Chicago Dermatological Society

November 2021
Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 10, 2021
Online via Zoom

Conference Host:
Department of Dermatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Program

Host: Northwestern University
Wednesday, November 10, 2021
Online Conference

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*** "Immunotherapy of Cutaneous T-cell Lymphoma: Lessons Learned" *Alain H. Rook, MD*
9:50 a.m. - 10:00 a.m.	**Questions & Answers**
10:00 a.m. - 11:00 a.m.	**Resident Case Presentations & Discussion** *Northwestern Residents*
11:00 a.m. - 11:45 a.m.	***Guest Lecture*** "Three Decades of Pearls Regarding Cutaneous T-cell Lymphoma" *Alain H. Rook, MD*
11:45 a.m. - 11:55 a.m.	**Questions & Answers**
11:55 a.m. - 12:00 p.m.	**Closing Remarks and Announcements** *Jordan Carqueville, MD*
12:00 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS meeting will be on Wednesday, December 8th – Co-hosted by the University of Chicago
Watch for details on the CDS website: www.ChicagoDerm.org

CME Reminder . . .

If you wish to receive CME credit for today's meeting, please be sure to submit your electronic claim form *no later than this Friday, November 12 at 10:00 a.m.* After that time, we will not be able to issue credit certificates. Each attendee eligible for CME will receive an email from the CDS office immediately after the meeting with a link to the online form, with a reminder on Thursday. We will post a link to the form on the meeting webpage, as well, just in case you do not receive the email. Thank you for adhering to this important deadline!

Guest Speaker

ALAIN ROOK, MD

Emeritus Professor of Dermatology,
Perelman School of Medicine,
University of Pennsylvania
Philadelphia, PA

Dr. Alain Rook is an Emeritus Professor of Dermatology at the University of Pennsylvania, and he is associated with the Institute for Translational Medicine and Therapeutics (ITMAT). His current research focuses on immunotherapeutic approaches to cutaneous T-cell lymphoma. Dr. Rook earned his medical degree from the University of Michigan in 1975 and completed an internal medicine residency at McGill University in 1977. He also finished fellowships in nephrology at McGill in 1979 and in immunology at the National Institute of Allergy and Infectious Disease (NIH) in 1986. Dr. Rook then completed a residency in dermatology at the University of Pennsylvania School of Medicine in 1989. He is board certified in Internal Medicine (1979), Nephrology (1980) and Dermatology (2011). Dr. Rook is the author or contributor in numerous clinical articles and publications.

CME Information

November 10, 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 our regular educational conferences, but these are providing in a somewhat shorter "virtual" setting.

Target Audience

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

Learning Objectives

At the conclusion of this meeting, the participant should be able to:
1. Discuss the disease progression of cutaneous T-cell lymphoma.
2. Describe the scientific basis for immunotherapy in treatment of cancer.
3. Discuss the application of immunotherapy for treatment of cutaneous T-cell lymphoma and how this regimen has improved over time based on experience with patients.
4. List major advances in managing patients with cutaneous T-cell lymphoma over the past 30 years.

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.

Continued next page

Contact Information

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

Americans with Disabilities Act

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

Disclaimer

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

Dislosure of Unlabeled Use

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

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

DERMATOLOGY RESIDENTS

Fourth Year Med-Derm
Parul Kathuria Goyal, MD

Third Year
Spencer Ng, MD, PhD
Alvin Li, MD
Liza Siegel, MD
Laura Walsh, MD, PhD
Rachel Eisenstadt, MD (Med-Derm)

Second Year
Nicole Stefanko, MD
Zachary Solomon, MD
Victor Quan, MD
Alyce Anderson, MD, PhD
Samantha Venkatesh, MD (Med-Derm)

First Year
Yoo Jung Kim, MD
Molly Hales, MD, PhD
Taylor Erickson, MD
Edward Li, MD, PhD
Joshua Prenner, MD (Med-Derm)

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CHICAGO DERMATOLOGICAL SOCIETY **Case 1**

Presented by **Yoo Jung Kim**; MD, **Parul Kathuria Goyal**, MD; **Cuong V. Nguyen**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 57-year-old male presented to the emergency department for evaluation of altered mental status. On presentation, he was noted to have a cutaneous eruption over the palms and extensor surfaces. In December 2019, the patient had presented to an outside pulmonologist with progressive shortness of breath and poor appetite and was diagnosed with an unspecified interstitial lung disease. In January 2020, skin changes on his hands were first noted. In July 2020, he presented to Northwestern Memorial Hospital with rapidly progressed interstitial lung disease and acutely deteriorating mental status, with his wife noting profound confusion leading to inability to respond to basic questions or perform activities of daily living. Dermatology was consulted during this admission for evaluation of painful erythematous papules and digital ulcerations.

PAST MEDICAL/SURGICAL HISTORY

His past medical history was notable for asthma, Type II diabetes mellitus, and hyperlipidemia. Regarding his diagnosis of interstitial lung disease, he presented to an outside pulmonologist in December 2019; at that time, he endorsed progressive dyspnea, poor appetite, fatigue, and a 30-pound weight loss. Workup including imaging and bronchoscopy with biopsy at the time revealed a diagnosis of interstitial lung disease, unspecified subtype.

FAMILY AND SOCIAL HISTORY

The patient had no significant personal or family history of dermatologic disease. The patient previously worked as property inspector and volunteered at a bird shelter for ten years. He was a former smoker with a 10 pack-year history.

MEDICATIONS

Albuterol, budesonide-formoterol, metformin, montelukast, pravastatin, prednisone

PHYSICAL EXAMINATION

On exam, the patient was in no apparent distress but was disoriented to place and time. Faintly erythematous to violaceous plaques were visualized over the bilateral upper and lower eyelids. Thin erythematous papules were noted over the bilateral palms, prominently over the interjoint creases. Scattered erythematous papules with gray-white hyperkeratotic cores were seen over the lateral aspect of the digits. Small shallow ulcerations at the distal tips were also noted.

LABS/IMAGING

Dermatologic/rheumatologic workup:
C-reactive protein 14.6 mg/L (<10)
WBC 11.3 K/uL (4.5-10.5)
ANA 1:640 (nucleolar, speckled, and homogenous pattern)
Ferritin 4083 µg/L (24-336)
Aldolase 10.5 U/L (0-8.2)
ESR 136 mm/hour (1-20)
MyoMarker 3 profile: anti-MDA5 antibodies strongly positive at 117 units

Neurologic workup:
EEG with moderate encephalopathy with no seizure-like activity
CSF protein elevated to 97 (15-45), otherwise unremarkable
Meningitis, paraneoplastic, Creutzfeldt-Jakob, autoimmune encephalopathy panels negative

Heavy metal panel negative
Vitamin/mineral studies including zinc, copper, ceruloplasmin, folate, vitamin B12, vitamin D normal
HIV, syphilis, hepatitis serologies negative

Imaging:
CT Brain, MR Brain: unremarkable
CT Chest: Lower and peripheral lung fields with predominant reticulation, ill-defined nodular opacities, mild bronchiectasis, and areas of consolidation, suggestive of a nonspecific interstitial pneumonitis or organizing pneumonia with a possible underlying connective tissue etiology

HISTOPATHOLOGY
Punch biopsy of a palmar digit on the right hand demonstrated a pauci-inflammatory process on low power. On higher power, focal intraluminal thrombi within the mid-reticular dermis were visualized, consistent with a cutaneous vasculopathy. Basement membrane zone thickening was visualized on DPAS and increased mucin deposition was seen on colloidal iron stain, suggestive of a connective tissue process.

DIAGNOSIS
Anti-MDA5 clinically amyopathic dermatomyositis with acute encephalopathy

TREATMENT AND COURSE
Rheumatology and pulmonology were consulted and the patient was initially started on prednisone 50 mg daily and tacrolimus 1 mg twice daily. Hydroxychloroquine 300 mg daily, aspirin 81 mg daily, and pentoxifylline 400 mg twice daily were eventually added as adjunctive therapy. The patient's pulmonary disease was noted to be overall stable in the months following hospital admission with persistence of ground-glass opacities on most recent CT scan. After immunosuppressive treatment was initiated, his mental status was noted to dramatically improve. His palmar papules faded and cutaneous ulcerations resolved.

DISCUSSION
Dermatomyositis is an idiopathic inflammatory myopathy with a variety of systemic and cutaneous manifestations, leading to significant variability in clinical presentation. Cutaneous findings, pulmonary disease, muscle involvement, joint disease, and malignancy are all variably present in DM patients. Within the larger category of patients with dermatomyositis, there are myositis-specific antibody subtypes, an aspect of DM not seen with other inflammatory myopathies. Myositis-specific antibody subtypes demonstrate unique clusters of clinical features along the DM spectrum with associated phenotypes. Understanding the clinical features of these various subtypes ensures that patients at risk of a more severe cutaneous phenotype or systemic disease course receive appropriate treatment.

