Chicago
Dermatological
Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, April 13, 2022
Gleacher Center, Chicago

Conference Host:

COOK COUNTY HEALTH & HOSPITALS SYSTEM
CCHHS

Stroger Hospital of Cook County
Division of Dermatology
Chicago, Illinois

Program

Host: Stroger Hospital of Cook County
Wednesday, April 13, 2022
Gleacher Center, Chicago

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *All activities will take place on the 6th Floor of the Gleacher Center*
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** Slide viewing/posters – ongoing through the early morning **Welcome and Opening Comments** *Jordan Carqueville, MD - CDS President*
9:00 a.m. - 10:00 a.m.	**Morning Session** *Barsky Lecture* – "Calciphylaxis Updates in Controversies, Pathogenesis, Diagnosis and Treatment" *Arturo R. Dominguez, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:00 p.m.	**Resident Case Presentations & Discussion**
12:00 p.m. - 12:30 p.m.	**Box Lunches & visit with exhibitors**
12:30 p.m. - 1:15 p.m.	**CDS Business Meeting** *Jordan Carqueville, MD - presiding* Corporate Sponsor Presentations • UCB, Inc. – Justin Williams • Sanofi – Ramesh Candadai • Janssen BioTech – Katelyn Rowland & Paul Labron *Business meeting adjourns and clinical session resumes*
1:15 p.m. - 2:15 p.m.	**Afternoon Lecture** “Questions in infectious disease prophylaxis in immunosuppressed dermatological patients” *Arturo R. Dominguez, MD*
2:15 p.m.	**Meeting adjourns**

Guest Speaker

ARTURO DOMINGUEZ, MD

Associate Professor
UT Southwestern Medical Center
Dallas, TX

Dr. Dominguez is an Associate Professor in the Department of Dermatology and the Department of Internal Medicine at UT Southwestern Medical Center. He specializes in complex medical dermatology, autoimmune blistering diseases, teledermatology, and hospital dermatology, and he founded the inpatient dermatology consult service for UT Southwestern-affiliated hospitals.

He earned his undergraduate degree at Princeton University and his medical degree at UT Southwestern. He completed an internal medicine residency at the University of Washington School of Medicine and then a dermatology residency at UT Southwestern.

His research focuses primarily on autoimmune blistering diseases, teledermatology, inpatient dermatology, and community health education interventions. He has published a number of scholarly articles and delivered more than 50 research-related presentations. He takes part in UT Southwestern-based clinical trials to evaluate diseases such as severe cutaneous drug reactions and autoimmune blistering diseases such as pemphigus vulgaris.

Dr. Dominguez attends on the internal medicine teaching service at Parkland Hospital and is active in residency education in that department.

He is a member of the American College of Physicians and the American Academy of Dermatology.

CME Information

April 13, 2022

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 regular educational conferences in a virtual setting. Now, with the April 2022 meeting, we are very pleased to return to the in-person format with which members will be familiar.

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. Discuss the disease progression of Calciphylaxis and describe the clinical manifestations it causes.
2. List the diagnostic and treatment options which would be most effective in managing a patient with calciphylaxis.
3. Discuss infectious disease prophylaxis in immunosuppressed dermatological patients

Physician Accreditation Statement

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

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

Attendees are required to submit a CME claim form 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.

COOK COUNTY HEALTH & HOSPITALS SYSTEM
CCHHS

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Meena Manivannan
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Key location(s): abdomen, lower extremities **CASE 1**

Non-Uremic Calciphylaxis

Presented by Brigitte Frett Utter MD, MPH, MSW, Warren Piette MD, and Vesna Petronic-Rosic MD, MSc, MBA

History of Present Illness

A 48-year-old woman presented to the hospital with hypotension and painful, indurated erythema of her bilateral thighs and abdomen that had been progressing over the last four weeks. She denied any recent anticoagulant or antiplatelet use. The patient had been recently admitted for new-onset congestive heart failure with exacerbation including anasarca with a 50-pound weight-gain requiring aggressive diuresis.

Past Medical History

Asthma, bipolar I disorder, type 2 diabetes mellitus, hypertension, heart failure, iron deficiency anemia

Medications

Paliperidone, metformin, carvedilol, clonazepam, enalapril, furosemide, metformin, spironolactone, sertraline, nifedipine, albuterol

Social History

Denied alcohol and illicit drug use.

Review of Systems

Negative for fever/chills, vomiting/diarrhea, easy bruising, and bleeding
Positive for nausea and pain of abdomen and legs

Physical Exam

Skin:	Violaceous retiform purpura and mottled ecchymosis overlying ill-defined, firm subcutaneous plaques of bilateral thighs and lower abdomen Few erosions and ulcerations with heme crusting scattered in areas of involvement

Laboratory Data

WBC	13	[4.4-10.6 x 10^3 cells/μL]
Creatinine	0.6	[0.6-1.4 mg/dL]
PT	14.9	[11.3-14.5 sec]
aPTT	32.3	[23.9-35.9 sec]
INR	1.13	[0.8-1.2]
ANA	Negative	[Negative]
C3	191	[80-201 mg/dL]
C4	38	[12-42 mg/dL]
PR3-ANCA	<0.2	[0.0-0.9 IU/mL]
MPO-ANCA	<0.2	[0.0-0.9 IU/mL]
Rheumatoid Factor	<20	[<20 IU/mL]
Lupus Anticoagulant	Negative	Negative
Anti-cardiolipin	Negative	Negative
β2-glycoprotein	<15 U/mL	[<15 U/mL]
Protein C function	123%	[85-193%]
Protein S function	129%	[63-140%]
Parathyroid hormone	65.08	[12-88 mg/mL]
Calcium	9	[8.5-10.5 mg/dL]
Phosphorus	4.3	[2.5-4.5mg/dL]
Albumin	3.6	[3.8-5.2 g/dL]
Vitamin D	17	[30-100 ng/mL]

Histopathology
LEFT THIGH, PUNCH BIOPSY:
Microcalcifications in septa of the subcutaneous fat.

LEFT LEG ULCER, PUNCH BIOPSY:
Dermal and subcutaneous fat necrosis with scattered deep vascular microcalcifications. Sections of skin with epidermal necrosis and ulceration overlying dermal and subcutaneous fat necrosis in association with a mildly dense perivascular and interstitial infiltrate composed of neutrophils, lymphocytes, and histiocytes. Scattered subcutaneous small-caliber blood vessels demonstrate calcification of the tunica media (highlighted by a von Kossa stain). PAS, and AFB stains are negative for microorganisms. The Gram stain highlights gram-positive cocci within the scale crust on the surface.

Microbiology
Left leg, bacterial tissue culture: 2+ *E.coli*, 2+ *P. mirabilis,* 3+ *E. faecalis*

Radiology
CT Abdomen and Pelvis, with contrast:
Small nonspecific focus of subcutaneous fat stranding along the right lower anterior abdominal wall. Few additional small superficial skin defects noted along the right lower anterior abdominal wall. No evidence of abscess in the subcutaneous soft tissues of the abdominal wall or proximal thighs.

Diagnosis
Non-uremic calciphylaxis

Treatment and Course:
The patient was started on IV sodium thiosulfate 25 gm three times weekly while inpatient in addition to meticulous wound care with enzymatic debridement. Her wounds continued to progress with worsening retiform lesions and painful necrotic eschars. Due to concern for infection, her wounds were surgically debrided in conjunction with the Burn Service and vacuum-assisted wound closure was performed. After debridement and one month of sodium thiosulfate treatment, there were no new areas of skin involvement and her existing wounds stabilized. She was discharged home to continue wound care and complete outpatient follow up with the Dermatology and Burn Services.

