Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 13, 2019
Gleacher Center – Chicago, IL

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

Program

Host: Northwestern University
Wednesday, November 13, 2019
Gleacher Center, Chicago

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *All conference activities take place on the 6th Floor*
8:30 a.m. - 10:30 a.m.	**Clinical Rounds** Slide viewing and posters
9:00 a.m. - 10:00 a.m.	**Morning Lecture** "Infectious Disease Update" *Theodore Rosen, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:15 p.m.	**Resident Case Presentations & Discussion;** **MOC Self-Assessment Questions**
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors**
12:55 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**General Session** BLUEFARB LECTURE – "Cutaneous Infectious Disease: New and Emerging Therapies" *Theodore Rosen, MD*
2:00 p.m.	**Meeting adjourns**

PLEASE NOTE THE FOLLOWING POLICY ADOPTED BY THE CDS TO COMPLY WITH HIPAA PRIVACY RULES:

Taking personal photos of posters or other displays, of images included in general session lectures or presentations, and of live patients at CDS conferences is strictly prohibited. Making audio recordings of any session at a CDS conference also is prohibited.

Mark the Date!

Next CDS meeting will be on Wednesday, December 4th at the Gleacher Center downtown.

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

Guest Speaker

TED ROSEN, MD

Professor of Dermatology and Vice Chair,
Department of Dermatology
Baylor College of Medicine
Houston, TX

Dr. Rosen describes himself as an "old school" physician who puts the patient first, not the protocol. He feels blessed to be entrusted with their care and to receive their trust. Patients, he says, deserve his full attention.

Dr. Rosen attended Michigan State University and graduated cum laude from the University of Michigan Medical School. He trained in internal medicine at the University of Alabama and completed his residency in dermatology at Baylor College of Medicine in Houston, TX. He a Professor of Dermatology and Vice Chair of Baylor's Department of Dermatology.

Dr. Rosen has served on the Board of Directors of the American Academy of Dermatology. He has written more than 325 peer-reviewed journal articles, 24 textbook chapters, and three textbooks. He has been a guest professor at many university training programs, as well as speaking at numerous city, state, regional, national, and international dermatology organizations.

CME Information

November 13, 2019

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. In addition, posters, microscopic slides and occasionally live patients prepared by the residents are made available during the "clinical rounds" portion of the meeting. CDS also offers a session that qualifies for "Maintenance of Certification" self-assessment questions under the auspices of the American Board of Dermatology.

Target Audience

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

Learning Objectives

At the conclusion of the 2019/20 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for various diseases and conditions of the skin, including use of new or emerging medication options.
2. Describe the surgical techniques for treatment of skin cancers, as well as for cosmetic and other purposes.
3. List the therapeutic options available to the dermatologist for a variety of skin diseases, both medical and surgical, and discuss how new emerging treatments can be successfully incorporated into a dermatology practice.

Physician Accreditation Statement

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

Credit Designation for Physicians – IAO designates this live activity for a maximum of 4.75 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

Disclosure of Conflicts of Interest

The IAO and CDS require instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by IAO and CDS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are asked to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk. Today's guest speaker, Ted Rosen, MD, has disclosed that he is a non-paid consultant to Cutanea. He also plans to discuss off-label or investigative uses of several commercial products. None of the planning committee members have disclosed any 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.

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

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Andrew Para, MD (PGY-5)
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Rachel Eisenstadt, MD (PGY-2)

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CHICAGO DERMATOLOGICAL SOCIETY **Case 1**

Presented by Alvin Li, MD, Andrew Para, MD, and Lauren Guggina, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 27-year-old female presented with progressive, painful ocular, oral, and vulvar ulcerations. Symptoms first began two months prior to presentation with painful oral ulcerations. Over the subsequent weeks, she experienced odynophagia, ocular irritation, dysuria, mucus-like rectal discharge, and vulvovaginal pain and mucus-like discharge. The patient was initially treated with courses of oral acyclovir, azithromycin, and fluconazole with no improvement. She achieved temporary relief with a short course of systemic corticosteroids, but her symptoms recrudesced when tapered off. The patient denied a recent history of fevers, chills, night sweats, unintentional weight loss, a recent cold sore, cough, sore throat, or dyspnea.

PAST MEDICAL AND SURGICAL HISTORY

The patient was previously healthy and was up to date on age-appropriate cancer screening, including Pap smear.

FAMILY AND SOCIAL HISTORY

The patient had no family history of autoimmune disease or malignancy.

MEDICATIONS

None

PHYSICAL EXAM

The patient appeared well-nourished and in no apparent distress. Exam was notable for severe conjunctival injection bilaterally with scant, clear discharge. Extensive, confluent ulcerations were noted on the vermillion and mucosal lips, bilateral buccal mucosae, and maxillary and mandibular attached and non-attached gingivae with overlying thick, adherent, fibrinous exudate. Similar ulcerations were noted circumferentially on the tongue. Heme crusting was noted on the vermillion lips. The labia minora, clitoral hood, interlabial sulci and vaginal introitus had diffuse erosions with similar fibrinous exudate. The bilateral palms had numerous erythematous papules which later evolved into tense vesicles and bullae.