Clinically amyopathic anti-MDA5 dermatomyositis is a distinct subtype of dermatomyositis. The phenotype of this subtype includes interdigital ulcerations, painful palmar papules, and progressive interstitial lung disease. This subtype has been described more commonly in Asian populations and is not commonly associated with underlying malignancy. Muscle biopsies typically lack classic DM findings such as perifascicular fiber atrophy. Mortality in this population is approximately 60% at 6 months, most commonly due to rapidly progressive interstitial lung disease.

Although dermatomyositis is not classically associated with acute encephalopathy, associated neurologic manifestations such as neuromyelitis optica, CNS vasculopathy, and encephalomyelitis have been described in the literature. It has been hypothesized that these findings are potentially due to underlying microvascular injury. A parallel to lupus cerebritis, a

neuropsychiatric condition that presents with confusion and cognitive dysfunction in the setting of a CNS inflammatory response, has also been theorized. Given that our patient had an extensive negative workup for an alternative etiology of his encephalopathy as well as significant improvement once immunosuppressive therapy had been initiated, his altered mental status was favored to be related to his underlying dermatomyositis.

KEY POINTS

- Anti-MDA5 dermatomyositis is clinically amyopathic, associated with rapidly progressive interstitial lung disease, and characterized by a distinctive cutaneous phenotype including erythematous palmar papules and digital ulcerations.
- Mortality in this subtype of patients approaches 60% in 6 months, most commonly due to rapidly progressive interstitial lung disease.

REFERENCES

1. Kurtzman DJB, Vleugels RA. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: A concise review with an emphasis on distinctive clinical features. J Am Acad Dermatol. 2018 Apr; 78(4): 776-785
2. du Bois R, Fischer A. Interstitial lung disease in connective tissue disorders. The Lancet. 2012 Aug; 380: 689-98
3. DeWane M, Waldman R, Lu J. Dermatomyositis: Clinical features and pathogenesis. J Am Acad Dermatol. 2020 Feb; 82(2): 267-281
4. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, Sun L. Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. Arthritis Care and Research. 2013 Feb; (8): 1316-24
5. Okiyama N and Fujimoto M. Cutaneous manifestations of dermatomyositis characterized by myositis-specific autoantibodies. F1000Research. 2019 Nov; 8(F1000 Faculty Rev): 1951

CHICAGO DERMATOLOGICAL SOCIETY **Case 2**

Presented by **Samantha Venkatesh**, MD; **Pedram Yazdan**, MD; **Inderjit Kaur Gill**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 48–year-old male presented for evaluation and treatment of painful skin lesions over his ankles. Two years prior to presentation, he first developed tender erythematous lesions that progressively enlarged on his bilateral ankles after self-administering ipamorelin, a growth hormone secretagogue. A lesion on his left ankle was biopsied at the time and demonstrated vasculitis per patient report, but he was then lost to follow up without treatment initiation. Over the following two years, the patient developed new lesions primarily over the ankles, knees, and hands. He would intermittently self-administer steroids of unclear dosage for muscle growth and continued to inject ipamorelin twice daily. The patient presented to Northwestern Regional Medical Group Dermatology clinic for further evaluation. Repeat skin biopsy and tissue cultures were performed.

PAST MEDICAL/SURGICAL HISTORY

Attention deficit hyperactivity disorder, gastroesophageal reflux disease, obstructive sleep apnea

FAMILY AND SOCIAL HISTORY

The patient's brother had a history of diabetes. There was no family history of autoimmune disease. The patient endorsed prior marijuana and cocaine use but no active substance use.

MEDICATIONS

Amphetamine/dextroamphetamine 15 mg daily, ipamorelin subcutaneous injections (obtained online, not prescribed by a provider)

PHYSICAL EXAMINATION

Relatively symmetric pink to pink-yellow papules, plaques, and soft fibrotic papulonodules were noted over the bilateral lateral feet, ankles, patella, and elbows. No palpable cervical, axillary, or inguinal lymphadenopathy was appreciated.

LABS/IMAGING

Abnormal:
IgA 416 mg/dL (80-350)

Norma/negative:
CBC, CMP, ACE level, C3, C4, Quantiferon gold, CRP, ESR, ANCA, RF, CCP, IgG, ANA, HIV; tissue cultures without growth

HISTOPATHOLOGY

Punch biopsy revealed a dense superficial and deep perivascular and interstitial dermal infiltrate composed of neutrophils and mononuclear cells. Focal fibrinoid necrosis with perivascular fibroplasia and karyorrhexis was noted in the small vessels. An interstitial histiocytic process with some necrobiosis was also noted. There was notable perivascular, concentric, and storiform fibrosis of the dermis. Alcian blue, AFB, and GMS stains were negative. IgG4 stain was negative. CD68 highlighted histiocytes. DIF was without evidence of immune deposits.

DIAGNOSIS

Erythema elevatum diutinum

TREATMENT AND COURSE

The patient was initiated on a course of oral dapsone 25 mg twice daily which was gradually increased to 25 mg TID. He also received topical betamethasone dipropionate 0.05% ointment BID. He was counseled to avoid further hormone treatments. Clinical improvement was initially noted but the patient was unfortunately hospitalized after a motor vehicle accident complicated by liver laceration and hemoperitoneum requiring exploratory laparotomy. His dapsone has been held since this hospitalization in the setting of post-operative anemia. He is currently using topical betamethasone dipropionate 0.05% and recently started topical dapsone 7.5% gel BID.

DISCUSSION

Erythema elevatum diutinum (EED) is a rare and chronic cutaneous small vessel leukocytic vasculitis. Typical lesions are soft red to brown papulonodules which may coalesce and later become more fibrotic and yellow-brown with dyspigmentation. These are often distributed symmetrically over extensor surfaces, including the joints of the hands, feet, elbows, and knees. Less common locations have been described, including the palms, soles, and face. Though typically asymptomatic, lesions may be pruritic or have a burning sensation.

EED is thought to be caused by a complement cascade from endothelial immune complex deposition in postcapillary venules. This cascade may be triggered by chronic antigen exposure due to infections, autoimmune disease, or malignancy. Histopathology of early lesions shows a dense infiltrate of neutrophilic cells in a wedge-shaped infiltrate with fibrin deposition and leukocytoclasia in the superficial to mid-dermis. Pathology of older lesions demonstrates perivascular 'onion skin' fibrosis, intracellular lipid deposition, and capillary proliferation.

EED is typically associated with systemic conditions, including autoimmune diseases, malignancies, or infection. Autoimmune triggers include rheumatoid arthritis, ulcerative colitis, relapsing polychondritis, and systemic lupus erythematosus. Certain hematologic malignancies have been implicated as causative entities, such as paraproteinemias and other myeloproliferative disorders. EED was originally associated with streptococcal infections, though other inciting infectious causes have since been discovered. Notably, HIV has been described as an associated condition, and the presentation of EED may be the first clinical presentation of AIDS. Other viral causes include hepatitis B, hepatitis C, and human herpesvirus 6. Very few case reports have described drug-induced EED; implicated medications include anti-tuberculosis medications, cisplatin, and erythropoietin.

The first-line treatment for EED is dapsone, which acts via inhibition of neutrophil chemotaxis. No randomized trials have been performed, but dapsone was shown to be effective in 80% of 59 cases in a literature review. One case report demonstrated efficacy of topical dapsone gel as an alternative to systemic dapsone. However, in later-stage, nodular lesions, dapsone may be ineffective due to progression of fibrosis. Other alternate treatments have been described, including systemic steroids, intralesional corticosteroids, methotrexate, tetracyclines, niacinamide, colchicine, and surgical excision; these modalities have all been used as monotherapies or in combination therapies with variable success.

KEY POINTS

- EED is a rare cutaneous small vessel vasculitis that is typically associated with an underlying infectious, autoimmune, or malignant etiology.
- Drugs have rarely been implicated as potential causative agents of EED, though there have been a few case reports with this association.
- Dapsone is the first line treatment, though this may be less effective in more fibrotic lesions.