Discussion
Cutaneous calciphylaxis, also known as calcific uremic arteriolopathy, is a cutaneous ischemic small vessel vasculopathy classically seen in patients with chronic kidney disease (CKD) on hemodialysis. This is a rare condition characterized by nonhealing skin ulcers thought to be caused by arterial, arteriole, and soft tissue calcification and thrombosis that leads to tissue ischemia and necrosis. Clinical manifestations include painful violaceous to erythematous plaques, subcutaneous nodules, and induration, usually with associated livedo reticularis, that then progress to necrotic ulcers and eschars. Superinfection of eschars can occur. The condition tends to favor the lower extremities, abdomen, and areas with greatest adiposity but can also include diffuse presentations. Our patient presented with typical ischemic and necrotic lesions on the thighs and abdomen.

When calciphylaxis occurs in a patient without CKD, as in our patient, it is termed non-uremic calciphylaxis. Risk factors for calciphylaxis in the absence of CKD include hyperparathyroidism, alcohol-related liver disease, warfarin administration, malignancy, connective tissue disease, prior corticosteroid use, protein C or S deficiencies, diabetes, rapid fluid loss, and hypoalbuminemia, among others. Demographic risk factors include female sex and Caucasian race. Our patient received an extensive workup for connective tissue diseases, metabolic and endocrine disorders, malignancy, and hypercoagulable states as well as a drug review from a clinical pharmacist in an effort to determine the cause of her calciphylaxis. No clear trigger was elucidated through this process. There are several case reports that cite rapid weight loss and hypotension as potential triggers for calciphylaxis, with hypotension possibly predisposing to or worsening calciphylaxis via its exacerbation of cutaneous hypoperfusion and ischemia. In our case, the patient's 50-pound weight gain in the setting of CHF followed by rapid diuresis and hypotension may have precipitated a new state of or worsened

an ongoing calciphylaxis, though the precise mechanism in her case remains unclear. She was also noted to have mild hypoalbuminemia which may have contributed.

The pathogenesis of non-uremic calciphylaxis has not been clearly elucidated but seems to include the dysregulation of multiple factors involved in calcium homeostasis including calcium, phosphate, and parathyroid hormone levels. The process appears to involve deficiencies in vascular calcification inhibitors such as matrix Gla protein, and increased activity of factors that promote bone remodeling and subsequent intravascular accumulation of calcium, such as bone morphogenetic protein-4. Localized hypercoagulability, even in the absence of an identifiable systemic hypercoagulable state, may also play a role through the action of cytokines including TNF-α, IL-1 and IL-6 which may foster local endothelial cell dysfunction/injury and coagulation via the release of tissue factor (a primary initiator of coagulation), and downstream reductions in the activity of proteins C and S and other physiologic anticoagulants.

Unlike in vessel calcification associated with atherosclerosis, where calcium deposits in the vascular intima, calcium deposition in calciphylaxis occurs mainly in the arterial media. Diagnosis is typically made based on the clinical picture in conjunction with a cutaneous biopsy, though some argue a biopsy may not be necessary if the clinical findings are convincing due to the potential for increased morbidity and poor wound healing from tissue manipulation. If a biopsy is performed, findings can include small-vessel endovascular fibrosis, vasculopathy, ischemia, calcification, panniculitis, and fat necrosis. Microcalcifications can be revealed with special stains such as von Kossa or Alizarin red. There are no consistent laboratory findings in nonuremic calciphylaxis, with only some patients presenting with elevated calcium, phosphorous, or parathyroid hormone.

Importantly, some experts have provided views to suggest that the traditional paradigm for calciphylaxis, in which calcium is the primary inciting agent, could be too narrow. Support for this concept comes from studies that show that calcification of vessels identical to that found in calciphylaxis can also be found in normal appearing skin samples without clinical evidence of calciphylaxis in both patients with ESRD and normal controls. Additionally, there appears to be a subset of patients who otherwise meet the clinical criteria for calciphylaxis but do not demonstrate typical calcification on biopsy and are labeled "subcutaneous thrombotic vasculopathy" or "calciphylaxis sine calcifications." These patients otherwise have a similar disease course and prognosis to patients with calciphylaxis.

In either case, it is clear that patients with the constellation of findings consistent with non-uremic calciphylaxis have a poor prognosis, with one study estimating a mortality rate as high as 52% at one year. The most common cause of death from this condition is sepsis. Unfortunately, we lack evidence-based treatments for nonuremic calciphylaxis. Standard supportive measures include tissue debridement, analgesia, infection control, and treatment or removal of any underlying causative factors. Some authors advocate for the use of enzymatic agents, hydrocolloid dressings, and other atraumatic debridement strategies over surgical debridement due to risk of promoting skin trauma and propagating the calciphylaxis with surgical techniques. Surgical tissue debridement was performed in this case due to concern for devitalized tissue and risk for subsequent sepsis.

Sodium thiosulfate (STS), a calcium chelating agent, has increasingly been used for the treatment of both uremic and non-uremic calciphylaxis, though data supporting its efficacy is weak and comes primarily from case reports, case series, and retrospective analyses. STS is believed to have the potential for efficacy in calciphylaxis via several mechanisms including antioxidation, local vasodilation, and chelation of intravascular and intraparenchymal calcium. Dosing of STS is not standardized but ranges from 5-25 g IV 1-5 times weekly for at least two months. A common dosing paradigm from the literature is 25g IV 3 times weekly for two or more months. Dosing and duration are adjusted based on patient tolerance of the medication and clinical response to the treatment. Adverse effects to be aware of with STS administration include anion gap metabolic acidosis, QT prolongation, and volume overload. Our patient was discharged after completing one month of therapy as it was felt that her wounds were healing appropriately, her overall clinical picture was improving, and she no longer met inpatient criteria. Other treatments used for non-uremic calciphylaxis include: (i) bisphosphonates, which are typically used in patients who have a co-occurring hypercalcemia, (ii) cinacalcet, which is typically used in patients who have a co-occurring hyperparathyroidism, and (iii)

phosphate binders such as sevelamer in patients with hyperphosphatemia. There is no high-quality data to support the use of any of these treatments.

In summary, non-uremic calciphylaxis is a rare ischemic vasculopathy where patients present with painful areas of ischemia, ulceration and necrosis. Diagnosis can be made on the basis of clinical suspicion, often paired with a cutaneous biopsy that demonstrates vasculopathy, ischemia, and calcifications. A wide range of causes are implicated in triggering this condition and patients warrant an extensive workup when diagnosed with non-uremic calciphylaxis if an inciting factor is not clear at presentation. The pathogenesis of this condition is not clear and remains an area of active debate. Supportive care, including local wound care, is the mainstay of treatment, with IV STS also being increasingly trialed as a therapeutic modality.

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Key location(s): Eyelid **CASE 2**

Neoadjuvant Pembrolizumab for Sebaceous Carcinoma in Muir-Torre Syndrome

Presented by Elena Gonzalez Caldito MD, and Aleksandar L. Krunic MD

History of Present Illness

58-year-old male with Muir-Torre syndrome (MTS) and sebaceous carcinoma (SC) of the inferior eyelid was referred to Dermatology for Mohs micrographic surgery and full-body skin exam.

Past Medical History

Colorectal cancer treated with right hemicolectomy at outside hospital in 2003
Co-occurring clear cell carcinoma of left kidney with second de novo colon adenocarcinoma treated with radical nephrectomy and subtotal colectomy in 2021

Medications

Ferrous sulfate, docusate-senna

Review of Systems

No vision changes

Physical Exam

Non-skin:	Extraocular movements intact
Skin:	Right medial canthus and extending to the inferior eyelid with 2 x 1 cm ulcerated and necrotic tumor

Histopathology

RIGHT EYELID, INCISIONAL BIOPSY:
Proliferation of atypical sebocytes in lobules extending from the epidermis into the dermis. Some tumor cells show abundant clear to vacuolated cytoplasm. Mitotic figures frequently observed. Tumor necrosis and focal stromal invasion were appreciated, features were consistent with sebaceous carcinoma.