LABS/IMAGING

Dermatologic Evaluation: Anti-desmoglein 3 IgG – 55 (normal: 0-9 units), Anti-desmoglein 1 IgG - <14 (normal: 0-14 units), indirect immunofluorescence for IgG to rat bladder substrate – 1:2560 (normal: 0), HHV-8 DNA Quantitative RT-PCR (serum) – not detected

CXR: Fullness of the left paratracheal region with mild contralateral tracheal deviation
CT Chest: 3.0 cm superior mediastinal soft tissue mass
PET CT Skull to Thigh: Mildly hypermetabolic activity involving a large, well-circumscribed soft tissue mass involving the left superior mediastinal region

Punch biopsy, right interlabial sulcus of the vulva: H&E demonstrated intraepidermal blisters, acantholysis, and tomb-stoning of the basal cell layer. Direct immunofluorescence of a perilesional specimen showed IgG1, C3 and IgG4 intercellular deposits within the epidermis.
Punch biopsy, vesicular lesion on palm: H&E demonstrated suprabasal acantholytic blistering and interface dermatitis. A dermal perivascular lymphohistiocytic infiltrate with eosinophils was also noted.

Excisional biopsy, paratracheal nodal mass: Infiltrate consisting of many small, involuted lymphoid follicles separated by large areas of highly vascular stroma containing numerous histiocytes and spindle cells consistent with hyaline vascular Castleman disease.

DIAGNOSIS

Paraneoplastic pemphigus in the setting of unicentric Castleman disease

TREATMENT AND COURSE

The patient was started on an aggressive topical regimen including clobetasol 0.05% ointment TID to vulvar and anal mucosal surfaces, triamcinolone 0.1% ointment TID to vermillion lips, dexamethasone 0.5 mg/5 ml solution swish/spit QID, and prednisolone acetate 1% ophthalmic suspension QID. A vaginal dilator was constructed using a condom filled with kerlix gauze, which was coated with clobetasol 0.05% ointment and inserted in the vaginal canal daily. The patient was also initiated on leuprolide for menstrual suppression to prevent vulvovaginal irritation due to bleeding.

In addition to her topical regimen, the patient received intravenous immunoglobulin (IVIG) (1g/kg weekly for two weeks) with moderate improvement in her mucosal and cutaneous lesions. She was discharged on prednisone 40 mg (1 mg/kg) daily with a plan for a slow taper as an outpatient and monitoring disease remission after resection of the Castleman disease. One week after discharge, the patient reported near-resolution of her palmoplantar and ocular involvement but incomplete resolution of her oral and vulvar mucosal disease. Subsequently, rituximab 375 mg/m^2 weekly for four weeks was added to her treatment regimen.

DISCUSSION

Paraneoplastic pemphigus (PNP), also known as paraneoplastic autoimmune multiorgan syndrome (PAMS) is a mucocutaneous blistering disease associated with underlying neoplasms, most commonly lymphoproliferative disorders. The pathogenesis of PNP is driven by both humoral and cell-mediated components. The humoral component primarily involves autoantibodies targeting desmoplakin, though numerous other targets have been identified. The cell-mediated component primarily consists of a mixed inflammatory infiltrate including CD8+ cytotoxic lymphocytes, CD56+ NK cells, and CD68+ monocytes/macrophages.

Patients with PNP present with severe mucositis and polymorphous skin lesions. Erosions and ulcerations involving the entirety of the oral mucosa including the tongue and extending onto the vermillion lips is a common presentation. The conjunctivae, nasopharynx, esophagus, and anogenital area can be also involved. Cutaneous lesions can be heterogenous, making diagnosis challenging. Diagnosis can be further complicated by the heterogeneity of histopathologic findings. In our patient, based on initial vulvar biopsy, a diagnosis of mucosal-predominant pemphigus vulgaris was highest on our differential diagnosis given the findings of intraepidermal acantholysis. However, the classic findings of PNP were identified on histopathologic evaluation of the palmar vesicular lesions that evolved during her hospitalization. This diagnosis was then corroborated by the indirect immunofluorescence studies showing a highly positive titer with the rat bladder substrate.

Castleman disease (CD) is a rare group of lymphoproliferative disorders characterized by an abnormal proliferation of morphologically benign lymphocytes. Currently, CD is classified into three distinct subtypes: unicentric CD (UCD), HHV-8-associated multicentric CD, and HHV-8 negative/idiopathic multicentric CD. Treatment for UCD involves complete resection of the involved lymph node(s). Surgical excision of the tumor is also the treatment of choice for PNP associated with UCD. While the evidence is weak, several case series have suggested that the prognosis of PNP associated with UCD is more favorable when compared to that of PNP

associated with other neoplastic processes. Most patients in these small studies saw clear, albeit slow, clinical improvement anywhere from six months to two years after surgery. If non-surgical treatment is required, limited data show the best efficacy for the early initiation of systemic glucocorticoids. Glucocorticoids are often combined with glucocorticoid-sparing agents including cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosporine, and more recently, rituximab. Lastly, combination therapy of rituximab with intravenous immunoglobulin has been used to successfully treat several cases that were initially unresponsive to conventional therapy.

KEY POINTS

1. PNP is a severe mucocutaneous blistering disease most commonly associated with lymphoproliferative neoplasms.
2. Affected individuals present with severe and painful mucositis, most often involving the oral mucosa with extension onto the vermillion lip. Cutaneous lesions have considerable variability making clinical diagnosis challenging.
3. The prognosis of PNP associated with UCD is favorable. Surgical excision of affected lymph nodes can be curative.

REFERENCES:

1. Kaplan, I. (2004). Neoplasms associated with paraneoplastic pemphigus: a review with emphasis on non-hematologic malignancy and oral mucosal manifestations. Oral Oncology, 40(6), 553–562. doi: 10.1016/j.oraloncology.2003.09.020
2. Fang, Y., Zhao, L., Yan, F., Cui, X., Xia, Y., & Duren, A. (2009). A critical role of surgery in the treatment for paraneoplastic pemphigus caused by localized Castleman's disease. Medical Oncology, 27(3), 907–911. doi: 10.1007/s12032-009-9304-y
3. Bolognia, J., Cerroni, L., & Schaffer, J. V. (2018). Dermatology. Philadelphia: Elsevier.