REFERENCES

1. Ahmad, S., Delarosa, M., Kleinman, W., & Ahmad, R. (2019). Primary Surgical Treatment of Erythema Elevatum Diutinum. The Journal of hand surgery, 44(6), 522-e1.
2. Bevans, S. L., Keeley, J. M., & Sami, N. (2019). Erythema Elevatum Diutinum Treated With Mycophenolate Mofetil. JCR: Journal of Clinical Rheumatology, 25(6), e93-e94.
3. Cardis, Michael A., Madeleine G. Sowash, Karen Itumeleng Mosojane, and Carrie Kovarik. "HIV-associated erythema elevatum diutinum: a case report and review of a clinically distinct variant." Dermatology online journal 24, no. 5 (2018).
4. Doktor, V., Hadi, A., Hadi, A., Phelps, R., & Goodheart, H. (2019). Erythema elevatum diutinum: a case report and review of literature. International journal of dermatology, 58(4), 408-415.
5. Frieling GW, Williams NL, Lim SJ, Rosenthal SI. Novel use of topical dapsone 5% gel for erythema elevatum diutinum: safer and effective. Journal of Drugs in Dermatology : JDD. 2013 Apr;12(4):481-484. PMID: 23652900.
6. Gubinelli E, Cocuroccia B, Fazio M, Annessi G, Girolomoni G. Papular neutrophilic dermatosis and erythema elevatum diutinum following erythropoietin therapy in a patient with myelodysplastic syndrome. Acta Derm Venereol. 2003;83(5):358-61. doi: 10.1080/00015550310003791. PMID: 14609104.
7. Momen, S. E., Jorizzo, J., & Al-Niaimi, F. (2014). Erythema elevatum diutinum: a review of presentation and treatment. Journal of the European Academy of Dermatology and Venereology, 28(12), 1594-1602.
8. Muratori, S., Carrera, C., Gorani, A., & Alessi, E. (1999). Erythema elevatum diutinum and HIV infection: a report of five cases. The British journal of dermatology, 141(2), 335-338.
9. Paugam, C., Laghmari, O., Renaut, J. J., & Barbarot, S. (2018). Rare presentation of erythema elevatum diutinum. JAAD case reports, 4(8), 824.
10. Rover, P. A., Bittencourt, C., Discacciati, M. P., Zaniboni, M. C., Arruda, L. H. D. F., & Cintra, M. L. (2005). Erythema elevatum diutinum as a first clinical manifestation for diagnosing HIV infection: case history. Sao Paulo Medical Journal, 123, 201-203.
11. Wahl, C. E., Bouldin, M. B., & Gibson, L. E. (2005). Erythema elevatum diutinum: clinical, histopathologic, and immunohistochemical characteristics of six patients. The American journal of dermatopathology, 27(5), 397-400.

Presented by **Victor Quan**, MD; **Xiaolong Alan Zhou**, MD, MSc
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 50-year-old female with a history of systemic lupus erythematosus presented for evaluation of an eruption on the face, trunk, and upper extremities present for two weeks

CHICAGO DERMATOLOGICAL SOCIETY **Case 4**

Presented by **Taylor Erickson,** MD; **Karina Vivar**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University
Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago

HISTORY OF PRESENT ILLNESS

A 17-year-old male with a history of sickle cell disease complicated by frequent vaso-occlusive episodes and avascular necrosis of the hip now s/p allogeneic stem cell transplant 08/09/2019 presented to the Lurie Children's Hospital oncodermatology clinic on 06/08/2021 (post-transplant day +669) for evaluation of new-onset skin tightness and purple discoloration. The patient reported that he was experiencing a sensation of skin 'tightness' over the bilateral arms from the elbows to the hands. His mother described seeing "tears in the veins" as well as noticing purple patches over the dorsal hands. He denied any itch or pain within the skin and was applying a gentle emollient daily.

Associated symptoms included joint pain. He first developed bilateral wrist and hip pain approximately eight months prior to presentation. He was seen by rheumatology three months prior to presentation and was noted to have several joint contractures and muscle stiffness. He was diagnosed with arthritis and started on naproxen without improvement. His tacrolimus was restarted at that time for concern for arthritis related to GVHD in the setting of chronic low-level peripheral eosinophil elevation. At this time, he was also noted to have induration of the skin on the upper extremities, prompting referral to dermatology.

On review of systems, he noted diffuse joint pain, including in the TMJ and wrists. He also noted recent headaches relieved with acetaminophen. He denied difficulty swallowing, pain or color change in his fingertips, changes in vision, epistaxis, oral ulcers, shortness of breath, cough, vomiting, diarrhea, constipation, hematuria, or hematochezia.

PAST MEDICAL AND SURGICAL HISTORY

The patient had a history of sickle cell disease complicated by avascular necrosis of the hip, transfusion-related iron overload, and multiple vaso-occlusive episodes. He also had a history of asthma, acne vulgaris, seborrheic dermatitis and atopic dermatitis.

For his history of sickle cell disease, he underwent allogeneic hematopoietic stem cell transplantation (HSCT) from a matched unrelated donor on 08/09/2019. He was conditioned with a reduced intensity regimen which included alemtuzumab, fludarabine, thiotepa, and melphalan. Engraftment was first noted with ANC of 60 on 08/18/2019. GVHD prophylaxis included abatacept (through day 150 per study protocol), methotrexate (day +1, +3, +6, +11), and tacrolimus, which was discontinued 04/21/2021. Initial post-transplant course was complicated by ascites, CMV viremia, and mucositis but had otherwise been uncomplicated since this presentation.

FAMILY AND SOCIAL HISTORY

The patient's mother and father both had a history of sickle cell trait; his siblings were without sickle cell disease. His mother additionally had a history of type 2 diabetes mellitus. His mother and maternal grandmother had a history of asthma. His maternal great grandmother had a history of rheumatoid arthritis.

MEDICATIONS

Cyclobenzaprine, fluocinolone oil, hydrocortisone cream, ketoconazole shampoo, tacrolimus, trimethoprim-sulfamethoxazole, vitamin D

PHYSICAL EXAMINATION

The patient was well-appearing in no apparent distress. Bilaterally on the arms from elbow to dorsal wrist/proximal hand to MCPs, bound-down, immobile, indurated plaques were noted. The dorsal hands were noted to have a violaceous tone with subtle rippling noted by the right elbow and forearm. Slightly decreased oral aperture was also noted. Limited range of motion was noted in the shoulders, elbows, and fingers with visible asymmetry of the lower fingers.

LABS/IMAGING

Abnormal studies:

WBC 16.76 K/uL (4.5-13.0)

- Monocytes elevated to 11%, absolute 1.844 K/uL (1-10%, 0.151.45 thou/uL)
- Elevated absolute eosinophils 0.838 K/uL (0.0-0.725)

CRP 1.1 mg/dL (0-0.8)
Creatine kinase 510 IU/L (29-204)
ANA 1:160, nucleolar (<1:80)
CD3 40% (54-79%), absolute wnl, CD4/CD8 ratio 1.51 (0.98-2.51)

Negative or within normal limits: CMP, ESR, ferritin, PTH, CMV PCR, EBV PCR, adenovirus PCR, anti-CCP, rheumatoid factor, HLA-B27, total IgG level, urinalysis

Imaging:

MRI R Upper Extremity (05/26/21): 1. Limited evaluation, as the exam was terminated prior to administration of IV contrast secondary to patient discomfort. 2. Signal abnormality in the right humeral head compatible with bone infarct. No humeral head collapse. 3. Diffuse soft tissue edema, particularly involving superficial and deep fascia throughout the right upper extremity and included chest wall as above, greatest at the ulnar/medial aspect of the elbow. 4. Lesser patchy muscle edema, greatest in the supraspinatus and brachialis muscles, which can be seen with myositis.

HISTOPATHOLOGY

Punch biopsies of the left forearm and left hand were performed. The deep subcutaneous tissue and fascia were noted to have fibrinoid necrosis with edema and a mononuclear cell infiltrate with some plasma cells. The epidermis and dermis were unremarkable. There was no evidence of vasculitis.

DIAGNOSIS

Eosinophilic fasciitis-like chronic cutaneous graft-versus-host disease

TREATMENT AND COURSE

The patient was initially started on prednisone 30 mg twice daily and continued on tacrolimus with good response in joint pain. He was then initiated on extracorporeal photophoresis as well as ruxolitinib for further management. He was also seen by ophthalmology for evaluation of possible ocular chronic GVHD and was found to have bilateral ocular involvement (meibomian gland dysfunction without corneal involvement), for which he is being treated with warm compresses. He continues to follow in the outpatient setting with the stem cell transplant team, rheumatology, dermatology, and ophthalmology.