Diagnosis

Sebaceous carcinoma of the eyelid in the setting of Muir-Torre syndrome

Treatment and Course

The initial plan was Mohs micrographic surgery followed by post-excision repair by oculoplastic surgery. Unfortunately, the patient was lost to follow-up for three months, and on his return visit, the tumor had massively enlarged to 5 cm and was interfering with his vision. At that time, considering the size of the lesion and the potential substantial anatomic defect with Mohs, neoadjuvant chemotherapy prior to surgery was planned. In conjunction with medical oncology, the patient was started on off-label pembrolizumab 400 mg infusion every 6 weeks. The patient tolerated pembrolizumab well, and after just one dose, the tumor had decreased to 1/3 of the pretreatment size. Mohs surgery was then performed and oculoplastic surgery assisted in eyelid reconstruction with an advancement flap. The patient continued to receive pembrolizumab infusion 400 mg every six weeks without development of new lesions at his last clinic visit.

Discussion

We present a novel use of pembrolizumab as neoadjuvant therapy for periorbital sebaceous carcinoma in a patient with Muir-Torre syndrome (MTS). This therapy successfully minimized the size of the eyelid tumor before Mohs surgery, allowing for a better cosmetic and functional outcome.

Neoadjuvant chemotherapy is often used before surgical management of large tumors for tissue preservation. Commonly used chemotherapies such as 5-fluorouracil or carboplatin have not shown survival benefit in patients with microsatellite instability. PD-1 inhibitors are FDA approved for the treatment of solid tumors in patients with underlying microsatellite instability. Pembrolizumab is a highly selective humanized monoclonal

antibody that inhibits the PD-1 receptor on T-cells and prevents PD-1 ligands from binding to them. This interaction interferes with the negative immune regulation of the PD-1 pathway and eventually reverses T-cell exhaustion and induces anti-tumor responses. This mechanism is especially effective for tumors with impaired mismatch repair mechanisms and high levels of microsatellite instability, such as patients with MTS. Accumulation of mutations in cancer-related genes leads to the generation of neoantigens, which stimulate the anti-tumor immune response of the host. Hence, pembrolizumab increases the potential for immune system recognition by blocking the PD-1 pathway.

Literature is scarce regarding the use of pembrolizumab for the treatment of sebaceous carcinoma, especially in the setting of MTS. Pembrolizumab may be a potential therapeutic option for sebaceous carcinoma, especially in patients with MTS. While this case offers insight into the promising use of pembrolizumab as neoadjuvant therapy for locally advanced sebaceous carcinoma, further research needs to be conducted. Furthermore, the optimal number of doses of pembrolizumab needs to be elucidated—as our patient had a notable response after one dose, it is unclear how long the treatment should last to produce mortality benefit or prevent the development of new malignancies.

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Key location(s): Various **CASE 3**

Vasculitides in the setting of Systemic Lupus Erythematosus

Presented by Tina Hsu MD and Vesna Petronic-Rosic MD, MSc, MBA

Case 1:

History of Present Illness

A 53-year-old man presented with an asymptomatic rash of the head and trunk that had been present for two years.

Past Medical History

Non-Hodgkin lymphoma (diagnosed in 2015) s/p chemotherapy and in remission

Medications

None

Review of Systems

Negative for fevers, chills, mucosal ulceration, malar rash, photosensitivity, arthralgias, Raynaud phenomenon, abdominal pain, nausea, emesis, diarrhea, constipation, hematuria.
Positive for dyspnea, productive cough, and unintentional weight loss of 7 kg.

Physical Exam

HEENT:	No cervical, axillary, or inguinal lymphadenopathy
Skin:	Many scattered, depressed, indurated and hyperpigmented 1-2 cm plaques on the temporal and occipital scalp, forehead, cheeks, and 0.5-0.8 cm uniform plaques on the chest

Laboratory Data

WBC	3.6 x 10^3 cells/μL	[4.4-10.6 x 10^3 cells/μL]
Urinalysis	100+ protein	[Negative]
ANA	Positive	[Negative]
ANA pattern	Speckled	[Negative]
ANA titer	>1:160	[<1:160]
Anti-dsDNA	>300	[0-4]
Anti-Smith	>8	[0.0-0.9]
Anti-RNP	>8	[0.0-0.9]
Anti-SSA	2	[0.0-0.9]
Anti-SSB	<0.2	[0.0-0.9]
C3	<50	[88-201]
C4	6	[16-47]
RF	Negative	[Negative]
PR3-ANCA	<0.2	[0.0-0.9]
MPO-ANCA	<0.2	[0.0-0.9]
Anti-cardiolipin	Positive	[Negative]
Anti-B2-glycoprotein	Positive	[Negative]
Hepatitis A-C panel	Negative	[Negative]

Histopathology

RIGHT CHEST, PUNCH BIOPSY:
Atrophic epidermis, vacuolar interface changes, and a thickened basement membrane. There was a superficial and deep perivascular, periadnexal, and perineural lymphoplasmacytic infiltrate with increased mucin in the dermis. A granulomatous vasculitis of medium-sized blood vessels at the junction of the dermis and subcutaneous fat was present. Gram, Fite, AFB, and treponemal stains were negative.

Microbiology

Blood, M. tuberculosis PCR: Negative

Sputum, AFB: Negative
Urine, Legionella: Negative
Urine, Histoplasma: Negative
Urine, Blastomyces: Negative

Radiology
CT Chest: patchy bilateral ground-glass opacities and axillary, mediastinal, and bilateral hilar lymphadenopathy
Bronchoscopy: chronic inflammation with interstitial fibrosis; lymph node biopsies were negative for malignancy

Diagnosis
Granulomatous vasculitis in the setting of systemic lupus erythematosus

Treatment and Course
The patient was started on prednisone 60 mg PO QD with rapid improvement of his systemic symptoms. On two-week follow-up, anti-dsDNA had decreased from >200 to 61, and levels of C3 and C4 had increased. Mycophenolate mofetil 500 mg PO BID was introduced as a steroid-sparing agent with sustained improvement.

Case 2:
History of Present Illness
A 35-year-old woman presented with a rash of the lower extremities that had been present for eight months. The lesions were initially tender to palpation and later became pruritic.

Past Medical History
Cutaneous lupus erythematosus (discoid lupus erythematosus on face diagnosed in 2017, subacute cutaneous lupus erythematosus on chest diagnosed in 2017), systemic lupus erythematosus (initially presented in 2015)

Medications
Hydroxychloroquine 400 mg PO QD alternating with 200 mg PO QD

Review of Systems
Negative for fevers, chills, malar rash, photosensitivity, arthralgias, Raynaud phenomenon, dyspnea, dysphagia, abdominal pain, diarrhea, constipation, or hematuria
Positive for fatigue

Physical Exam

Skin:	Glabella with annular pink thin plaque Bilateral legs with >20 hyperpigmented circular macules and patches (left leg extending up to mid-thigh); few lesions with subtle nodularity and overlying faint erythema; no atrophy noted

Laboratory Data

WBC	3.5 x 10^3 cells/μL	[4.4-10.6 x 10^3 cells/μL]
ESR	10	[0-23]
Urinalysis	Negative for blood, protein, RBC casts	[Negative] [Negative]
ANA	Positive	
Anti-dsDNA	<1	[0-4]
Anti-Smith	1.5	[0.0-0.9]
Anti-RNP	0.6	[0.0-0.9]
Anti-SSA	0.2	[0.0-0.9]
Anti-SSB	0.2	[0.0-0.9]
C3	93	[88-201]
C4	16	[16-47]

PR3-ANCA	<0.2	[0.0-0.9]
MPO-ANCA	<0.2	[0.0-0.9]
Hepatitis A-C panel	Negative	[Negative]

Histopathology
LOWER LEFT LEG, PUNCH BIOPSY:
Thickening of the wall of a blood vessel with a focally dense infiltrate of neutrophils, lymphocytes, eosinophils, and plasma cells. Leukocytoclasis was prominent. These changes were segmental but involved the entire circumference of the artery. There was minimal extension of the infiltrate into the surrounding subcutaneous fat. The PAS and colloidal iron stains were unremarkable.