CHICAGO DERMATOLOGICAL SOCIETY **Case 2**

Presented by Parul Goyal, MD, Jessica Labadie, MD, and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 27-year-old black male with a history of well-controlled asthma presented to the hospital with new-onset numbness and tingling in the bilateral upper and lower extremities as well as an ulcerated plaque on the left chest

CHICAGO DERMATOLOGICAL SOCIETY **Case 3**

Presented by Derek Hsu, MD[1], Wendy Kim, DO[2], and Amy Paller, MD[1,3]
1. Department of Dermatology, Feinberg School of Medicine, Northwestern University
2. Department of Dermatology, Loyola University Medical Center
3. Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago

HISTORY OF PRESENT ILLNESS

A 10-month-old male infant who was born at 36.5 weeks gestational age presented with an extensive thick vernix and areas of denuded and shiny red skin. He had an extended neonatal intensive care unit (NICU) course at Loyola University Medical Center (Loyola), complicated by recurrent infections, poor feeding, and failure to thrive (FTT). Following discharge, he continued to have generalized redness and peeling of his skin, prompting multiple inpatient admissions to both Loyola and Lurie Children's Hospital of Chicago (Lurie), due to recurrent bacterial and viral infections.

His skin regimen included frequent moisturizer application, very dilute bleach baths, and intermittent use of topical anti-inflammatory medications, including triamcinolone 0.5% cream to the body and pimecrolimus 1% cream to the face and scalp. He was intensely pruritic and frequently rubbed his head against the bed.

PAST MEDICAL AND SURGICAL HISTORY

The patient was born via spontaneous vaginal delivery with an unremarkable prenatal course. APGAR scores were 5 and 9 and the patient required positive pressure ventilation briefly after birth. The mother received two doses of betamethasone for accelerated fetal lung maturity. She also received valacyclovir due to a past history of Herpes Simplex Virus type 1, though no active lesions were noted at time of delivery.

FAMILY AND SOCIAL HISTORY

The parents moved from Jordan 19 years ago and are first degree cousins. Prenatal genetic testing performed in Jordan was unremarkable. The patient has four healthy older siblings without any medical conditions. His father has a history of atopic dermatitis.

PHYSICAL EXAMINATION

The infant appeared small for age and screamed with discomfort when touched. His skin was diffusely erythematous with small foci of scaling alternating with superficial denudement on all body areas. He had no bullae. He had a hemorrhagic erosion on the right temporal scalp.

The palms and soles were erythematous and moderately thickened with erythema and fine scaling. He was alopecic, with scaling and scattered tufts of soft dark hairs on the scalp. The eyelids did not completely close, although no conjunctivitis was noted. Just lateral to the umbilicus, there was an intact gastrostomy tube without surrounding erythema or drainage.

LABS

Newborn screen: Positive for lysosomal storage disease (alpha-galactosidase level 10% of normal), concerning for Fabry disease. Unlikely to be associated with patient's current presentation, given the late onset of signs and cutaneous manifestations of Fabry disease.

Immune evaluation:
- Total Lymphocyte Enumeration with CD45 RA and CD45 RO, normal
- Immunoglobulins normal, except IgA <7, low
- T, B and NK cells, normal
- IgE <2kU/L, normal
- Eosinophils 0.5%, normal

Genetic testing (congenital ichthyosis panel, XomeDxSlice): Homozygous deletion in a codon in the Desmoglein-1 (Dsg1) gene

DIAGNOSIS

Severe dermatitis, multiple allergies, and metabolic wasting (SAM syndrome)

CURRENT TREATMENT AND COURSE

For the FTT, and given the propensity to eosinophilic gastritis and esophagitis, the patient was started on Elecare, a hypoallergenic formula composed of hydrolyzed proteins. In addition, the patient received olive oil supplementation and G-tube based nighttime supplemental feeding, as well as ranitidine 21mg daily and multivitamins. For his skin care, he was started on a regimen of Aquaphor ointment every two hours (with nursing assistance at home) and pimecrolimus 1% cream twice daily to the head and neck.

For his recurrent infections, he was prescribed prophylactic sulfamethoxazole-trimethoprim 160mg-32mg daily. Although dilute bleach baths were recommended, the standard 0.005% bleach bath was too drying and seemed to increase his pruritus. The current concentration of sodium hypochlorite in the bath is minute.

Based on the immunophenotype now recognized for ichthyosis, the responsiveness of patients with a similar disorder (erythrokeratoderma-cardiomyopathy, or EKC syndrome) to ustekinumab, and the good response of patients with SAM syndrome to secukinumab reported at the European Society for Pediatric Dermatology (ESPD) in May 2019, a course of secukinumab was considered. Compassionate use application to Novartis (manufacturer of secukinumab), an emergency Investigational New Drug (IND) to the FDA, and a rapid institutional review board (IRB) approval process were initiated.

As a result, the patient was initiated on a research study of secukinumab 75 mg monthly with the first dose given on August 19, 2019, the 2nd dose given on September 23, 2019, and the 3rd dose given on October 23, 2019, with a plan for injections every four weeks. Although the skin appears unchanged at this time, the patient has not had a recent infection, and he is growing.

DISCUSSION

Severe dermatitis, multiple allergies, and metabolic wasting, or SAM syndrome, is a rare condition most commonly attributed to a loss-of-function mutation in desmosomal plaque protein desmoglein-1 (Dsg1). Few cases have been reported in the literature. The disease is characterized by erythroderma and desquamation, failure to thrive, recurrent infections, multiple allergies and intense pruritus. This condition was first reported in 2013 by Samuelov *et al*. in patients born to families of Arab Muslim (in healthy first degree cousins) and of Druze descent. All patients demonstrated the triad of symptoms in addition to hypotrichosis and a palmoplantar keratoderma-like presentation. Histopathological examination showed psoriasiform dermatitis with alternating para- and ortho-keratosis, hypo- and hyper-granulosis and widespread acantholysis within the spinous and granular layers. Using NextGen sequencing through whole-exome capture, different mutations in Dsg1 were identified. Two of the six patients studied succumbed to sepsis at an early age.