DISCUSSION

The most significant predictor of both acute and chronic graft-versus-host disease in patients who undergo hematopoietic stem cell transplantation is HLA compatibility. In sickle cell disease (SCD), <14% of patients have HLA-identical or matched related donors; matched unrelated and haploidentical (mismatched related) donors are therefore often used. The incidence of GVHD is

increased in these mismatched recipients by approximately 20-30 percent. Differing conditioning regimens also affect rates of GVHD. One retrospective cohort review reported that myeloablative and reduced intensity conditioning conferred the highest risk of chronic GVHD in patients with SCD as compared to non-myeloablative regimens. Interestingly, patients with sickle cell disease undergoing non-myeloablative conditioning regimens have an increased likelihood of mixed chimerism (both donor and recipient-derived blood cells present after HSCT). Mixed chimerism seems to be associated with reduced risk of all types of GVHD. Though our patient received a reduced intensity conditioning regimen with an HSCT from a matched unrelated donor, his peripheral chimerism demonstrated >98% donor cells.

Cutaneous manifestations of both acute GVHD (aGVHD) and chronic GVHD (cGVHD) greatly contribute to the overall morbidity and mortality of HSCT patients. Acute cutaneous GVHD classically presents as a morbilliform eruption within 100 days of HSCT, while chronic cutaneous GVHD occurs after 100 days post-transplant and can be highly polymorphic. Chronic cutaneous GVHD that presents between 3 and 9 months after transplant more commonly has non-sclerotic features, whereas late-onset (>9 months) chronic cutaneous GVHD is more likely to present with sclerotic features.

Eosinophilic fasciitis is a rare manifestation of cGVHD with a reported incidence of 0.5% to 6%. It tends to present as a late-onset manifestation of cutaneous cGVHD, with mean time of onset reported as 740 days after transplantation. EF-like cGVHD has a predilection for the extremities, usually sparing the hands and feet. Patients often present with edema initially followed by skin induration, skin rippling overlying deeper nodularity, and myalgias/arthralgias resulting from fibrosis of subcutaneous tissue and fascia. Some patients will develop the "groove sign", a linear depression along sites of fascial involvement. Later manifestations can include the development of ulcers and benign angiomatous nodules. Lab findings include peripheral blood eosinophilia.

The diagnosis of EF-like cGVHD is based on clinical presentation and histopathology. MRI is additionally useful to identify deep fibrosis and fasciitis. First-line therapy consists of systemic glucocorticoids and calcineurin inhibitors such as tacrolimus. The condition is often recalcitrant to treatment, with first-line treatment failure reported as greater than 50 percent. Efficacy has also been reported for a wide range of steroid-sparing agents, such as cyclophosphamide, procarbazine, azathioprine, penicillamine, anti-thymocyte globulin, cyclosporine, thalidomide, clofazimine, and etretinate. Newer targeted therapies include ruxolitinib, ibrutinib, belumosudil, imatinib, sirolimus, and everolimus. Over the past 4 months, ruxolitinib and belumosudil have gained FDA approval for second-line treatment of steroid-refractory chronic GVHD in children 12 and older. Ibrutinib has yet to gain FDA approval for pediatric cGVHD, although it has been approved for use in adults with cGVHD since 2017. Phototherapy, electron beam radiation therapy, thoracoabdominal irradiation, and extracorporeal photopheresis are also used as adjuvant therapies. Physical therapy for prevention of joint contractures, ophthalmologic assessment for ocular GVHD, and avoidance of skin trauma are additionally important components of treatment.

In conclusion, EF-like cGVHD is a poorly understood, rare entity which can present insidiously with edema, myositis, and arthralgias prior to the development of skin involvement. The presence of peripheral eosinophilia is helpful in assisting with this diagnosis, and a multidisciplinary treatment team is necessary to halt progression.

KEY POINTS

- EF-like cGVHD is a rare sclerodermatous form of chronic cutaneous GVHD which can present clinically with skin induration, skin rippling overlying deeper nodularity, and a "groove sign" along sites of fascial involvement. MRI and incisional biopsy can reveal

fibrosis of the subcutaneous tissue and fascia. Deeper and adjacent tissues can also be affected, resulting in myalgia, arthralgia, arthritis, and joint contractures.

- The pathogenesis of EF-like cGVHD is not yet well understood. In 50% of patients, EF-like cGVHD is recalcitrant to standard first-line therapy and requires multiple modalities of second-line treatment including immunosuppressants, biologics, phototherapy, thoracoabdominal irradiation, and extracorporeal photophoresis.

REFERENCES

1. Sarantopoulos, S, Cardones A, Sullivan K. "How I Treat Refractory Chronic Graft-versus-Host Disease." Blood, 2019;133 (11): 1191–1200.
2. Sbano, P, Rubegni, P, De Aloe, GB, et al. Extracorporeal photochemotherapy for treatment of fasciitis in chronic graft-versus-host disease. Bone Marrow Transplantation. 2004; 33: 869-870
3. Schaffer, J, McNiff, J, Seropian, S. et al. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease: Expanding the sclerodermoid spectrum. J of American Acad of Dermatol. 2005; 53 (4): 591-601.
4. Khoury, H, Langston, A, Kota, V, et al. Ruxolitinib - a Steroid Sparing Agent in Chronic Graft-versus-Host Disease. Bone Marrow Transplant. 2018; 53(7): 826–831.
5. Ganta, C, Chetterjee, S, Pohlman, B et al. Chronic Graft-Versus-Host Disease Presenting as Eosinophilic Fasciitis Therapeutic Challenges and an Additional Case. Journal of Clinical Rheumatology. 2015. 2 (2);86-94.
6. Bolognia, J, Schaffer, J, Cerroni, L. Dermatology: Graft-vs Host Disease. 2018. 753-760
7. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014 Jul 17;124(3):344-53.
8. Guilcher GMT, Truong TH, Saraf SL, et al Curative therapies: Allogeneic hematopoietic cell transplantation from matched related donors using myeloablative, reduced intensity, and nonmyeloablative conditioning in sickle cell disease. Semin Hematol. 2018 Apr;55(2):87-93.
9. MacDonald K, Hill GR, Blazar BR; Chronic graft-versus-host disease: biological insights from preclinical and clinical studies. Blood 2017; 129 (1): 13–21.
10. Shenoy S. Hematopoietic stem cell transplantation for sickle cell disease: current practice and emerging trends. Hematology Am Soc Hematol Educ Program. 2011;2011:273-9.
11. Shenoy S, Eapen M, Panepinto JA, Logan BR, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. Blood. 2016 Nov 24;128(21):2561-2567.
12. Eapen M, Brazauskas R, Walters MC, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. Lancet Haematol. 2019 Nov;6(11):e585-e596.
13. Gluckman E, Cappelli B, Bernaudin F, et al; on behalf of Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research, Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 2017; 129 (11): 1548–1556.
14. Kurian, T, Locke, F. Belumosudil: A Rising Star for the Management of Chronic Graft-Versus-Host Disease and the First FDA-Approved ROCK2 Inhibitor. The Hematologist. 2021 (18) 6.

15. US Food and Drug Administration. "FDA approves ruxolitinib for chronic graft-versus-host disease" https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ruxolitinib-chronic-graft-versus-host-disease. 2021
16. Miklos D, Cutler CS, Arora M, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017 September 18.

CHICAGO DERMATOLOGICAL SOCIETY **Case 5**

Presented by **Molly Hales**, MD, PhD; **Spencer Ng**, MD, PhD; **Joaquin Brieva**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 73-year-old male with a history of atopic dermatitis presented to clinic with an erythematous eruption on his chest, back, and bilateral upper and lower extremities. Three months prior to presentation, the patient had presented with a diffusely pruritic eruption and was initially treated with topical medications, phototherapy, and dupilumab for suspected worsening atopic dermatitis without improvement. One month prior to presentation, the patient had been seen by an outside dermatologist and was noted to have worsening pruritus and crusting. Skin biopsy at that time revealed evidence of scabies and the patient was treated with oral ivermectin and topical permethrin. After this treatment course was completed, he noted an increasingly purpuric eruption on his lower extremities with progressive edema and exudate as well as worsening full-body erythema, prompting him to seek care at Northwestern Dermatology. He was otherwise in his usual state of health with no recent fevers, chills, or systemic symptoms. Remainder of review of systems was negative.

PAST MEDICAL AND SURGICAL HISTORY

The patient had a longstanding history of atopic dermatitis, with prior treatments including topical clobetasol, NB-UVB phototherapy, oral gabapentin, and dupilumab. He also had a history of atrial fibrillation, chronic kidney disease, gastroesophageal reflux disease, and hypertension. His past surgical history included total knee replacement surgery, biceps tendon repair, and rotator cuff repair.

FAMILY AND SOCIAL HISTORY

The patient had a family history of hypertension in both parents. He smoked a cigar once per week and had one glass of wine per week. He wrestles for exercise. He had been using exogenous testosterone and growth hormone for many years, though at the time of presentation he denied ongoing use.

