep dermis. Additionally, a Periodic acid-Schiff (PAS) stain was unremarkable for a thickened basement membrane zone.

Immunohistochemical stain with CD34 demonstrated loss of expression within the deep dermis.

DIAGNOSIS
Pembrolizumab-induced sclerodermatous dermatitis

TREATMENT AND COURSE
Pembrolizumab was discontinued by her oncologist, and the patient was initially managed with desonide ointment to the face and neck and fluocinonide ointment to the trunk and hands, with mild improvement of the pruritus. However, her dermatosis gradually progressed with increased thickening of the hands and persistent itch. Subsequent topical therapy included clobetasol and calcipotriene creams with only mild additional improvement.

The patient was referred to rheumatology for evaluation for any extracutaneous involvement; the workup was unremarkable. While the patient deferred management with hydroxychloroquine, she did agree to start mycophenolate mofetil 500 mg twice daily; response to this intervention awaits follow-up evaluation. Patient has remained off of treatment for NSCLC without further progression of her malignancy.

DISCUSSION
Recently, the use of immune checkpoint inhibitors, such as ipiliumab (a cytotoxic T lymphocyte-associated protein 4 inhibitor), and pembrolizumab and nivolumab (programmed cell death 1 inhibitors), have rapidly increased for the management of several cancers due to their significant clinical effects in patients with metastatic disease. However, these agents can be associated with multiple adverse effects, including immune-related adverse events (irAEs), which are the most common type of side effect.[1] Development of irAEs may limit the use of checkpoint inhibitors due to increased morbidity and mortality. Common sites of irAE involvement include the gastrointestinal and endocrine systems in addition to multiple cutaneous manifestations. Cutaneous immune-mediated adverse events have been documented to occur with a variety of clinical presentations including vitiligo, psoriasis, bullous pemphigoid, lichenoid and granulomatous reactions, erythema multiforme/Stevens-Johnson Syndrome/toxic epidermal necrolysis, and lupus erythematous. [2,3]

Cases of scleroderma-like reactions to immune checkpoint inhibitors have been more rarely reported in

the literature. Tjarks *et al.* presented a report of a patient with oligometastatic renal cell carcinoma who was placed on nivolumab therapy for his metastatic disease and demonstrated skin thickening and edema of the abdominal wall and bilateral lower extremities after approximately 8 months of therapy. Nivolumab was discontinued, however with discontinuation the patient reported no significant improvement of the skin thickening or edema. Histopathologic evaluation demonstrated thickened dermal collagen in the deep dermis with entrapment of eccrine coils and loss of peri-adnexal adipose tissue. Immunohistochemical staining for CD34 was absent throughout the dermis, demonstrating replacement of the dermal fibroblasts with collagen. Rheumatologic evaluation was remarkable for elevated erythrocyte sedimentation rate and C-reactive protein with normal antinuclear, anticentromere, antiribonucleoprotein, and anti-topoisomerase (Scl-70) antibodies. Ultimately, this patient was started on prednisone with a taper over multiple weeks and transitioned to mycophenolate mofetil and experienced gradual improvement of skin tightness and joint mobility.[1]

Additionally, Barbosa *et al.* described two similar cases of pembrolizumab-induced sclerodermatous-like changes in patients with metastatic melanoma. Patient 1 developed new-onset diffuse skin tightness after approximately 10 months of treatment with pembrolizumab, and patient 2 developed skin thickening of the hands and feet in addition to dyspnea and fatigue approximately 4 months into treatment with pembrolizumab. Histopathologic evaluation demonstrated deep dermal sclerosis with trapping of adnexal structures with minimal lymphocytic inflammation. Patient 1 discontinued pembrolizumab at the onset of cutaneous findings, and was started on prednisone, monthly intravenous immunoglobulin, and mycophenolate mofetil. Rheumatologic work-up of both patients was remarkable for elevated C-reactive protein with normal antinuclear, anticentromere, antiribonucleoprotein, and anti-topoisomerase 1 (Scl-70) antibodies. Unfortunately, patient 1 died with cause unknown. Patient 2 was started on hydroxychloroquine and prednisone with improvement of acral stiffness, and pembrolizumab was discontinued. Patient 2 noted rapid improvement of fatigue, dyspnea, and acral stiffness after discontinuation of the immune checkpoint inhibitor and continuation of hydroxychloroquine and prednisone.[4]