There can be significant phenotypic overlap among those who have the condition. In Israel, Taliber *et al.* described three patients with SAM syndrome, all with dermatitis, palmoplantar keratoderma, food allergy, atopic manifestations, and elevated IgE levels. Remarkably, one patient demonstrated only limited skin involvement. Molecular analysis revealed a different splice

site mutation in the exon processing of Dsg1, leading to mislocalization rather than complete absence of desmoglein-1.

One patient who was originally described as having SAM syndrome based on clinical features had a biallelic mutation in DSP (encoding desmoplakin) in an exonic region that is typical for EKC (erythrokeratoderma-cardiomyopathy) syndrome. In fact, there is considerable phenotypic overlap between these two desmosomal disorders. DSP mutations and EKC syndrome have responded well to ustekinumab treatment. Another study from Israel reported a patient with SAM syndrome, although a mutation in Dsg1 was not found; indeed, a novel *de novo* compound heterozygous missense mutation in the desmoplakin gene was identified.

Minor cardiac developmental defects were noted in two patients in the study by Samuelov *et al*., which suggests further overlap between SAM and EKC syndrome, as would be consistent with a desmosomal disorder, given the important role of desmosomal proteins in cardiac function. Esophageal involvement can also be extensive in patients with SAM syndrome, with a few of the case reports detailing eosinophilic esophagitis as well as severe esophageal reflux. This may contribute to the metabolic wasting as well.

Treatment is primarily with supportive care, including frequent use of emollients, calcineurin inhibitors to the craniofacial areas, optimal nutritional support with hydrolyzed proteins and essential fatty acids, and close monitoring for any infectious sequelae. Based on the reports of the immunophenotype of ichthyotic disorders and the good response to ustekinumab in two children with EKC syndrome, Hernandez-Martin *et al.* from Spain tried ustekinumab in an infant with SAM syndrome. However, no clinical improvement was noted. They then used secukinumab in that infant, a 17-month-old boy, and another 10-month-old girl, also with SAM syndrome. IL-17 secreting T cell frequencies of up to 60 times higher than controls were observed in both patients, as shown by flow cytometry. After five to nine months of treatment with secukinumab, the patients showed a substantial improvement in their pruritus and were thriving. Clinical improvement was correlated with a reduction in the level of IL-17 secreting T cells, which suggests that secukinumab may be a promising treatment in patients with SAM syndrome.

KEY POINTS

1. Severe dermatitis, multiple allergies, and metabolic wasting, or SAM syndrome, is a rare condition due to a mutation in desmoglein-1.
2. Frequent use of emollients, nutritional support, and careful monitoring for infections is critical.
3. IL-17 blockade may represent a novel treatment in patients with SAM syndrome.

REFERENCES:

1. Paller, A.S., et al., *The spectrum of manifestations in desmoplakin gene (DSP) spectrin repeat 6 domain mutations: Immunophenotyping and response to ustekinumab.* J Am Acad Dermatol, 2018. 78(3): p. 498-505.e2.
2. Samuelov, L., et al., *Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting.* Nature genetics, 2013. 45(10): p. 1244-1248.
3. Taiber, S., et al., *SAM syndrome is characterized by extensive phenotypic heterogeneity.* Experimental Dermatology, 2018. 27(7): p. 787-790.
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5. Hernandez-Martin, A., et al., *Are Biologics a Therapeutic Hope for Keratinization Disorders? Our Experience in Two Patients with SAM Syndrome Treated with Secukinumab?* Pediatric Dermatology, 2019. 36(S1): p. S3-S8.

CHICAGO DERMATOLOGICAL SOCIETY **Case 4**

Presented by Spencer Ng, MD, PhD, and Jennifer Choi, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 63-year-old Caucasian male with a past medical history of a Stage IIIB melanoma of the left parietal scalp excised 7 months prior presented for evaluation of new pink nodules near his surgical scar.

PAST MEDICAL AND SURGICAL HISTORY

The patient received a kidney transplant from an unrelated living donor in 2017 due to polycystic kidney disease. His melanoma was excised 7 months prior to presentation with surgical pathology demonstrating a BRAF V600E positive tumor that was 3.2 mm deep. A sentinel lymph node biopsy revealed a positive post-auricular lymph node. Complete lymph node dissection was positive for another Level IV lymph node (pT3aN2a; Stage IIIB). He was subsequently treated with adjuvant encorafenib, but this medication was discontinued after one week due to severe hand-foot syndrome. He had a history of ischemic cardiomyopathy resulting in heart failure with reduced ejection fraction (left ventricular ejection fraction 35% at the time of presentation).

MEDICATIONS

Tacrolimus 2 mg qAM, 1 mg qHS, Everolimus 1 mg BID, Sulfamethoxazole-trimethoprim 400-80 mg qMWF, Metoprolol succinate 12.5 mg qd, ASA 81 mg qd, Rosuvastatin 5 mg qd

PHYSICAL EXAM

Examination of the head and neck revealed a scar from his prior wide local excision on the left parietal scalp. Extending from the left vertex scalp down to the left parietal scalp, there were 32 pink, firm nodules (2-6mm in size). On the left preauricular cheek, there were 7 pink nodules (2-5mm in size). No cervical, supraclavicular, or axillary lymphadenopathy was noted.