Microbiology
N/A

Radiology
N/A

Diagnosis
Cutaneous polyarteritis nodosa in the setting of systemic lupus erythematosus

Treatment and Course
Upon returning to clinic, most of her nodules had resolved with post-inflammatory hyperpigmentation and were no longer tender or pruritic. She denied the development of any new lesions. She was continued on hydroxychloroquine 400 mg PO QD alternating with 200 mg PO QD with sustained improvement.

Case 3:
History of Present Illness
A 21-year-old woman with a four-year history of bilateral ankle pain and intermittent lower extremity edema presented with multiple tender nodules of the lower extremities.

Past Medical History
Hypothyroidism

Medications
Levothyroxine 100 mcg PO QD

Review of Systems
Negative for fevers, chills, malar rash, photosensitivity, Raynaud phenomenon, dyspnea, dysphagia, abdominal pain, diarrhea, constipation, or hematuria.
Positive for bilateral ankle pain.

Physical Exam
Skin: Distal lower extremities with 1+ pitting edema and soft tissue swelling around the lateral>medial malleoli with overlying erythema

Laboratory Data

WBC	2.3 x 10^3 cells/μL	[4.4-10.6 x 10^3 cells/μL]
Urinalysis	100+ protein	[Negative]
ANA	Positive	[Negative]
ANA pattern	Homogenous	[Negative]
ANA titer	>1:160	[<1:160]
Anti-dsDNA	238	[0-4]
Anti-Smith	2.7	[0.0-0.9]
Anti-RNP	2.6	[0.0-0.9]
Anti-SSA	0.7	[0.0-0.9]
Anti-SSB	<0.2	[0.0-0.9]

C3	54	[88-201]
C4	6	[16-47]
CRP	10.95	[0.0-0.5]
PR3-ANCA	<0.2	[0.0-0.9]
MPO-ANCA	>8	[0.0-0.9]
Anti-cardiolipin	Negative	[Negative]
Anti-B2-glycoprotein	Positive	[Negative]
Hepatitis panel	Negative	[Negative]

Histopathology
LEFT DORSAL FOOT, INCISIONAL BIOPSY:
There is a substantially thickened and fibrotic dermis. Small and medium sized vessels in the dermis and at the junction with the subcutaneous fat had a tight, dense perivascular lymphoplasmacytic infiltrate. Small vessels in the superficial dermis had fibrin thrombi, degenerative changes of the vessel wall, and numerous extravasated red blood cells. Fibrin thrombi were also present within what appear to be lymphatic spaces. Within the inflammatory cell infiltrate, plasma cells dominated, comprising about 80% of all cells. In block B, in addition to the vascular changes noted above, there was dense perineural lymphoplasmacytic infiltration. The colloidal iron highlighted greatly increased mucin within the dermis and extending into the subcutaneous fat. PAS, Gram, AFB, and Fite stains were negative for microorganisms in all blocks. Staining for T. pallidum was negative, as well.

Microbiology
N/A

Radiology
N/A

Diagnosis
Plasma cell-dominant small and medium vessel vasculitis in the setting of systemic lupus erythematosus

Treatment and Course
The patient was initially treated with hydroxychloroquine 200 mg PO BID and prednisone 30 mg PO QD. Mycophenolate mofetil 1000 mg PO BID was introduced as a steroid-sparing agent with partial improvement, decreased pain and no new lesions.

Discussion
Vasculitis is not an uncommon complication of systemic lupus erythematosus (SLE), with an estimated prevalence of 11% to 36%.[2] Cutaneous small vessel vasculitis is the most common form of vasculitis in patients with SLE. Vasculitic lesions in SLE typically present with palpable purpura, petechiae, livedo reticularis, or ulcerations.[3] Leukocytoclastic vasculitis, which is characterized by fibrinoid changes in the vessel walls composed of immunoglobulin and complement, is the most common histopathologic finding.[3] In a cohort study of 540 SLE patients with vasculitis, cutaneous manifestations were the main clinical presentation in 89% of patients, with 86% of these patients presenting with small vessel vasculitis and 14% presenting with medium vessel vasculitis.[2] Moreover, patients with small vessel vasculitis almost always presented with cutaneous lesions, and were easily clinically distinguishable from patients with medium vessel vasculitis, who predominantly had visceral involvement rather than cutaneous lesions.[3]

Granulomatous cerebral small vessel vasculitis associated with SLE has previously been described in one case report, as have pleural granulomas.[2] However, no cases of cutaneous granulomatous vasculitis in SLE have been previously reported in the literature, and we present case 1 for clinicopathologic interest. Granulomatous medium- or large-vessel vasculitis is not thought to be a feature of SLE, though it can rarely be seen in sarcoidosis, some ANCA-associated vasculitides, and lymphoproliferative disorders, primarily lymphoma.[6] Although our patient had a distant history of non-Hodgkin lymphoma, he had been successfully treated with chemotherapy and in remission for four years, with multiple negative post-treatment PET/CT scans, as well as negative lymph node biopsies during this hospitalization. Our patient did not meet diagnostic criteria for sarcoidosis, and skin biopsy did not demonstrate any granulomas. The patient also had negative ANCAs,

which have an estimated 90% positivity rate in granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Additionally, without the glomerulonephritis that would be expected in GPA or the asthma and eosinophilia that would be expected in EGPA, SLE and ANCA-associated vasculitis overlap syndrome was not likely.[5] Our patient also denied joint pain and had a negative RF, excluding rheumatoid arthritis. Although polyarteritis nodosa (PAN) can cause a granulomatous medium-vessel vasculitis, the consulting nephrology service declined to perform additional studies such as renal angiogram or renal biopsy given their high suspicion for SLE.

Cutaneous PAN (cPAN), a subset of systemic PAN, is a type of vasculitis affecting mostly medium-sized vessels in the skin.[4] Systemic PAN may also affect the gastrointestinal tract, nervous system, and kidneys, and patients with cPAN should be monitored for progression to systemic PAN. The diagnosis of cPAN is generally made by a combination of physical examination, biopsy, and exclusion of other types of vasculitis or systemic involvement. Biopsy of cPAN demonstrates necrotizing inflammation of the medium sized vessels. As discussed above, cutaneous medium vessel vasculitis, rather than small vessel vasculitis, is very rare in SLE, and we present case 2 for clinicopathologic interest.

Plasma cell-dominant vasculitis, as demonstrated in case 3, has not been previously reported in conjunction with SLE, though small-vessel vasculitis with prominent IgG4 positive plasma cell infiltrates has been reported in one case of a patient with systemic IgG4-related disease involving the muscle, nerves, and kidneys.[1] However, other than this case, a similar pathology comprising of a cutaneous small- and medium-sized vessel vasculitis with a predominantly plasma cell infiltrate, was not found. Our patient had no evidence of IgG4-related disease or plasma cell dyscrasias, and *in situ* hybridization with kappa and lambda light chain showed normal distribution and ratio. Indirectly, lymphoplasmacytic infiltrates and increased mucin may be indicative of connective tissue disease, and our case may be a unique presentation of these features.

The clinical presentation and histopathologic findings in SLE are highly variable, and we report these three distinct cases to illustrate the heterogenous types of vasculitides that may present in the setting of SLE.