MEDICATIONS

Aspirin, benazepril, dupilumab, metoprolol, omeprazole

PHYSICAL EXAMINATION

The patient was well-appearing in no apparent distress and breathing comfortably on room air. Generalized erythema was noted on the chest, back, and bilateral upper and lower extremities. There was minimal facial involvement and no palpable lymphadenopathy. In addition, over the bilateral lower extremities, purpuric papules coalescing into plaques with surrounding bright erythema and edema were noted. Several linear erosions with yellow crusting were also noted on the bilateral anterior lower shins.

LABS/IMAGING

Abnormal:
LDH 334 U/L (0-271)
Urea nitrogen 58 mg/dL (2-25)
Creatinine 1.64 (at patient's baseline)
Superficial bacterial culture: pan-susceptible *Staphylococcus aureus*

Normal/negative:
Complete blood count, remainder of basic metabolic panel
Urinalysis

Serum protein electrophoresis
Anti-nuclear antibody
Anti-myeloperoxidase antibodies, anti-proteinase 3 antibodies
Flow cytometry
Repeat mineral oil preparation

HISTOPATHOLOGY

On punch biopsy of the left and right thigh, a perivascular dermatitis with neutrophils, ulcer, and erythrocyte extravasation was seen. Along the superficial vascular plexus, some neutrophil extravasation with nuclear debris in the adjacent dermis was noted without frank fibrinoid necrosis, suggestive of late resolving leukocytoclastic vasculitis. DIF of the right knee demonstrated IgA, C3 and fibrinogen vascular deposits.

DIAGNOSIS

Post-scabietic erythrodermic IgA vasculitis

TREATMENT AND COURSE

The patient was admitted directly to Northwestern Memorial Hospital and started on prednisone 60 mg daily, cefazolin 1 g IV every 8 hours, and triamcinolone 0.1% ointment wet wraps twice daily. He was ultimately discharged after 48 hours with a planned prednisone taper, oral cephalexin, and triamcinolone 0.1% ointment twice daily. He was seen in clinic 10 days after hospital discharge with resolution in erythroderma, although he was noted to have residual left lower extremity ulceration and persistent bilateral purpuric lesions on the lower extremities. Long-term monitoring of creatinine and urinalysis did not reveal worsening in his kidney function. His lower extremity ulceration and purpura gradually improved over the following months.

DISCUSSION

Cutaneous small vessel vasculitis (CSVV) is a group of inflammatory disorders affecting the postcapillary venules of the superficial and mid dermis. Cutaneous small vessel vasculitis is most commonly mediated by immune complex deposition, which triggers mast cell degranulation and neutrophil chemotaxis. In ANCA-associated CSVV, circulating ANCA antibodies activate neutrophils to release reactive oxygen species and pro-inflammatory mediators. In both cases, the intense neutrophilic vascular inflammation causes extravasation of red blood cells from damaged blood vessels. This extravasation leads to the most common clinical finding in cutaneous small vessel vasculitis: palpable purpura favoring dependent sites. Less common presentations of CSVV include urticarial papules, pustules, vesicles, petechiae, or targetoid lesions. A minority of patients with CSVV with develop systemic symptoms, the most common of which are arthralgias and arthritis, followed by genitourinary or gastrointestinal symptoms.

IgA vasculitis is a type of cutaneous small vessel vasculitis caused by IgA deposition within the walls of small blood vessels. It commonly develops within 1 to 2 weeks after an upper respiratory infection, with several studies suggesting a link to beta-hemolytic streptococcal infection. In adults, IgA vasculitis may also be associated with a solid organ malignancy, particularly in the lung. More rarely, IgA vasculitis may be caused by an inflammatory disorder or drug exposure, with ivermectin reported as one possible causative agent. Compared to the other types of cutaneous small vessel vasculitis, IgA vasculitis is much more common in children, with an average age of onset of 6 years. It is also more likely to be associated with systemic symptoms including arthritis, nephritis, abdominal pain, and fever. Arthritis affects up to 75% of patients with IgA vasculitis, most commonly in the knees and ankles, while up to 50% of patients will have microscopic hematuria or proteinuria indicating renal involvement. The cutaneous presentation of IgA vasculitis is similar to that of other cutaneous small vessel vasculitis, with erythematous macules and papules that develop into palpable purpura distributed primarily on dependent

areas of the lower extremities and buttocks. The diagnosis is commonly made when DIF demonstrates perivascular IgA, C3, and fibrin deposits. In some patients, IgA ANCA may also be present.

Fortunately, the vast majority of cases of IgA vasculitis spontaneously resolve within weeks to months. For this reason, treatment is mainly supportive. There is some evidence that dapsone and colchicine may reduce the duration of skin lesions. In patients with more severe disease, systemic corticosteroids may also be used to reduce the duration of illness and treat any associated systemic symptoms, such as abdominal pain and arthritis. While IgA vasculitis is more common in children, adults with the disease often have more severe illness including longer hospital stays and higher rates of chronic renal insufficiency, often necessitating more aggressive treatment.

Scabies infection has been associated with multiple dermatoses. Three case reports show an association between scabies infection and granuloma annulare. An additional four case reports link Norwegian crusted scabies to erythroderma. At least nine reports link scabies and vasculitis, most commonly cutaneous small vessel vasculitis. Highlighting the rarity of this condition, a 2015 review of the histopathological findings associated with scabies infection found that only 1 in 25 cases (or about 4%) showed features of vasculitis.

Pertinent to our case, at least one published case report links IgA vasculitis to scabies. The patient was an 86-year-old male who developed palpable purpura, hemorrhagic bullae, and erosions on the bilateral lower extremities, as well as an acute kidney injury and abdominal pain following scabies infection and ivermectin treatment. He was found to have IgA vasculitis based on clinical symptoms and dermatopathology, with resolution of his symptoms after a short course of prednisone. The authors hypothesized that his vasculitis might have been due to a severe hypersensitivity reaction to circulating antigens from dead mites or from an ivermectin-induced vasculitis.

KEY POINTS

- IgA vasculitis is a type of cutaneous small vessel vasculitis that is most common in children. While it is classically associated with an antecedent upper respiratory infection (notably beta-hemolytic streptococcal infections), it has also been associated with other infections, solid organ malignancies in adults (especially lung), and drug exposures.
- Scabies can rarely be associated with post-treatment dermatoses. Among these associated dermatoses are granuloma annulare, erythroderma, and cutaneous small vessel vasculitis, including IgA vasculitis.

REFERENCES

1. Yamamoto, T, Okabe, H, Chen, K. IgA Vasculitis After Initiation of Ivermectin for Scabies: Coincident or Drug-Induced?, The American Journal of Dermatopathology. 2020; 42(7): 555-556
2. Shinkai, K and Fox, L. Cutaneous Vasculitis. In Bolognia, J, Schaffer, JV, and Cerroni, L. (2018) Dermatology: 385-410.
3. Kedia, P, Tirumalae, R, Puttegowda, D, and Antony, M. Joining the Spots in Adults and Young Tots: A Clinicopathological Study of Henoch–Schönlein Purpura (IgA Vasculitis). The American Journal of Dermatopathology. 2017; 39(8): 587-592.
4. Elwood H, Berry RS, Gardner JM, Shalin SC. Superficial fibrin thrombi… and other findings: a review of the histopathology of human scabietic infections. J Cutan Pathol. 2015; 42: 346–352.

5. Nishihara K, Shiraishi K, Sayama K. Leukocytoclastic vasculitis associated with crusted scabies. Eur J Dermatol. 2018;28:242–343.
6. Paparizos V, Vasalou V, Velissariou E, Kourkounti S, Daskalakis E, Rigopoulos D. Norwegian scabies presenting as erythroderma in HIV: A case report. Infez Med. 2019 Sep 1;27(3):332-335.
7. Kulkarni S, Shah H, Patel B, Bhuptani N. Crusted Scabies: Presenting as erythroderma in a human immunodeficiency virus-seropositive patient. Indian J Sex Transm Dis AIDS. 2016 Jan-Jun;37(1):72-4.
8. Quay ER, Lam C. An important cause of erythroderma. BMJ. 2017 Apr 12;357:j1205.
9. Wilsmann-Theis D, Wenzel J, Gerdsen R, Uerlich M, Bieber T. Granuloma annulare induced by scabies. Acta Derm Venereol. 2003;83(4):318.
10. Piana S, Pizzigoni S, Tagliavini E, Serra S, Albertini G. Generalized granuloma annulare associated with scabies. Am J Dermatopathol. 2010 Jul;32(5):518-20.
11. Al Aboud K, Al Aboud D. Multiple lesions of granuloma annulare on the hand in a patient with scabies. Clin Cosmet Investig Dermatol. 2011;4:131-2.
12. Harris J, Nathoo R, Vincek V. Scabies Associated with Granulomatous Dermatitis. Case Rep Dermatol. 2017 Jul 13;9(2):60-64.