LABS

Normal: CBC, CMP

PATHOLOGY

A deep shave biopsy of the largest nodule on the left parietal scalp was performed. Pathology showed malignant melanoma (nodular type), with a Breslow depth of 1.1 mm extending to the deep margin.

DIAGNOSIS

In-transit cutaneous metastatic melanoma

TREATMENT AND COURSE

After discussion at our Multidisciplinary Melanoma Tumor Board, the decision was made to perform a trial of localized immunotherapy with talimogene laherparepvec (T-VEC) in order to avoid risk of organ rejection with systemic therapies. Importantly, with guidance from the patient's nephrologist, his immunosuppression was decreased as much as was deemed possible. Tacrolimus was discontinued and everolimus 1 mg BID was continued.

After two courses of T-VEC (1 million PFU/mL and 100 million PFU/mL per protocol), he continued to show progression of cutaneous disease with over 50 nodules on the scalp and over 20 nodules on the left cheek. Given the thus far lack of response to T-VEC monotherapy, the patient was instructed to add topical imiquimod 5% cream, 2 packets nightly (1 gram) over the affected areas 3 nights on and 1 night off.

Two weeks after adding adjuvant imiquimod, he presented with significant crusting of the left parietal scalp nodules and almost complete flattening of the nodules on the left cheek. There was notable associated left postauricular and cervical adenopathy. T-VEC injections (100 million PFU/mL) every two weeks and nightly imiquimod 5% cream were continued for a total of 16 weeks and 8 sessions of T-VEC injections until all visible nodules resolved completely. To date, 8 months after his last T-VEC injection, he remains free of disease.

DISCUSSION

In-transit cutaneous metastatic melanoma is defined any metastases to the skin and subcutaneous tissues in the same draining lymph node basin as the primary tumor and occurs in 2-13% of patients diagnosed with malignant melanoma. Treatment of this condition involves regional or systemic approaches including surgical resection, localized chemotherapy, or systemic immunotherapy with targeted kinase inhibitors or immune checkpoint inhibitors, all of which were not possible given our patient's intolerance of BRAF inhibitors, his history of renal transplant and the anatomic location of his metastases.

Talimogene laherparepvec (T-VEC) is an oncolytic virus and is FDA approved for the treatment of Stage III/IV melanoma.[2] It is a herpesvirus (based on HSV-1) that is genetically altered to selectively replicate in transformed cells causing them to lyse. It also contains a transgene for the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate anti-tumor immunity. Given this mechanism of immune activation, there is potential concern for the risk of transplant rejection. However, the only published report of T-VEC's use in a transplant patient was in a case report of a heart transplant recipient with recurrent locally advanced melanoma, who experienced a complete local response without signs of allograft rejection. Due to our patient's limited therapeutic options, it was the recommendation of our institution's multidisciplinary tumor board that he be treated with a trial of intralesional T-VEC.

To our knowledge, this is the first report utilizing T-VEC in combination with topical imiquimod for the treatment of in-transit cutaneous metastasis in melanoma, and the first report of their use together in a transplant patient. The clinical improvement seen in the patient after the addition of imiquimod to T-VEC highlights the importance of the combinatorial approach to therapy. Imiquimod, a TLR-7 agonist, has long been used as an adjuvant to other therapies for the treatment of cutaneous melanoma. A phase I/II study in 13 patients with malignant melanoma treated with the combination of IL-2 and imiquimod showed a durable clinical response in approximately 50% of the lesions, with no recurrence on treatment cessation. Similarly, a case series of 11 patients showed that combining intralesional IL-2, a topical retinoid, as well as imiquimod also showed a 100% response rate. In a separate retrospective case series of 9 patients, intralesional Bacille-Calmette Guerin (BCG) given together with imiquimod was also shown to have a significant clinical effect.

From this case, it appears that T-VEC can be considered as a treatment option when used with caution and very close monitoring in the setting of renal transplant and immunosuppression. Further, in patients with limited therapeutic options including disease that is inoperable, where targeted kinase therapy inhibitor is not tolerated or not an option, or in those where systemic immune checkpoint blockade therapy is contraindicated, the use of T-VEC in combination with topical imiquimod can be a consideration to treat in-transit cutaneous metastatic melanoma.

KEY POINTS

1. Melanoma may metastasize to skin and subcutaneous tissues in the same draining lymph node basin as the primary tumor and is known as in-transit cutaneous metastases.

2. Talimogene laherparepvec (T-VEC) is an oncolytic HSV1-based virus approved by the FDA for the treatment of metastatic melanoma and may be safely used with caution in transplant patients with systemic immunosuppression.
3. Topical imiquimod may be used as an adjuvant with T-VEC for the treatment of cutaneous metastases.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 5**

Presented by Molly Stout, MD and Alan Zhou, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 29-year-old Puerto-Rican male with a past medical history of Hermansky Pudlak syndrome (HPS) and granulomatous colitis presented for evaluation and management of chronic painful parastomal ulcerations following a hospitalization for a colitis flare. The patient denied a recent history of easy bleeding or bruising, shortness of breath, or cough.

PAST MEDICAL AND SURGICAL HISTORY

The patient was originally diagnosed with colitis in 2006 after presenting to gastroenterology with chronic diarrhea. In 2009, the patient was formally diagnosed with Hermansky Pudlak syndrome sybtype 1, which was confirmed with genetic testing. The patient's colitis had been complicated by several perirectal abscesses and numerous bowel surgeries, including proctocolectomy and end ileostomy in 2017. He reported a history of easy bruising as a child. He also had a history of visual impairment, nystagmus, strabismus and asthma.

FAMILY AND SOCIAL HISTORY

The patient had no family history of albinism, bleeding diathesis, pulmonary disease or inflammatory bowel disease. He is of Puerto-Rican and Mexican descent.