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Delusions of Parasitosis

Presented by Meenakshi Manivannan MD, Joerg Albrecht MD, and Amanda Kleinman MD

History of Present Illness

A 69-year-old female presented to the clinic with a pruritic rash of her back and right shoulder. Her rash was initially treated with triamcinolone cream and resolved. Six months later, the patient returned with worsening of her rash and an associated sensation that there were "bugs crawling out of her skin." She also had recurrent cutaneous abscesses treated with doxycycline and incision and drainage. She was up to date on age-appropriate malignancy screening.

Past Medical History

Recurrent cutaneous abscesses, lung nodules
No history of psychiatric conditions

Medications

None

Social History

Former tobacco smoker, denied alcohol or illicit drug use

Review of Systems

Negative for auditory or visual hallucinations, mood changes, history of mania or depression

Physical Exam

Non-skin: Thin habitus with bony protrusions, no acute distress, alert and oriented x 3, pleasant with normal psychomotor function, non-depressed, non-anxious. Normal speech and thought pattern. Presence of mild delusional thoughts regarding insect infestation.

Skin: Right shoulder with erythematous tender nodule with seropurulent drainage
Left lower back with multiple angulated geometric pink superficial ulcerations and erosions and light pink plaques with surrounding hyperpigmentation. Scattered pink erythematous and excoriated papules

Laboratory Data

The following labs were normal:

HIV	Negative	[Negative]
ANA	Negative	[Negative]
Rheumatoid factor	<20 IU/mL	[<20 IU/ml]
C3	109 mg/dL	[88-201 mg/dL]
C4	30 mg/dL	[16-47 mg/dL]
TSH	0.438 IU/L	[0.34-5.60 IU/L]
T4	0.56 ng/dL	[0.61-1.64 ng/dL]
B12	302.5 pg/mL	[180-915 pg/mL]
Folate	12.57 ng/mL	[5.9-24.8 ng/mL]
Ferritin	39.86 ng/mL	[11-306.8 ng/mL]

Histopathology

RIGHT LATERAL BACK, PUNCH BIOSPY:
Superficial necrosis of the epidermis and focal areas of parakeratosis.

Microbiology
Buttock, bacterial culture: 1+ *S. aureus*
Blood culture: Negative

Diagnosis
Delusions of parasitosis

Treatment and Course
The patient was initially treated with gabapentin 300 mg nightly as well as triamcinolone 0.1% ointment twice daily and counseled on gentle skin care. Due to persistence of symptoms, hydroxyzine 10 mg and narrowband UVB (NbUVB) light therapy was initiated, which initially improved the pruritus and crawling sensations. After two months, however, the patient self-discontinued NbUVB treatments due to minimal symptomatic improvement. She began having frequent visits to the emergency department for self-inflicted excoriations and was eventually seen for follow-up in the dermatology clinic with a team psychiatrist. She was educated about the possibility of delusions of parasitosis and offered a trial of low dose risperidone. Due to fears about antipsychotic medication, she initially declined risperidone and was trialed on amitriptyline 10 mg PO twice daily and then naltrexone 25 mg nightly without improvement. At this point, she was agreeable to trialing risperidone and was started on 0.5 mg nightly. At follow-up, she reported significant relief of her pruritic symptoms with no adverse events from risperidone. Lesions showed clear evidence of healing and patient endorsed a feeling of "control" over her disease. Patient agreed to continue this regimen for the recommended six months with a plan to reevaluate at that time.

Discussion
Delusions of parasitosis (DoP) is a condition in which a patient presents with persistent beliefs that they are infected with a living organism, such as a parasite or worm. DoP is most commonly found in patients greater than age 45 with a greater incidence (2:1) in females than males. Patients typically present with somatic symptoms such as pruritus and dysesthesias and may or may not have evidence of a rash. Patients with DoP often fail multiple topical and antibiotic therapies and may attempt to find other causes of their symptoms. These patients often provide lengthy histories of failed attempts at self-treatment and often multiple visits to many healthcare providers and dermatologists. Many times, there is skin damage caused by obsessive cleaning or using substances/pesticides in an attempt to remove the presumed parasite. Physical exam findings do not corroborate with the patients' histories. Many times, patients may attempt to bring samples or images of the fictitious parasite. This behavior is referred to as the "matchbox sign" or "specimen sign."

DoP can be found alongside other disorders such as nutritional deficiencies, metabolic abnormalities, neurologic conditions, substance abuse, infectious etiologies and/or medication side effects. Evaluation for DoP includes a thorough past and current medical history, making sure there is no underlying infection or malignancy.

The pathophysiology of DoP is not well understood but has been hypothesized to be due to increased extracellular dopamine within the striatum of the brain. This is postulated to be due to decreased functionality of dopamine transporters leading to aberrant dopamine transport.

DoP is characterized in DSM-5 as a delusional disorder, somatic type. Patients must meet 5 diagnostic criteria including:

1. The presence of one or more delusions for greater than one month.
2. Not meeting the criteria of schizophrenia and any hallucinations the patient may have are directly related to the delusion.
3. No impaired functionality is noted, and patients do not have odd or bizarre behaviorr.
4. Only brief manic or major depressive episodes if applicable .
5. And these behaviors cannot be attributed to the effects of a substance or another medical or psychiatric condition.

Treatment for DoP first focuses on establishing a strong patient-physician relationship. These patients are often dismissed by the medical system, and as a result become wary of physicians and traditional medical care. A

neutral approach that acknowledges and validates the patient's subjective experience is recommended for improved treatment adherence and effectiveness. This approach encourages open communication through non-judgmental language and helps build trust and compliance. Patients may insist on having a biopsy performed and it may benefit the provider to perform a biopsy in an effort to support the physician patient relationship. Explaining the origin and neurochemical nature of DoP can be helpful but may not guarantee acceptance of the diagnosis. It is important to emphasize that although the medications used for treatment are officially indicated for schizophrenia, the provider is not stating that this is the patient's diagnosis. Physicians should explain to patients that while it is often difficult to delineate the cause of their symptoms, these pharmacologic therapies have been successful for many other patients with similar symptoms and presentations.

Previously, patients were treated with pimozide as a first line therapeutic agent. This practice-has fallen from favor due to adverse cardiac side effects, although pimozide remains an effective treatment. Current first line therapy for DoP consists of low dose risperidone, a second-generation antipsychotic, because of its safer side effect profiles. Risperidone therapy is typically initiated at 0.5 mg qHS and increased by 0.5 mg per month until patient has sufficiently satisfactory symptomatic improvement. Most patients typically find relief with doses between 1 and 2 mg and patients can be given a max dose of 6 mg daily. Once patients are stabilized on a dose, treatment typically continues for 6 months and then patients are reassessed to see if treatment should be continued. If symptoms persist, treatment can be continued for another six months. Treatment can possibly be stopped at 1-2 years after initiation of risperidone. Patients should be counseled regarding potential side effects of risperidone including sedation, muscle cramps, and possibly Parkinsonian tremors.

We present this case as a brief review of DoP but also to convey the need for a strong interprofessional team (Primary Care, Psychiatry, Dermatology) for the best patient outcomes. As dermatologists, it is imperative to be able to recognize these conditions and provide appropriate and supportive treatment to these patients. Patients with DoP have a significantly decreased quality of life; therefore, timely identification and treatment can greatly impact once quality of life.

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Key location(s): Generalized **CASE 5**

Generalized Edema in Dermatomyositis

Presented by Joanna Jaros MD and Shilpa Mehta MD

History of Present Illness

A 48-year-old man with no significant past medical history presented to the emergency department with a 4-month history of progressively worsening generalized swelling and muscle weakness. The swelling first began at the right upper extremity, then included the lower extremities, and finally the left upper extremity. Associated symptoms included facial darkening and intermittent facial swelling which he attributed to a past facial trauma two years ago. Of note, the patient was seen at an outside emergency department for these complaints and was prescribed furosemide and short courses of prednisone without any improvement.