Presented by **Zachary Solomon**, MD; **Lida Zheng**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 34-year-old female presented to dermatology clinic for evaluation of an inguinal rash present for ten years

CHICAGO DERMATOLOGICAL SOCIETY **Case 7**

Presented by **Nicole S. Stefanko**, MD; **Anthony J. Mancini**, MD
Departments of Dermatology and Pediatrics, Feinberg School of Medicine, Northwestern University
Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago

HISTORY OF PRESENT ILLNESS

A 2-month-old female born at 40 weeks gestation to a 37-year-old G1P1 mother presented to Lurie Children's dermatology clinic with a persistent acneiform eruption of the face and scalp. The eruptions were first observed at 2 weeks of age, and cultures grew *Staphylococcus aureus.* She was treated with several courses of cephalexin and clindamycin for presumed staphylococcal pustulosis prior to presentation. Despite antibiotic treatment, the patient developed additional pruritic lesions on the neck, chest, arms, and labia with drainage of clear yellowish fluid. Five vascular papules were also noted at several weeks of age.

PAST MEDICAL AND SURGICAL HISTORY

The patient was born at 40 weeks gestation via Cesarean section for fetal decelerations. Delivery was complicated by prolonged rupture of membranes and nuchal cord. The patient's mother reported routine prenatal care, and prenatal labs were negative by report.

FAMILY AND SOCIAL HISTORY

Non-contributory

MEDICATIONS

IVIG, posaconazole, trimethoprim-sulfamethoxazole

PHYSICAL EXAMINATION

The patient was well-appearing and in no apparent distress. Over the forehead and cheeks, there were numerous erythematous to pink papules, and coarse facial features were noted. On the scalp, face, chest, and medial labia majora, there were minimally crusted erythematous papules, some coalescing into plaques, admixed with erythematous papulopustules. There was a 4 mm vascular papule with atrophy and central notching involving the left nasal ala. On the left upper abdomen, there was a 1 cm superficial vascular plaque. The mid lower abdomen demonstrated a 1 mm punctuate vascular papule, and the left anterior shoulder had a 6 mm agminated vascular plaque composed of smaller vascular papules. No splenomegaly was appreciated, and the liver edge was palpable 1 cm below the right costal margin.

LABS/IMAGING

Abnormal:
WBC 22.96 K/uL (5.0-19.5)
Eosinophils 19% (0-6%)
Absolute eosinophils 4.362 K/uL (0.0-1.17)
IgE 6.66 KU/L (<5.2)

Normal/negative:
IgM 98.2 mg/dL (39-142)
IgG 470 mg/dL (282-1026)
IgA 21.5 mg/dL (16-83)
TSH 7.00 mIU/L (0.5-8.5)
T4 1.37 ng/dL (0.87-1.8)
Abdominal ultrasound

Given the presence of peripheral eosinophilia and elevated IgE level and clinical concern for hyper IgE syndrome, genetic testing using the *STAT3* Gene/Hyper IgE Syndrome (HIES) panel was performed and demonstrated a heterozygous nucleotide substitution resulting in a R832Q missense mutation in the *STAT3* gene.

DIAGNOSIS

Hyper IgE syndrome presenting with eosinophilic folliculitis

TREATMENT AND COURSE

The patient was treated with fluocinolone 0.01% solution and hydroxyzine three times daily for presumed eosinophilic folliculitis with marked improvement at initial follow-up. She was also started on timolol gel 0.5% twice daily for the hemangioma on the left nasal ala, which led to resolution with some residual deformity of the lateral naris after 5 months of therapy.

The patient was referred to Immunology for evaluation and genetic testing. Repeat IgE levels revealed an elevation to 1,559 KU/L (<22.6), and genetic testing was positive for a *STAT3* mutation. The patient follows with immunology, dermatology, pulmonology, and the National Institutes of Health and has been treated for pneumonias, pneumatoceles, and pneumothorax. Additionally, eight retained primary teeth have been extracted. She has developed several recurrences of facial rashes with a variety of morphologies including eosinophilic folliculitis, periorificial dermatitis, and Demodex folliculitis.

DISCUSSION

Hyper IgE syndrome (HIES), previously called Job syndrome, is a rare primary immunodeficiency disorder characterized by eosinophilia and elevated serum IgE levels in association with atopic dermatitis, cutaneous candidiasis, *Staphylococcus aureus (S. aureus)* infections, recurrent sinopulmonary infections, and dental and skeletal abnormalities. Patients may present in infancy with pruritic facial papulopustules, which demonstrate eosinophilic dermatitis or eosinophilic folliculitis when biopsied. In childhood, patients develop characteristic coarse facial features, including broad nose, prominent forehead, and thickened skin.

Both sporadic and autosomal dominant forms of HIES (AD-HIES) are caused by dominant negative mutations in the human signal transducer and activator of transcription 3 (*STAT3*) gene, while loss-of-function mutations in dedicator of cytokinesis 8 (*DOCK8*) have been implicated in the pathogenesis of the less common autosomal recessive form. *STAT3* mutations lead to impaired Th17 differentiation and ultimately to deficiency of both IL-17 and IL-22, cytokines that drive the expression of antimicrobial peptides CXCL8 and β-defensin 2 and 3, thus making patients more susceptible to *S. aureus* and candidal infections.

The differential diagnosis of the dermatitis associated with elevated IgE levels includes atopic dermatitis, Wiskott-Aldrich syndrome (WAS), DiGeorge syndrome, immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome, and Omenn syndrome. Thrombocytopenia and cutaneous petechiae are seen in WAS, a rare X-linked recessive disorder characterized by platelet dysfunction, thrombocytopenia, and atopic dermatitis.

Treatment of eosinophilic folliculitis consists of low-to-mid-potency topical steroids and oral antihistamines. The mainstay of treatment of HIES consists of anti-staphylococcal antibiotic prophylaxis, IVIG, and appropriate treatment of other bacterial and fungal infections. Surgical removal of pneumatoceles is warranted to prevent superinfection, and atopic dermatitis can be treated with topical or systemic medications. While hematopoietic stem cell transplantation is important for patients with AR-HIES, it is not typically warranted in the autosomal dominant form of the disease.

KEY POINTS

- HIES is a rare immunodeficiency disorder most commonly caused by dominant negative mutations in the human signal transducer and activator of transcription 3 *(STAT3)* gene.
- Affected individuals may present with eosinophilic folliculitis, coarse facial features, recurrent cutaneous and sinopulmonary infections, and dental and skeletal abnormalities.
- Eosinophilic folliculitis may be the presenting feature of HIES in young infants.

REFERENCES

1. Chamlin SL, McCalmont TH, Cunningham BB, Esterly NB, Lai CH, Mallory SB, Mancini AJ, Tamburro J, Frieden IJ. Cutaneous manifestations of hyper-IgE syndrome in infants and children. J Pediatr. 2002 Oct;141(4):572-5. doi: 10.1067/mpd.2002.127503. PMID: 12378200.
2. Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med. 2007 Oct 18;357(16):1608-19. doi: 10.1056/NEJMoa073687. Epub 2007 Sep 19. PMID: 17881745.
3. Paller AS, Mancini AJ (2021). Hurwitz's Clinical Pediatric Dermatology: A textbook of skin disorders of childhood and adolescence (6th ed.). Elsevier.
4. Park B, Liu GY. *Staphylococcus aureus* and Hyper-IgE Syndrome. Int J Mol Sci. 2020 Dec 1;21(23):9152. doi: 10.3390/ijms21239152. PMID: 33271763; PMCID: PMC7729741.
5. Tsilifis C, Freeman AF, Gennery AR. STAT3 Hyper-IgE Syndrome-an Update and Unanswered Questions. J Clin Immunol. 2021 Jul;41(5):864-880. doi: 10.1007/s10875-021-01051-1. Epub 2021 May 1. PMID: 33932191; PMCID: PMC8249299.

CHICAGO DERMATOLOGICAL SOCIETY **Case 8**

Presented by **Joshua Prenner**, MD; **Xiaolong Alan Zhou**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 50-year-old male with a past medical history significant for autoimmune hepatitis leading to cirrhosis now status post orthotopic liver transplantation (OLT) one month prior was admitted to the hospital for evaluation and management of diarrhea, hyponatremia, and a diffuse erythematous eruption present for approximately 6 days.