MEDICATIONS

Medications included dicyclomine as needed as well as tacrolimus 0.1% and triamcinolone 0.01% ointment applied to the parastomal ulcerations. Previously, his colitis had been managed with sulfasalazine, azathioprine, infliximab, adalimumab, tacrolimus, and vedolizumab until he experienced treatment failure.

PHYSICAL EXAM

The patient was well-appearing, in no apparent distress. Exam demonstrated notable pigmentary dilution diffusely with brown hair and light irises with strabismus and nystagmus. The ostomy site showed a well demarcated ulcerated plaque with overlying granulation tissue. Scattered at the periphery of his ostomy bag adhesive were beefy-red erosions and ulcerations. The right inguinal crease had a beefy-red ulcerations and background scarring. Perianal skin had few superficial linear fissures and erosions.

LABS

Normal: CBC, CMP

PATHOLOGY

Biopsy near the edge of the parastomal ulceration showed granulomatous and suppurative dermatitis. Stains were negative for microorganisms.

DIAGNOSIS

Crohn's disease-like colitis in the setting of Hermansky Pudlak syndrome, with cutaneous involvement

TREATMENT AND COURSE

The patient received intralesional triamcinolone to six inflamed sites around the stoma, which resulted in temporary improvement in pain. He was instructed to start clobetasol 0.05% ointment daily to the affected areas. At follow up visit one month later, he was started on a 14-day course

of doxycycline 100 mg BID as well as daily clindamycin 1% lotion due to concerns for superinfection. One month later, due to progression of both cutaneous and gastrointestinal disease, ustekinumab was recommended. The patient underwent induction with 520 mg intravenous ustekinumab followed by 80 mg subcutaneously every 8 weeks, resulting in modest improvement in ulcerations and pain. He was referred to pulmonology for baseline evaluation and pulmonary function tests for his diagnosis of Hermansky Pudlak syndrome.

DISCUSSION

Hermansky Pudlak syndrome is a rare, autosomal-recessive disorder of pigmentation, characterized by pigmentary dilution, a bleeding diathesis and variable organ involvement. There are nine subtypes of HPS recognized, each due to a gene mutation affecting one of four protein complexes (AP-3, BLOC-1, BLOC-2, BLOC-3), which support intracellular protein trafficking. Affected lysosome-related organelles include melanosomes, platelet dense bodies, lamellar bodies of pneumocytes and granule proteins of immune cells. Founder mutation effect has been attributed to large populations of HPS1 and HPS3 in north east Puerto Rico, as in our patient.

Clinically, all patients with HPS present with pigmentary dilution and a bleeding diathesis. Patients may exhibit decreased pigmentation of skin and hair, often lighter than family members. Hair color may range from silver white to light brown or red and eyes demonstrate reduced iris pigment, varying in color from light blue to light green. Ocular features also include early nystagmus, photosensitivity, reduced visual acuity, and reduced retinal pigmentation. Bleeding diatheses may range from easy bruising and epistaxis to prolonged bleeding after procedures. Additional manifestations, including pulmonary fibrosis and granulomatous colitis, vary by associated mutation. The average lifespan is 30-50 years with death commonly attributed to pulmonary fibrosis.

Diagnosis is suspected in patients with pigmentary dilution and nystagmus in the setting of bleeding history, respiratory problems or granulomatous colitis. Genetic testing, if available, can confirm the diagnosis and specify the type of HPS. Management includes a multidisciplinary approach involving dermatology, ophthalmology, hematology, gastroenterology, and pulmonology when relevant. Dermatologic care includes the prevention of skin cancer with sun protection from infancy and skin exams every 6-12 months from adolescence.

The granulomatous colitis seen in our patient is associated with HPS subtypes 1 and 4 and is phenotypically similar to Crohn's disease (CD). There are several proposed mechanisms for the colitis in HPS, including attribution to the accumulation of ceroid-like pigment in intestinal macrophages, leading to the release of lysosomal hydrolases and resultant tissue damage. In addition, the BLOC complex of proteins mutated in HPS co-locates with proteins identified as susceptibility genes for CD when mutated, raising the question of whether these patients are predisposed to develop CD. Though this granulomatous colitis is well-described in the HPS literature, there is little data regarding cutaneous findings in these patients. In our patient, his peristomal lesions appeared clinically and histologically similar to cutaneous CD, which we feel may be a rare or under-reported association with HPS-associated colitis.

Given the clinical similarity of HPS-associated granulomatous colitis to CD, the therapeutic approaches are similar. In patients with HPS colitis, pro-inflammatory conditions often overwhelm the strongest immunomodulators, leading to treatment resistance. Our patient had failed numerous biologic medications including adalimumab and infliximab, and therefore ustekinumab was chosen due to reports of its use in patients with TNF-a inhibitor-refractory CD and cutaneous CD.

We present this case to highlight a rare condition with an unusual presentation. Early recognition of HPS by a dermatologist may facilitate referrals to appropriate specialists as these patient's require multidisciplinary care.

KEY POINTS

1. Hermansky Pudlak syndrome is an autosomal-receive disorder of vesicle trafficking that presents with oculocutaneous albinism, a bleeding diathesis and variable systemic manifestations including pulmonary fibrosis and granulomatous colitis.
2. Granulomatous colitis is associated with HPS Types 1 and 4 and has a phenotype similar to Crohn's disease, which may be refractory to standard treatments.