Past Medical History

None

Medications

None

Allergies

No known allergies

Review of Systems

Negative for photosensitivity, nasal or oral ulcers, chest pain, shortness of breath, cloudy or frothy urine, scalp pruritus, Raynaud phenomenon, alopecia, seizure, headaches, or joint pain

Physical Exam

General:	Firm pitting edema on the head, neck, torso and extremities extending to the groin and involving the scrotum
Face:	Mottled brown to dusky red-violaceous scaling, most pronounced periorbitally
Hands:	Pink-white, depressed papules over dorsal MCPs
Nails:	Nail fold capillaroscopy revealed dilated loops with alternating vessel drop out and cuticular dystrophy
Strength:	5/5 in biceps, triceps 3/5 in quadriceps

Laboratory Data

The following labs were normal:

Creatinine	0.4	[0.6-1.4]
Urine protein:creatinine	0.17	[<0.2]
Urinalysis	Negative	[Negative]
TSH	1.492 IU/mL	[0.34-5.620 IU/mL]
T4	0.95 ng/mL	[0.61-1.64 ng/mL]
BNP	33 pg/mL	[<100 pg/mL]
AST	47 U/L	[0-40 U/L]
ALT	18 U/L	[5-35 U/L]
Albumin	4.1 g/dL	[3.8-5.2 g/dL]
Total serum protein	6.7 g/dL	[6.4-8.3 g/dL]

The following rheumatologic work up was performed:

ANA	Positive	[Negative]
ANA titer	>1:160	[<1:160]

ANA pattern	Speckled	[Negative]
C3	105 mg/dL	[88-201 mg/dL]
C4	29 mg/dL	[16-47 mg/dL]
Creatinine kinase	495 U/L	[0-163 U/L]
Aldolase	17.3 U/L	[<8.1 U/L]
Myositis specific panel	TIF-1-γ antibody >100	[0-11]
ESR	31 mm/hr	[0-24 mm/hr]
CRP	0.34 mg/dL	[0-0.50 mg/dL]

Radiology
Nerve conduction study and electromyography: proximal myopathy concerning for inflammatory or necrotizing myopathy

Histopathology
LEFT DELTOID, MUSCLE BIOPSY:
Inflammatory perifasicular myopathy most consistent with dermatomyositis.

Diagnosis
Generalized edema in dermatomyositis

Treatment and Course
Patient was worked up for other common causes of generalized edema. The patient's renal function, including urine protein:creatinine ratio, thyroid function, and liver function were normal. Additionally, his BNP, serum protein, and albumin were within normal limits.

The patient was started on 60 mg prednisone daily with a prolonged taper. Given the high positive predictive value of anti-TIF1y antibodies for malignancy-associated DM,[1] a complete screen including a positron emission tomograph (PET) scan, CT scan of the chest, abdomen, and pelvis, a colonoscopy, and an EGD were performed and unrevealing. His symptoms including his edema had improved at his five-month follow-up.

Discussion
Despite "pathognomonic" features, dermatomyositis (DM) can be a challenging diagnosis often requiring clinical, laboratory, and histological evidence. Mainetti et al. proposed a classification scheme for cutaneous findings in DM into seven types: pathognomonic (Gottron's sign and papules), characteristic (heliotrope rash, shawl sign, nail-fold changes, and scalp scaly dermatosis), compatible (poikiloderma, holster sign, scalp involvement, periorbital edema, and facial swelling), less common (vesiculobullous, necrotic, erosive and ulcerative lesions, cutaneous vasculitis manifestations, and calcinosis cutis), rare (mechanic's hands, follicular hyperkeratosis, flagellate erythema, panniculitis, mucinosis, erythroderma, and oral mucosal changes), recently-described (inverse Gottron's sign, digital tip ulcerations) and non-specific (Raynaud phenomenon).[2] Interestingly, edema in DM was not classified.

There is scant literature on DM presenting with localized or generalized subcutaneous edema. Only a handful of case reports of such cases exist in dermatologic literature, notably in association with juvenile DM and NXP-2 positivity.[3-8] The pathogenesis of localized and/or generalized edema in DM is unknown, but is thought to be related to endothelial inflammation and increased vessel permeability, possibly associated with immune complex deposition.[4] Dermal edema can rarely be observed on histological examination.[9]

Generalized and/or localized edema is a rare presentation of dermatomyositis. Other more common causes of generalized edema, including nephrotic syndrome, renal failure, liver disease, thyroid disease, protein-losing enteropathy, and heart failure, must be ruled out. In isolated limb edema, hereditary angioedema can also be considered in the appropriate clinical setting and with a suggestive family history. Additionally, venous obstruction, burns, trauma, and malignancy may also present with edema. Once these more common entities are ruled out, one should consider DM, especially in the setting of certain cutaneous and extracutaneous features as well as parallel improvement of skin findings and myopathy after initiation of immunotherapy.

Historically, NXP2-associated DM appears to be the most common subtype to present with generalized or limb edema. Interestingly, Rogers et al. found that that in 20 patients with NXP-2 positivity, peripheral edema was present in 35%.[10] Interestingly our patient presented with transcription intermediary factor 1γ (TIF-1γ) DM. A recent case series by Xu et al. described five out of eight patients with generalized edema that were positive for TIF-1-γ.[6] All patients had a deteriorating clinical course requiring high dose steroids and immunotherapy.[6]

In three case series of DM-associated edema by Milisenda et al., Chai et al., and Xu et al., many of the patients had a highly aggressive clinical course with one death from pulmonary complications.[3,6,11] It appears that most with DM and edema will require high-dose oral prednisone and immunosuppressants. Treatment resistant cases are treated with IVIG, and rituximab is an emerging potential treatment. Therefore, recognizing edema in the setting of DM is important, as it can be a presenting sign and may be utilized in the future for prognostication. We report this case to highlight a unique presentation of DM.

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Key location(s): Groin **CASE 6**

Langerhans Cell Histiocytosis with Rosai-Dorfman Disease (Mixed Histiocytosis)

Presented by Jeena Sandhu MD, David Othman MD and Vesna Petronic-Rosic MD, MSc, MBA

History of Present Illness

A 58-year-old man with a six-year history of diabetes insipidus and a three-month history of panhypopituitarism presented to John H. Stroger Hospital (JSH) with blurry vision, headaches, dizziness, and diaphoresis. An MRI of the brain revealed intracranial lesions and the patient was admitted for further work-up. Dermatology was consulted for a pruritic inguinal rash that had been present for the last two years and had been unresponsive to topical antifungals.

Past Medical History

Type 2 diabetes mellitus, hypertension, diabetes insipidus, panhypopituitarism

Medications

Desmopressin, dexamethasone, enalapril, glucagon, hydrochlorothiazide, hydrocortisone, glargine, lispro, levothyroxine, sertraline

Review of Systems

Negative for pain, bleeding, discharge, or burning in groin
Positive for mild pruritus in groin

Physical Exam

General:	Mild psychomotor retardation, NAD
Skin:	Inguinal folds with eroded, pink and light brown, thin well-circumscribed plaques with peripheral scale

Laboratory Data

The following labs were remarkable/abnormal:

Sodium	133 mEq/L	[135-145 mEq/L]
Glucose	175 mg/ml	[65-110 mg/ml]
White Blood Cell Count (WBC)	8.2 k/uL	[4.6-10.6 k/uL]
Hemoglobin (HGB)	12.5 g/dL	[12.9-16.8 g/dL]
Hematocrit (HCT)	36.8%	[38.1-49.0 %]
Neutrophil	75.0%	[45.3-74.5 %]
Lymphocytes	16.4%	[18.1-43.2 %]

Histopathology

LEFT GROIN, PUNCH BIOPSY:
The epidermis is hyperplastic and focally eroded. There are clusters and sheets of large ovoid cells with abundant eosinophilic cytoplasm and an indented or reniform nucleus in the superficial dermis. Some of the cells arein the epidermis as well. The cells are positive for CD1a, S100, and lingering. They are negative for CD68 and CD163. The PAS stain is negative for fungal organisms or basement membrane thickening.