Histopathologic features of immune checkpoint inhibitor induced sclerodermatous dermatitis is similar to the findings of scleroderma including deep dermal sclerosis and fibrosis with eccrine trapping and loss of peri-eccrine adipocytes. Additionally, loss of CD34 expression demonstrates replacement of dermal fibroblasts with collagen.
Currently, recommendations for management of irAEs associated with immune checkpoint inhibitors vary according to the severity of the irAEs, ranging from topical emollients to topical and systemic corticosteroids and discontinuation of the immune checkpoint inhibitor. Management may also include non-corticosteroid immunosuppressive agents such as mycophenolate mofetil, infliximab, or tacrolimus.[1] These sclerodermatous changes have shown variable responses to therapeutic intervention.[4]

REFERENCES

1. Tjarks B, Kerkvliet A, Jassim A, et al. Scleroderma-like skin changes induced by checkpoint inhibitor therapy. JCP. 2018; 45:615-618.
2. Hwang S, Carlos G, Wakade D, et al. Cutaneous adverse events (AEs) of anti-programmed cell death (PD)-1 therapy in patients with metastatic melanoma: a single-institution cohort. J Am Acad Dermatol. 2016; 74:455-461.
3. Birgitte Simonsen A, Kaae J, Ellebaek E, et al. Cutaneous adverse reactions to anti-PD1 treatment – A systematic review. J Am Acad Dermatol 2020; 83:1415-1424.
4. Barbosa N, Wetter D, Wieland C, et al. Scleroderma induced by pembrolizumab: A case series. Mayo Clin Proc. 2017; 92:1158-1163.

CASE 10

PRESENTERS
Margaret Boyle MD; Mark D. Hoffman MD; Christopher R. Shea MD

HISTORY OF PRESENT ILLNESS
A 65-year-old man presented with diffuse, pruritic, concentric, polycyclic and serpiginous, scaly, pink plaques and brown patches with a wood grain pattern. These skin changes first occurred 24 years previously and had progressed over the past eight years. Ten years prior to presentation, he had a skin biopsy at an outside clinic, reportedly consistent with eczema.

PAST MEDICAL HISTORY
Possible history of benign prostatic hypertrophy

MEDICATIONS
None

PHYSICAL EXAMINATION
Innumerable polycyclic and serpiginous, scaly, pink plaques and wood-grain-pattern brown patches on his face, trunk, upper and lower extremities. Focally, both lower legs had depigmented patches with folliculocentric pigmentation. A few hyperkeratotic circular plaques were present on bilateral palms and soles. There was no lymphadenopathy.

LABORATORY DATA
The following were positive or abnormal:
LDH: 257 (116-245 U/L)

The following were negative or within normal limits:
CBC/diff, CMP, Sézary panel, KOH

IMAGING
CT chest/abdomen/pelvis: scattered symmetric mildly enlarged mediastinal/hilar/axillary lymph nodes and sclerosis involving the sternal manubrium, right iliac bone, L3 vertebral body

DERMATOPATHOLOGY
Initial shave and punch biopsy specimens demonstrated an atypical lymphoid infiltrate without definitive evidence of a T-cell lymphoproliferative process. Repeat punch biopsy specimens demonstrated superficial dermal lymphoid infiltrate and prominent epidermotropism. Epidermotropic lymphocytes were enlarged and hyperchromatic, with convoluted nuclei. Epidermotropic lymphocytes tagged along the dermal-epidermal junction and formed small intraepidermal aggregates. Immunohistochemical stains demonstrated partial (~25%) loss of CD7. The CD4:CD8 ratio was increased (~4:1). CD30 highlighted small to medium-sized lymphoid cells that that constituted ~10% of the infiltrate, some of which were epidermotropic. The findings were diagnostic cutaneous T-cell lymphoma. Insufficient tissue was available for T-cell receptor gene arrangement studies.