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Emily Merkel, MD, Raj Chovatiya, MD, PhD, Lauren Guggina, MD, Joan Guitart, MD, and Alan Zhou, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 64-year-old male presented for evaluation of a worsening eruption and facial swelling

CHICAGO DERMATOLOGICAL SOCIETY **CASE 7**

Presented by Rachel Eisenstadt, MD, Lida Zheng, MD, and Jennifer Choi, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 43-year-old female presented to the Northwestern hepatology service for expedited evaluation of recently diagnosed decompensated cirrhosis. Dermatology was consulted for painful, erythematous to violaceous papules affecting the face, chest, upper and lower extremities, hands, and feet of two months duration.

The patient was in her usual state of health until four months prior to presentation, when she developed progressive lower extremity edema. In addition to the sequelae of her cirrhosis, she noted chronic chills, low-grade fevers, persistent cough productive of white-yellow sputum, and chronic back pain. She denied a history of recent travel.

PAST MEDICAL AND SURGICAL HISTORY

The patient had a history of recently diagnosed nonalcoholic steatohepatitis (NASH) cirrhosis, which was diagnosed four months prior to presentation at Northwestern. Cirrhosis was complicated by ascites, hepatopulmonary syndrome, hemolytic anemia and thrombocytopenia. Additionally, the patient had a history of obesity and hypothyroidism.

FAMILY AND SOCIAL HISTORY

Family history was significant for liver disease in grandmother and aunt. The patient worked as an embalmer and funeral home director, however was unable to work at the time of presentation due to illness.

MEDICATIONS

Prior to admission, the patient's medications included gabapentin100 mg TID, levothyroxine 75 mcg, and furosemide 40 mg daily. The patient was started on ciprofloxacin 500 mg BID, ceftriaxone 1 g daily, prophylactic subcutaneous heparin, and lactulose 15 ml TID.

PHYSICAL EXAM

Examination demonstrated a chronically ill-appearing, obese female with scleral icterus and diffuse jaundice. Involving the face, upper back, chest, and arms were approximately 40 violaceous papules and papulonodules, some with central hemorrhagic crusting, and collarettes of scale. Involving the palm was a single hemorrhagic bulla.

LABS/IMAGING

Abnormal:
CBC: Hemoglobin 7.2 [ref 11.6 - 15.4 g/dL], Platelets 96 [140 – 390 K/UL], C-Reactive Protein 3.7 [ref 0.0-0.5 mg/dl] AST 61 [ref 0-39 units/L], ALT 27 [ref 0-52 units/L], ALP 234 [ref 34 – 104 units/L], Total Bilirubin 10.7 [ref 0.0-1.0 mg/dl], INR 2.7 [ref 0.8-1.2]
Chest CT: large right-sided pleural effusion and numerous pulmonary infiltrates

Histology, right upper arm: H&E demonstrated superficial and deep collection of neutrophils and nuclear debris. The adjacent dermis demonstrated reactive changes and fibroplasia consistent with a suppurative and granulomatous dermatitis. DPAS, Gram Stain, Acid Fast Bacilli stains were negative. Repeat biopsy demonstrated similar findings with cultures negative for fungi, bacteria, or mycobacteria.

Normal/Negative:
CBC: WBC 9.9 [ref 3.5-10.5 K/UL] 71% Neutrophil
Infectious work-up: HIV, RPR, Quant Gold, Blastomyces, Histoplasmosis, Toxoplasma, Cryptococcus, Respiratory Virus Panel, Pneumocystis and Legionella serologies negative
Cultures: Wound culture, pleural fluid culture, blood culture, fungal blood culture, bronchoscopy culture all negative for growth of organisms
Tissue Culture: Bacterial, fungal and mycobacterial tissue cultures negative for growth of organisms

DIAGNOSIS
Acute Febrile Neutrophilic Dermatosis (Sweet syndrome)

TREATMENT AND COURSE
The patient underwent thoracentesis and bronchoscopy with both pleural fluid and bronchoalveolar lavage negative for growth of microorganisms. The patient remained on antibiotics due to continued concern for infectious process, however her clinical status continued to decline, requiring ICU transfer for respiratory failure. At this time, the patient was removed from the liver transplant list given high suspicion for underlying infection. After extensive work-up to rule out infectious etiologies, including multiple sets of negative tissue cultures, a clinical diagnosis of Sweet syndrome was made. The patient was initiated on corticosteroid therapy at 1 mg/kg/day with rapid improvement in her skin lesions and cough. Subsequently, she continued to decompensate from her underlying cirrhosis and underwent orthotopic liver transplantation. She received post-transplant immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone without clinical decompensation. Approximately eight months post-transplant, she had an episode of CMV viremia and colitis, with recurrence of approximately 100 painful pink papules involving the scalp, back, lower extremities and hands. Repeat biopsy was demonstrated a dense neutrophilic infiltrate consistent with Classical Sweet syndrome. She was treated with a two week course of IV Ganciclovir for CMV viremia and topical fluocinonide 0.01% cream with resolution of lesions and without further recurrence.

DISCUSSION
Sweet syndrome is a neutrophilic dermatosis hypothesized to result from localized dysregulation of neutrophil-predominant cytokines, including IL-1, G-CSF, IFN-gamma. Histopathologically, Sweet syndrome presents with predominantly dermal, neutrophil-rich infiltrates, edema in the superficial dermis, without evidence of associated leukocytoclastic vasculitis. Histiocyotoid and lymphocytic variants are increasingly recognized. Sweet syndrome may be further divided into classical (or idiopathic), malignancy associated (15-30%, favoring hematologic malignancy), or drug-associated (10%, G-CSF as frequent culprit). Well-established associations for classical Sweet syndrome include preceding infection, pregnancy, and inflammatory bowel disease.

Classical sweet syndrome typically presents abruptly as painful, non-pruritic papules, papulonodules, and plaques favoring the head, neck, and upper extremities in a middle aged female. In addition to associated fevers, patients may present with extra-cutaneous manifestations including arthralgias, pulmonary infiltrates as well as ocular, and renal manifestations.