LEFT PARIETAL MASS, CRANIOTOMY AND RESECTION:
Sections show a mixed proliferation of histiocytes with intermixed plasma cells and lymphocytes. There is multifocal emperipolesis within these histiocytes which are present in a streaming and occasionally storiform architecture. There is a second population of xanthomatous histiocytes (foamy cytoplasm). Immunohistochemical stains performed show that the histiocytes are positive for CD68, CD163, patchy variable S100, and are negative for Langerin and CD1a. CD3 and CD20 highlight scattered T- and B-lymphocytes, respectively. GFAP, synaptophysin, and neurofilament highlight background entrapped brain parenchyma. Special stains are negative for bacteria, fungi,and acid-fast micro-organisms (Gram, PAS, AFB, and FITE stains).

NEXT GENERATION SEQUENCING (NGS), GROIN PUNCH BIOPSY:
BRAF V600E

NEXT GENERATION SEQUENCING (NGS), BRAIN BIOPSY:
BRAF V600E
TET2 Y1661

Radiology
CT scan without contrast, head:
There are 3 enhancing masses within the brain, the largest is centered within the right frontal lobe/lentiform nucleus region, 4.2 x 4.7 x 3.7 cm in size. Lesions are avidly enhancing with foci of internal hypoattenuation and a few course calcifications. Smaller lesions are seen in the left frontoparietal lobe (1.3 cm) and suprasellar cistern (2.1 cm). Moderate vasogenic edema surrounds lesions. There is mass effect associated with the larger lesion in the left frontal lobe, which significantly compresses the anterior horn of the right lateral ventricle. There is mild compensatory dilation of the left lateral ventricle. Leftward midline shift measures 3 mm. Small focus of enhancement near the foramen of Magendie/obex may also represent another small mass.

MRI with and without contrast, brain:
A total of 3 intracranial masses. A circumscribed mass overlying the left posterior frontal lobe is extra-axial and could reflect a small meningioma. A second mass centered within the suprasellar cistern is inseparable from the infundibulum/hypothalamus. The relationship between the mass and the optic chiasm is difficult to discern. Metastatic disease is a possibility, as is Langerhans cell histiocytosis. The signal characteristics are atypical for a glioma or hamartoma. Large mass centered within the medial aspect of the right inferior frontal lobe, with significant surrounding vasogenic edema and mass effect resulting in partial effacement of the right lateral ventricle.

Diagnosis
Langerhans Cell Histiocytosis with Rosai-Dorfman disease (Mixed Histiocytosis)

Treatment and Course
In conjunction with the hematology service, the patient was initially treated with a dexamethasone taper. Upon discovery of his positive BRAF V600E mutation status, the patient was subsequently started on dabrafenib 150 mg BID, a BRAF inhibitor. After several months of therapy, the patient's cutaneous lesions and overall cognition improved, and repeat imaging verified that his intracranial lesions decreased in size. For the management of his resultant comorbidities, including diabetes insipidus and panhypopituitarism, the patient required multidisciplinary care with endocrinology, hematology, neurology, neurosurgery, and ophthalmology.

Discussion
The histiocytoses are a group of rare proliferative disorders that share a common CD34+ progenitor cell in the bone marrow. They are commonly classified as either Langerhans cell histiocytosis (LCH), non-Langerhans cell histiocytoses, or malignant histiocytic disorders. Among the histiocytoses, LCH is the most common histiocytic disorder, and is driven by mutations in mitogen-activated protein kinase pathway. It typically presents between the ages 1-3, although in rare cases it can present later in life. LCH can range from mild, asymptomatic, and single-organ disease to severe, progressive multisystem disease. Classic cutaneous findings consist of erythematous to brown papules and plaques on the scalp and skin folds. When there is systemic involvement, LCH commonly affects the bone, liver, lung, and pituitary.[3] Our patient presented with both cutaneous findings as well as pituitary involvement, specifically diabetes insipidus and panhypopituitarism.

In addition to his diagnosis of LCH, our patient was also found to have a concomitant non-Langerhans cell histiocytosis, Rosai-Dorfman disease (RDD). In the systemic form of RDD, as seen in our patient with brain involvement, only 10% of cases have cutaneous findings. Classic cutaneous findings when present include red to brown papules, nodules, or plaques most commonly located on the eyelids or malar areas. Non-cutaneous findings of RDD classically consist of significant lymphadenopathy, while 40% of patients can have extra-nodal involvement, affecting the soft tissue, bone, ocular region, salivary glands, upper respiratory tract, or

Key location(s): Generalized **CASE 7**

Tumor Stage Mycosis Fungoides with Large Cell Transformation

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History of Present Illness

A previously healthy 20-year-old man presented with a one-year history of a generalized pruritic eruption, keratoderma of the palms and soles, and dystrophic nails. The patient was treated by an outside dermatologist for suspected eczema with triamcinolone ointment, dicloxacillin, and methotrexate for one month. He was then treated as psoriasis with topical medications (triamcinolone and tazarotene) and a series of systemic medications over six months: cyclosporine, prednisone, methotrexate, and mycophenolate mofetil. His management was complicated by poor compliance. The patient exhibited limited improvement, prompting multiple biopsies as discussed below.

Past Medical History

He has no personal or family history of psoriasis, eczema, asthma, or allergies.

Medications

None

Review of Systems

Positive for pedal edema and arthralgias
Negative for fever, chills, changes in weight, muscle aches

Physical Exam

Non-skin:	Left occipital lymphadenopathy*
Skin:	Vertex scalp with a 2 cm asymmetric hairless patch
	Chin with a firm, smooth red-pink nodule*
	Trunk and extremities with scattered scaly plaques
	Palms and soles with thick, hyperkeratotic yellow plaques
	All 20 nails with pronounced subungual hyperkeratosis with multiple deep fissures, dystrophic nail plates, and onycholysis

*Discovered on physical exam one year after initial presentation.

Laboratory Data

CMP and CBC with no abnormalities
EIA, HTLV I/II, HIV I/II nonreactive

Histopathology

RIGHT MID-BACK, PUNCH BIOPSY:
Diagnosis: Psoriasiform dermatitis with diminished granular cell layer, overlying thin patchy mounds of parakeratosis, broad band of lymphocytes in papillary dermis extending down and around hair follicle and piloerector muscle.
Comment: The observed histopathology shows features of psoriasis, however, it is unusual that one does not see neutrophils. It is also unusual that this is accompanied by an underlying broad band of lymphocytes in the papillary dermis that extends down and around the hair follicle, including piloerector muscle. Although, one does see a diminished granular cell layer, thinning of the supra-papillary epidermal plates and elongation of the rete ridges. A panel of immunostains including: CD3/CD20, CD 4, CD 7, CD8, CD30 and CD 68 show a reactive pattern of uptake by a predominant T cell lymphoid population admixed with histiocytes. The CD8+ lymphocytes are increased in number with an approximate CD4 to CD8 ratio of 1:1.

RIGHT THIRD TOENAIL, NAIL CLIPPING:

Diagnosis: Thickened nail plate with entrapped pockets of serum and parakeratotic cellular/neutrophilic debris, and surface Gram+ cocci.
Comment: Tissue findings most consistent with psoriatic nail dystrophy.