DIAGNOSIS
Erythema gyratum repens-like presentation of mycosis fungoides

TREATMENT & COURSE
His presentation was concerning for erythema gyratum repens (EGR)-like eruption, so he was worked up for a possible underlying malignancy versus cutaneous T-cell lymphoma, as described above. He was referred to oncology for further work-up of a possible underlying internal malignancy, but his

lymphadenopathy was thought to be reactive from his cutaneous pathology. Oncology recommended age-appropriate cancer screening, including prostate-specific antigen testing. He was prescribed triamcinolone 0.1% cream BID and terbinafine 250 mg PO daily for 14 days given reports of erythema gyratum repens-like eruptions associated with tinea. At his follow-up visit, he did not have any improvement in his findings. Given a high concern for cutaneous T-cell lymphoma, repeat biopsies were pursued and led to the diagnosis of cutaneous T-cell lymphoma.

He was referred to the dermatologic lymphoma clinic and diagnosed with stage IB (T2bNxM0B0) mycosis fungoides. He was started on methotrexate 15 mg PO weekly with daily folic acid, which was increased to methotrexate 20 mg weekly. His disease progressed and developed soft tissue infections requiring hospitalization while on methotrexate, so it was discontinued after one month of therapy. When he returned to clinic three months later, his exam was notable for rapidly worsening disease with near-erythrodermic findings and progression to at stage IIIA (T4N0M0B0). Repeat Sézary panel did not demonstrate peripheral blood involvement. He was referred to radiation oncology for urgent total skin electron beam therapy with plans to deliver a total of 12 Gy over the course of three weeks; however, when the patient presented for therapy he was unable to stand for treatment due to declining functional status. He was lost to follow-up and subsequently died.

DISCUSSION

Erythema gyratum repens is characterized by concentric, serpiginous, annular, gyrate plaques with a wood-grain appearance and scaling edge that spreads centrifugally. It tends to spare the hands, feet and face. Vesicular/bullous lesions, psoriasiform lesions, palmoplantar hyperkeratosis, and ichythyosis have been associated with the eruption. Pruritus may be present. Histopathologic features of EGR are non-specific, and include focal parakeratosis, mild hyperkeratosis, acanthosis, spongiosis, and a superficial perivascular lymphocytic infiltrate with scattered eosinophils. EGR-like eruptions associated with a dermatosis exhibit specific histopathologic findings corresponding to that specific dermatosis. Direct immunofluorescence is usually negative. EGR is usually a paraneoplastic phenomenon, most often associated with lung cancer. The pathogenesis of paraneoplastic EGR is unknown but is suspected to be an immunological mechanism. EGR-like eruptions may be idiopathic or associated with pityriasis rubra pilaris, psoriasis, ichthyosis, connective tissue disease, systemic infection (tuberculosis), drugs, or hypereosinophilic syndrome. Treatment for EGR is targeted towards the underlying disease.

Swanson et al and McCaughey et al summarized nine reported cases of EGR-like eruptions associated with MF. Four cases had a prior history of MF, and in five cases the eruption was associated with a new diagnosis of MF. One patient had underlying lung adenocarcinoma. One patient had a history of Sézary syndrome prior to the onset of the EGR-like eruption. Two patients had a prior history of large cell transformation of MF. Skin biopsies were consistent with MF in all but one case. Non-specific EGR features were present in one case. The prognosis of patients with an EGR-like eruption in the setting of MF is unclear. Two patients had clearance of the EGR-like eruption with treatment for MF. Two patients had progression of MF after onset of the EGR-like eruption, including one patient who developed Sézary syndrome.