The patient had noted progressively poor oral intake and fatigue as well as a whole-body burning sensation over the previous several weeks. Over this time, he was noted to be persistently hyponatremic despite multiple infusions of normal saline as an outpatient. The night prior to admission, he noted the acute onset of watery diarrhea. Six days prior to admission, he had noticed the onset of a rash that first appeared on the dorsal hands and spread to the arms, trunk, legs and palms. He could not recall any sick contacts, recent travel, or other new exposures. He was adherent to his immunosuppressive regimen which included tacrolimus, mycophenolate mofetil, and prednisone. He was also taking trimethoprim-sulfamethoxazole and valganciclovir as prescribed for opportunistic infection prophylaxis. Since his liver graft came from a Hepatitis C virus (HCV) positive donor, he had also been taking Epclusa (sofosbuvir-velpatasvir) since the time of transplantation.

At the time of admission, he noted feeling overall unwell. He had no fevers or chills but did describe that his skin felt like it was "on fire". He also had lower abdominal pain that was associated with his frequent episodes of watery diarrhea. He had no mucosal symptoms. Remainder of review of systems was negative.

PAST MEDICAL AND SURGICAL HISTORY

The patient had a history of cirrhosis, thought to be due to autoimmune hepatitis, which had been complicated by bleeding esophageal varices, hepatic encephalopathy, refractory ascites and hepatic hydrothorax. He underwent successful OLT with an increased risk donor who was cytomegalovirus (CMV) positive and HCV positive. His post-transplantation course had been generally uncomplicated prior to the current presentation.

FAMILY AND SOCIAL HISTORY

There was no family history of liver disease or skin disease. He had no previous history of drug, alcohol, or tobacco use. He lived at home with his wife and daughter.

MEDICATIONS

At the time of admission, the patient was taking aspirin, acetaminophen-hydrocodone, calcium-vitamin D, mycophenolate, omeprazole, prednisone, simethicone, Epclusa (sofosbuvir-velpatasvir), tacrolimus, trimethoprim-sulfamethoxazole, and valganciclovir.

PHYSICAL EXAMINATION

The patient was alert and in no acute distress but appeared uncomfortable. On the trunk, there were nearly confluent diffuse erythematous patches with follicular accentuation and few islands of sparing noted on the back. On the upper and lower extremities, there were scattered pinpoint erythematous papules. Over the dorsal hands, there were pink papules; on the palms, there were erythematous macules favoring the creases.

LABS/IMAGING

Abnormal:

White blood cell count 2.4 K/uL (3.5-10.5)
Hemoglobin 8.3 g/dL (13.0-17.5)
Platelets 114 K/uL (140-390)
Absolute lymphocytes 0.1 K/uL (1.0-4.0)
Absolute neutrophils 2.1 K/uL (1.5-8.0)
Sodium 119 mEq/L (133-146)
HCV RNA 209 IU/mL (<15)

Normal/negative:
HSV and VZV PCR
EBV PCR
CMV PCR
HIV PCR
HHV6 PCR
Parvovirus B19 PCR
West Nile virus PCR
Stool ova & parasites
C. difficile PCR

HISTOPATHOLOGY
A punch biopsy of a papule on the dorsum of the left hand was performed. The biopsy demonstrated a sparse superficial interface and perivascular lymphocytic infiltrate with prominent vacuolar degeneration of the basal cell layer. Scattered necrotic keratinocytes with satellite lymphocytes were noted consistent with lymphocyte-associated apoptosis. Vesicle formation was not noted. The dermis showed some edema as well as a variable mostly perivascular lymphohistiocytic infiltrate.

DIAGNOSIS
Solid organ transplant-associated acute graft-versus-host disease (GVHD)

TREATMENT AND COURSE
The patient was started on triamcinolone 0.1% ointment twice daily to all affected areas as well as hydroxyzine nightly, which relieved the sensation of skin burning that he was experiencing. The hematology/oncology team was consulted and recommended increasing the patient's immunosuppressive regimen. His hyponatremia was thought to be secondary to SIADH, and he improved with several days of diuretic medications and sodium chloride tabs.

Since discharge, the patient has been followed closely in the outpatient setting and his rash has continued to improve. Chimerism studies confirmed the diagnosis of GVHD, demonstrating a pathologic 2% donor CD3+ lymphocyte count in the peripheral blood. The patient continues to feel well and his immunosuppression has been gradually tapered back to prior doses.

DISCUSSION
Graft-versus-host disease commonly complicates hematopoietic stem cell transplantation (HSCT) but only rarely occurs in patients who have undergone solid-organ transplantation. The small bowel is the most frequently transplanted organ associated with solid-organ GVHD, followed by the liver. The pathogenesis of solid-organ GVHD involves donor lymphocytes within the transplanted organ that target host antigens in the setting of immunosuppression, leading to a variety of clinical manifestations. In both scenarios, the skin is the most frequently involved organ, but there are several defining features of solid-organ GVHD that underscore the importance of viewing this condition as a separate clinical entity from HSCT GVHD.

In contrast to HSCT GVHD, which usually occurs during the first 3 months after transplantation, solid-organ GVHD occurs more quickly, typically within 3-5 weeks. Both conditions may affect the skin and cause rash, fevers, diarrhea (due to gastrointestinal tract involvement) and pancytopenia (due to bone marrow involvement), but mortality is significantly higher in solid-organ GVHD, with estimates ranging from 85-90% in these patients compared to 50% in HSCT recipients. What specifically accounts for the increased mortality seen in solid-organ GVHD is unknown, but risk of GVHD following OLT may be increased in patients older than 50 and those diagnosed with hepatocellular carcinoma.

Clinically, the skin is usually the first organ affected by solid-organ GVHD, with physical examination typically demonstrating a diffuse erythematous maculopapular eruption with desquamation that may be asymptomatic or associated with pruritus. Histologically, both forms of cutaneous GVHD present similarly, with skin biopsy typically demonstrating vacuolar interface dermatitis with scattered necrotic keratinocytes; however, solid-organ GVHD has been associated with more dense lichenoid inflammation compared to HSCT GVHD. Chimerism studies, which detect donor lymphocytes in recipient peripheral blood or tissue, can help confirm the diagnosis of GVHD when macrochimerism (>1% donor lymphocytes) is detected.

Treatment for solid-organ GVHD mirrors that of HSCT GVHD, owing in large part to the low incidence and lack of studies focusing on solid-organ GVHD specifically. High-dose corticosteroids are the backbone of therapy, though patients may also be treated with reduction in immunosuppression as well as a variety of other agents including anti-thymocyte globulin, anti-tumor necrosis factor drugs, anti-metabolites, and calcineurin inhibitors. Monotherapy with corticosteroids or calcineurin inhibitors alone has been associated with worse prognosis.

KEY POINTS

- Solid-organ GvHD is a rare but potentially devastating complication following solid organ transplantation that typically affects the skin first, making the dermatologist and dermatopathologist key players in this condition's timely diagnosis and management.
- Affected individuals present with a diffuse erythematous maculopapular eruption which may be asymptomatic. Mortality is high, and an interdisciplinary team is needed to guide individualized therapy.

REFERENCES

1. Auerbach JS, Schott CK. Solid-Organ Graft-Versus-Host Disease After Liver Transplant: A Case Report. Crit Care Nurse. 2016 Jun;36(3):e7-e11. doi: 10.4037/ccn2016988. PMID: 27252108.
2. Bitar C, Olivier K, Lee C, Vincent B, Martin J. Acute graft-vs-host disease following liver transplantation. Cutis. 2019 Jun;103(6):E8-E11. PMID: 31348462.
3. Barton-Burke M, Dwinell DM, Kafkas L, Lavalley C, Sands H, Proctor C, Johnson E. Graft-versus-host disease: a complex long-term side effect of hematopoietic stem cell transplant. Oncology (Williston Park). 2008 Oct;22(11 Suppl Nurse Ed):31-45. PMID: 19856578.
4. Murali AR, Chandra S, Stewart Z, et al. Graft Versus Host Disease After Liver Transplantation in Adults: A Case series, Review of Literature, and an Approach to Management. Transplantation. 2016;100(12):2661-2670. doi:10.1097/TP.0000000000001406
5. Kim GY, Schmelkin LA, Davis MD, El-Azhary RA, Wieland CN, Leise MD, Meves A, Lehman JS. Clinical and histopathologic manifestations of solid organ transplantation-associated graft-versus-host disease involving the skin: A single-center retrospective study. J Cutan Pathol. 2018 Nov;45(11):817-823. doi: 10.1111/cup.13326. Epub 2018 Aug 19. PMID: 30039546.