OCCIPITAL SCALP AND MID-LOWER BACK, PUNCH BIOPSIES:
Diagnosis: CD4+ / TCRbetaF1+ T-cell lymphoma with pleomorphic features and Ki-67 proliferation index >90%.
Comment: There is a dense superficial dermal infiltrate (with sparing of the epidermis and dermal epidermal junction) that is composed of medium to large cells with prominent nucleoli and increased mitotic activity and apoptosis. By immunohistochemistry, lymphoma cells are positive for TCRbetaF1, CD3 (weak diffuse), CD4, CD2, CD5, GATA3 and BCL-6 with complete loss of CD7 and are negative for cytotoxic markers (TIA-1 and granzyme-B; expressed on background CD8 cells), EBER-ISH, CD56, and CD10. Very weak CD30 expression is seen in <10% lymphoma cells. Ki-67 proliferation index is markedly increased (> 90%). CD20 highlights background B-cells. Based on the immunophenotype, transformation of mycosis fungoides (MF) and primary cutaneous versus secondary systemic involvement by peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) are considered.

CENTRAL CHIN, PUNCH BIOPSY:
Diagnosis: Morphologically and immunophenotypically consistent with previously diagnosed CD4+/TCRbetaF1+ T-cell lymphoma with pleomorphic features and Ki-67 proliferation index >90%.
Comment: Medium to large cells with prominent nucleoli, increased mitotic activity and apoptosis in the dermis (there is relative sparing of the epidermis and a grenz zone). By immunohistochemistry, lymphoma cells are positive for CD3 (weak diffuse), CD4, and CD5, with almost complete loss of CD7 and are negative for CD8, EBER-ISH, and CD56, consistent with prior immunophenotype. Very weak CD30 expression is seen in <1% lymphoma cells. Ki-67 proliferation index is markedly increased (> 90%). CD20 highlights background B-cells. Based on the immunophenotype, transformation of mycosis fungoides (MF) and primary cutaneous versus secondary systemic involvement by peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) are considered. T-cell clonality (TCRB and TCRG) positive.

Radiology
PET, whole body:
Multiple enlarged lymph nodes with significant hypermetabolic activity identified throughout the scalp, cervical, anterior mediastinum, infraclavicular, axillary, inguinal and popliteal lymph nodes. Hypermetabolic activity identified within the upper extremities, anterior abdominal wall, and supraclavicular fat extending to the neck.

Diagnosis
Tumor stage mycosis fungoides with large cell transformation

Treatment and Course
Our medical oncology department initiated narrow band UVB (NBUVB) full body phototherapy and bexarotene therapy at dose of 300 mg/m^2/day. The patient was then referred to the Northwestern Cutaneous Lymphoma Clinic for further management, where he continued bexarotene and started total skin electron beam therapy (TSEBT) with improvement in both pruritus and cutaneous lesions. The patient found further symptomatic relief using triamcinolone ointment, hydroxyzine, and gabapentin.

Discussion
Primary cutaneous T cell lymphoma (CTCL) and its variants can loom over the diagnosis of relatively benign inflammatory skin diseases. It can have an insidious onset by mimicking chronic disorders such as eczema, psoriasis, folliculitis, pityriasis lichenoides chronica, and parapsoriasis. Moreover, CTCL can respond to the topical immunosuppressives used in the treatment of these inflammatory conditions, adding to its delayed diagnosis. It is only when cutaneous lesions persist or evolve despite treatment that we are more likely to recognize its identity.

Multiple viable, though not mutually exclusive, theories can explain the relationship between inflammatory conditions and CTCL diagnoses. The first is transformation or progression. Few cases in the literature describe

a transformation of spongiotic dermatoses and psoriasiform dermatoses into CTCL[1,10]. In the case of psoriasiform presentation and CTCL, as seen in our patient, there are several shared pathogenetic mechanisms and clinical features such as the abnormal activation of T-cells[4]. The increased immune system activation seen in psoriasis can theoretically lead to CTCL. A second thought is that psoriasis does not actually evolve into CTCL, but rather CTCL was merely mimicking the inflammatory disease. As the clinical lesions fail to respond to treatment, our suspicion for the sly imitator increases. We then become keen on CTCL's clinical and histologic features. A more punitive phrasing of this theory is that the early CTCL may have been misinterpreted as psoriasis.

These theories coexist in the "pre-CTCL stage." Repeat biopsies are required until a detectable CTCL stage is reached. Signs that should lower our threshold for biopsies include persistence of lesions despite appropriate treatment for the presumed diagnosis, changes in the appearance of lesions, new presentation of induration or nodules, and poikilodermatous or atrophic areas in sun-protected areas[12]. Repeat biopsies are suggested if initial biopsies indicate parapsoriasis and/or the presence of lymphocytic exocytosis[11]. Cutaneous lymphoma may be difficult to diagnose because it lacks clear histologic criteria and shares several features with inflammatory disorders like psoriasis and parapsoriasis. Haloed lymphocytes, exocytosis, epidermotropism, Pautrier's microabscess, large hyperconvoluted and hyperchromatic lymphocytes in the epidermis, and lymphocytes aligned within the basal layer are findings seen in histologic sections of CTCL[2].

Our patient initially demonstrated both clinical and histological features of psoriasiform dermatitis. While similar cases have been described in the literature, we must note the atypical features of this case. The patient was young, 20 years old, compared to the median age of CTCL presentation of 60 years. There are case reports in the literature that describe presentations of CTCL in similarly young patients. However, the patients in these cases endured years of immunosuppression. There is an established relationship between immunosuppressive treatment and lymphoproliferative malignancies, mainly B-cell non-Hodgkin's lymphomas associated with EBV, but includes CTCL[8]. Although our patient was treated with six months of systemic immunosuppressants, treatment courses were inconsistent which may not have resulted in significant immune suppression. Thus, the rapid onset and subsequent aggressive progression is likely an indicator of CTCL's presence from the outset. We should also note that the extent of nail dystrophy seen in our patient is not typical for nail psoriasis. The majority of nail findings in CTCL cross over with psoriasis, except for curvature (seen in CTCL) and pitting (seen in psoriasis)[9].

The initial cutaneous biopsy reflected an atypical psoriasiform dermatitis with a lack of neutrophils. Interestingly, no epidermotropism was noted on multiple reviews of the biopsy. A confounding variable was if, and for how long, the patient ceased treatment prior to biopsy due to his noncompliance. It is important to wait two weeks from the last topical corticosteroid use to biopsy dermatitis properly for CTCL, otherwise key histologic features like epidermotropism may be suppressed[5]. In our patient, the persistence of cutaneous lesions despite treatment and, soon thereafter, the eruption of a new nodule, prompted additional biopsies, which showed clear features of CTCL.

The progression from patch to tumor stage with lymph node involvement in this patient was quite rapid, within two years of his first cutaneous lesions (based on patient history). Excluding the possibility of systemic lymphoma with secondary cutaneous involvement, we look to subtype the CTCL for prognosis and management purposes. Mycosis fungoides (MF) and primary cutaneous peripheral T cell lymphoma, not otherwise specified (PCTCL-NOS) are among the most important subtypes of CTCL relevant to our patient. MF restricted to the skin exhibits an indolent progression from patch stage to infiltrated plaque and tumor stage. PCTCL-NOS can present with a solitary, red-violaceous tumor-like nodule or scattered diffuse nodules on any part of the body, which become ulcerated and infected. Rapid cutaneous dissemination and systemic involvement are key features of PCTL-NOS. Similar histological features are seen in both subtypes; however, they markedly differ in clinical behavior. In our patient, we favor a diagnosis of MF with large cell transformation. While MF usually carries an excellent prognosis, our patient exhibits an aggressive form given the rapid advancement to tumor-stage, large cell transformation, and nodal involvement. Aggressive treatment with bexarotene, TSEB therapy, and chemotherapy is warranted.

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