Of the EGR-like eruptions associated with MF in the literature, skin cultures of three patients grew *Trichophyton rubrum*. EGR-like eruptions resolved with oral terbinafine in *T. rubrum*-associated cases, but MF persisted. In our case, empiric treatment with terbinafine did not result in resolution of EGR-like findings. Dermatophyte infections can coincide with MF. Some authors have hypothesized that MF is secondary to persistent cutaneous antigen stimulation such as a dermatophyte infection, and EGR-like eruptions may represent a delayed hypersensitivity reaction.

This case highlights an unusual presentation of MF and underscores the need for dermatologists to recognize this presentation of MF.

REFERENCES

1. Cerri A, Vezzoli P, Serini SM, Crosti C, Berti E, Marzano AV. Mycosis fungoides mimicking erythema gyratum repens: an additional variant? Eur J Dermatol. 2010 Jul-Aug;20(4):540-1. doi: 10.1684/ejd.2010.0992. Epub 2010 Jun 3. PMID: 20522416.
2. Holcomb M, Duvic M, Cutlan J. Erythema gyratum repens-like eruptions with large cell transformation in a patient with mycosis fungoides. Int J Dermatol. 2012 Oct;51(10):1231-3. doi: 10.1111/j.1365-4632.2010.04861.x. Epub 2011 Jul 5. PMID: 21726213.
3. Jouary T, Lalanne N, Stanislas S, Vergier B, Delaunay M, Taieb A. Erythema gyratum repens-like eruption in mycosis fungoides: is dermatophyte superinfection underdiagnosed in cutaneous T-cell lymphomas? J Eur Acad Dermatol Venereol. 2008 Nov;22(10):1276-8. doi: 10.1111/j.1468-3083.2008.02628.x. Epub 2008 Mar 7. PMID: 18331299.
4. McCaughey CD, Amarnani A, Longley BJ, Bennett DD, Wood GS. Erythema gyratum repens-like eruption in Sézary syndrome: evidence for the role of a dermatophyte. Cutis. 2019 Jun;103(6):357-360. PMID: 31348450.
5. Moore E, McFarlane R, Olerud J. Concentric wood grain erythema on the trunk. Arch Dermatol. 2008 May;144(5):673-8. doi: 10.1001/archderm.144.5.673-b. PMID: 18490600.
6. Nagase K, Shirai R, Okawa T, Inoue T, Misago N, Narisawa Y. CD4/CD8 double-negative mycosis fungoides mimicking erythema gyratum repens in a patient with underlying lung cancer. Acta Derm Venereol. 2014 Jan;94(1):89-90. doi: 10.2340/00015555-1618. PMID: 23694996.
7. Notay M, Petukhova TA, Kiuru M, Kunder CA, Hwang ST. Mycosis fungoides presenting as symmetric concentric patches mimicking figurate erythema. JAAD Case Rep. 2017 Jun 22;3(4):288-290. doi: 10.1016/j.jdcr.2017.03.013. PMID: 28702497; PMCID: PMC5484965.
8. Poonawalla T, Chen W, Duvic M. Mycosis fungoides with tinea pseudoimbricata owing to Trichophyton rubrum infection. J Cutan Med Surg. 2006 Jan-Feb;10(1):52-6. doi: 10.1007/7140.2006.00007. PMID: 17241575.
9. Rongioletti F, Fausti V, Parodi A. Erythema gyratum repens is not an obligate paraneoplastic disease: a systematic review of the literature and personal experience. J Eur Acad Dermatol Venereol. 2014 Jan;28(1):112-5. doi: 10.1111/j.1468-3083.2012.04663.x. Epub 2012 Jul 25. PMID: 22830929.
10. Swanson LA, Peters MS, Comfere NI. Concentric annular truncal eruption. JAMA Dermatol. 2020 Oct 1;156(10):1129-1130. doi: 10.1001/jamadermatol.2020.2779. PMID: 32822451.