6. Russell AJ, Musiek AC, Staser KW, Rosman IS. Histopathologic and immunophenotypic features of cutaneous solid organ transplant-associated graft-vs-host disease: Comparison with acute hematopoietic cell transplant-associated graft-vs-host disease and cutaneous drug eruption. J Cutan Pathol. 2021 Jun 26. doi: 10.1111/cup.14093. Epub ahead of print. PMID: 34173980.
7. Kang WH, Hwang S, Song GW, Jung DH, Park GC, Ahn CS, Moon DB, Kim KH, Ha TY, Kim WJ, Kim SH, Cho HD, Kwon JH, Jwa EK, Lee SG. Acute Graft-vs-Host Disease After Liver Transplantation: Experience at a High-volume Liver Transplantation Center in Korea. Transplant Proc. 2016 Dec;48(10):3368-3372. doi: 10.1016/j.transproceed.2016.08.051. PMID: 27931583.

Presented by **Alyce Anderson**, MD, PhD; **Joan Guitart**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 31-year-old female presented for evaluation of a faint eruption on the trunk and extremities and ulcerative, friable nodules on the face, ear, arm, and back that had been present for two months

CHICAGO DERMATOLOGICAL SOCIETY **Case 10**

Presented by **Edward Li**, MD, PhD; **Lida Zheng**, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 55-year-old male presented to clinic for evaluation of numerous raised bumps on the face, neck, and chest. These lesions are asymptomatic and have been present for several years. He had been referred to dermatology clinic for evaluation of his cutaneous lesions by his pulmonologist.

PAST MEDICAL AND SURGICAL HISTORY

Approximately one year prior to presentation to dermatology clinic, the patient presented to Northwestern Memorial Hospital with abdominal pain and was diagnosed with diverticulitis. Imaging studies obtained during this admission incidentally revealed an adrenal gland mass and a large pulmonary bulla in the lower lobe of the left lung, for which he was treated with a bullectomy followed by talc pleurodesis. During the recovery from this procedure, the patient experienced a spontaneous right-sided pneumothorax.

FAMILY AND SOCIAL HISTORY

The patient's father had similar cutaneous lesions and passed away from an unspecified kidney disease. His mother and sister do not have similar cutaneous lesions but have a history of ovarian and breast cancer respectively.

MEDICATIONS

Losartan-hydrochlorothiazide

PHYSICAL EXAMINATION

The patient was a well-appearing male in no acute distress, breathing comfortably on room air. Numerous 1-2 mm flesh-colored follicularly-based papules were visualized on the forehead, cheeks, perinasal area, chin, post-auricular area, neck, upper chest, and upper back.

LABS/IMAGING

MRI Abdomen: 3.5 cm lesion with peripheral nodular enhancement was noted in the retrocaval region adjacent but separate to the right adrenal gland. An additional 2.7 cm lesion was noted medial to the left adrenal gland, showing similar characteristics in imaging and enhancement.
CT Chest: Large 16x10 cm cystic structure in the left lower lobe/hemithorax with significant compressive atelectasis and trace effusion was noted. Multiple lower lung predominant thin-walled cystic lesions were also visualized, with some being intraparenchymal cysts and others being peripheral bulla.

HISTOPATHOLOGY

Punch biopsy of a right retroauricular papule revealed a dilated follicular unit with keratotic debris. Serosanguinous crusting with numerous inflammatory cells and prominent keratin retention were also noted as well as subtle expansion of the peri-adnexal dermis with some fibroplasia. On higher power, atypia was not identified. Overall, these histopathologic findings were consistent with a diagnosis of fibrofolliculoma or trichodiscomas.

DIAGNOSIS

Fibrofolliculoma associated with Birt-Hogg-Dubé syndrome

TREATMENT AND COURSE

Based on the patient's cutaneous lesions, imaging studies, and pathology results, a diagnosis of Birt-Hogg-Dubé syndrome was made. For his cutaneous lesions, the patient had previously trialed

cryotherapy, electrodessication, and shave excisions without significant improvement. Other treatments such as curettage and laser treatments were discussed but the patient ultimately deferred. As previously mentioned, the patient received a bullectomy for the largest bulla in the left lower lobe followed by left-sided talc pleurodesis but unfortunately experienced a spontaneous pneumothorax from rupture of a smaller bulla in the right lung. He was then subsequently treated with right-sided bullectomy and talc pleurodesis. His peri-adnexal masses were initially followed by MRI; he ultimately underwent a biopsy of one these lesions which showed a ganglioneuroma with signs of regression. Of note, the patient's sister has since been genetically tested and is positive for a Birt-Hogg-Dubé-associated mutation. The patient now has also received genetic testing and results are currently pending.

DISCUSSION

Birt-Hogg-Dubé (BHD) syndrome is a rare inherited disorder characterized by multiple benign skin lesions, pulmonary cysts, and renal neoplasia. This constellation of clinical presentations was first described in literature in 1977 by three Canadian physicians for whom the disease is named. At present, there are approximately 600 cases described in the literature, but the true disease prevalence is difficult to estimate due to variability in clinical expression.

Cutaneous lesions are the most common presentation of Birt-Hogg-Dubé syndrome, occurring in approximately 85% of patients. Characteristic skin lesions are fibrofolliculomas, trichodiscomas, and acrochordons. Fibrofolliculomas typically present as skin-colored dome-shaped 2-3 mm small papules on the scalp, face, and neck and are not associated with any additional symptoms. They usually appear after the second decade of life and may increase in number with age. The number of lesions can vary dramatically between patients from a few to hundreds. These skin lesions can be removed with a variety of methods, but recurrence rates are high.

Greater than 80% of patients also develop multiple pulmonary cysts. Although these cysts are most commonly asymptomatic with no impact on lung function, patients with BHD syndrome can experience repeated episodes of spontaneous pneumothorax due to spontaneous rupture of these bulla. Treatment usually consists of surgical removal of larger cystic lesions and/or pleurodesis if numerous smaller cysts are present.

Finally, approximately 15-30% of patients with BHD syndrome develop multiple renal neoplasms with a mean age at diagnosis of approximately 50 years old. These tumors are usually slow-growing and bilateral. The most common tumor types are hybrid oncocytic tumor (hybrid mix of oncocytomas and chromophobe cells) and chromophobe renal cell carcinoma. These malignant tumors are difficult to distinguish from other benign renal masses and require close radiographic follow-up or sampling for tissue diagnosis. Several other benign/malignant neoplasms have been reported in association with BHD syndrome but causal relationships between these entities have not been proven.

While the cutaneous lesions of Birt-Hogg-Dubé syndrome are typically benign, patients should undergo routine screening evaluation for pulmonary and renal pathologies. Risk for pneumothorax should be evaluated with a chest CT at the time of diagnosis then again with new onset of respiratory symptoms. Renal malignancy risk should be assessed by abdominal MRI starting at age 21 and repeated every 3 years until a mass is identified at which point a biopsy or surveillance imaging can be performed based on the size and growth rate of the mass.

BHD syndrome is caused by mutations in the FLCN gene and is inherited in an autosomal dominant fashion. The FLCN gene encodes folliculin whose precise function is not currently known. However, there is emerging evidence that folliculin is an upstream activator of members in the mTOR pathway. The inactivation of folliculin in BHD syndrome leads to dysregulated phosphorylation of

downstream transcription factors by mTORC1 and consequently uncontrolled proliferation of various cell types that underly the phenotypes observed such as renal neoplasms and benign skin proliferations.

Increased DNA testing has led to new understanding of genetic disorders. An updated diagnostic criteria has been proposed where patients should fulfill one major or two minor criteria. The two major criteria are as follows: 1) at least five fibrofolliculomas or trichodiscomas with at least one histologically confirmed and 2) pathogenic FLCN germline mutation. The three minor criteria are as follows: 1) multiple lung cysts that are bilateral basally located with no apparent other causes, 2) renal cancer with early onset (<50 years old) or multifocal/bilateral renal cancer, and 3) a first-degree relative with confirmed Birt-Hogg-Dubé syndrome.

KEY POINTS

- Birt-Hogg-Dubé syndrome is a rare autosomal dominant genetic disorder caused by mutations in FLCN characterized by fibrofolliculomas, pulmonary cysts, and malignant renal neoplasms.
- Characteristic skin lesions are a major diagnostic criterion and can precede manifestation of other internal presentations. Patients with suspected BHD syndrome should undergo chest and abdominal imaging to evaluate for pulmonary and renal involvement.

REFERENCES

1. Napolitano, Gennaro, et al. "A substrate-specific mTORC1 pathway underlies Birt–Hogg–Dubé syndrome." Nature 585.7826 (2020): 597-602.
2. Menko, Fred H., et al. "Birt-Hogg-Dubé syndrome: diagnosis and management." The lancet oncology 10.12 (2009): 1199-1206.
3. https://rarediseases.org/rare-diseases/birt-hogg-dube-syndrome/
4. Schmidt, Laura S., et al. "Birt-Hogg-Dube syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11. 2." The American Journal of Human Genetics 69.4 (2001): 876-882.
5. https://www.uptodate.com/contents/birt-hogg-dube-syndrome