The diagnostic criteria established by Su and Liu in 1986 require both major criteria and at least two minor criteria for diagnosis. Major criteria include 1) acute onset of classic lesions with 2) classic pathologic correlation. Minor criteria include 1) presence of associated conditions such as infection, auto-immune condition, malignancy, implicated drug, or pregnancy, 2) fever or

associated systemic manifestations, 3) leukocytosis with neutrophil predominance, and 4) responsiveness to corticosteroids.

Though cirrhosis is not classically linked to a diagnosis of Sweet syndrome, cirrhosis is a state of dysfunction of the innate and adaptive immune system. This subsequent cytokine dysregulation may be implicated in the inflammatory response seen in Sweet syndrome.

Treatment of classical Sweet syndrome generally includes topical or intralesional corticosteroids for mild disease and oral glucocorticoids for more severe presentations, including in patients who present with systemic involvement. Relapse is common and can occur in up to 30% of patients. Steroid-sparing agents used for long-term management of recurrent Sweet syndrome include dapsone and colchicine.

A diagnosis of Sweet syndrome should be considered in a patient with the abrupt onset of painful papulonodules, associated systemic findings and negative infectious work-up. In this case, identifying Sweet syndrome as a multi-system disease process was essential in the therapeutic decision to safely pursue orthotopic liver transplantation and immune suppression in a critically ill patient. We present this case to highlight a challenging case of atypical Sweet syndrome closely resembling infection.

KEYPOINTS

1. Sweet syndrome classically presents with painful papulonodules on the head neck and upper extremities and is commonly associated with underlying infection, malignancy, or drug exposure.
2. Sweet syndrome is often associated with systemic findings including fever, malaise, and joint pain and may involve internal organs.
3. First-line treatment is systemic glucocorticoids, with relapse occurring in approximately 30% of patients upon cessation; therefore, close follow-up is recommended.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 8**

Presented by Jessica G. Labadie, MD, and Jaehyuk Choi MD, PhD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 60-year-old Caucasian woman with no significant past medical history presented to Northwestern Memorial Hospital with a worsening pruritic eruption and diffuse hyperpigmentation of two years duration, encompassing >90 percent body surface area (BSA). History was also notable for myalgias, double vision, hot flashes, chills, night sweats and intentional weight loss. She had previously been treated by outside dermatologists for presumed diagnoses of tinea corporis and generalized granuloma annulare, with a number of agents including topical antifungals, prednisone, hydroxychloroquine, azathioprine, montelukast, dupilumab and topical corticosteroids with no improvement.

PAST MEDICAL AND SURGICAL HISTORY

The patient was otherwise in her usual state of health and was up to date on her routine cancer screening, including mammography, Pap smear, and colonoscopy. She reported a recent endometrial ablation due to uterine fibroids.

FAMILY AND SOCIAL HISTORY

The patient's family history was significant for her mother and two maternal aunts passing away from endometrial carcinoma. She denied recent travel or unique exposures.

MEDICATIONS

Triamcinolone ointment 0.1% BID, gabapentin 200 mg PO BID, pramoxine lotion liberally

PHYSICAL EXAM

The patient was well-appearing, in no apparent distress. She was Fitzpatrick skin type II with diffuse widespread bronze hyperpigmentation, including photo-protected areas. There were several large, raised annular and serpiginous wood grain-pattered plaques with light pink raised leading edges and yellow to light red centers (BSA> 90%). Oral, ocular and genital mucosae were clear, and she had no lymphadenopathy.

LABS/IMAGING

Pertinent Positive Labs: CBC with rising absolute eosinophil count to a peak of ~10.5 x 10^9/L
Pertinent Negative Labs: Normal WBC and peripheral smear, CMP, Immunoglobulins
Rheumatologic Evaluation: Negative SSA/SSB, C3/C4
Infectious Evaluation: Negative stool O/P, Borrelia IgG/IgM, HIV
Endocrinology Evaluation: Decreased AM cortisol (chronic corticosteroid use), normal ACTH
Dermatology Evaluation: Negative BP230/BP180 antibody titers; punch biopsy demonstrated perivascular eosinophilic infiltrate consistent with a hypersensitivity reaction; flow cytometry showed normal T cells and TCR V beta was negative
Oncologic Evaluation: Colonoscopy, mammogram, CT/PET, transvaginal ultrasound, chest x-ray were negative for malignancy; bone marrow biopsy demonstrated hypercellular marrow with increased eosinophils and eosinophilic precursors; FISH was negative for translocations

DIAGNOSIS: Idiopathic Hypereosinophilic Syndrome with Erythema gyratum repens (EGR)-type cutaneous eruption

TREATMENT AND COURSE

Initial treatment plan included a janus kinase inhibitor, however insurance approval was denied for this medication. Instead, dapsone was initiated and titrated to a dose of 50 mg BID. Within two

weeks of dapsone initiation, the patient's absolute eosinophil count decreased and the patient noticed improvement in her cutaneous and systemic symptoms.

DISCUSSION

Hypereosinophilic syndromes (HES) comprises a heterogenous group of uncommon disorders defined by: 1) blood eosinophilia greater than 1.5 x 10^9/L on two occasions separated by four weeks, 2) no evidence of an underlying condition causing hypereosinophilia (such as parasite, medication, or malignancy), 3) evidence of end organ damage or dysfunction, which results from infiltration of eosinophils and can affect any organ system. There are three main identifiable HES variants reported:

M-HES: The myeloproliferative variant of HES (M-HES) is characterized by features typically seen with myeloproliferative diseases. The majority of these patients will have an interstitial deletion on chromosome 4q12 that results in *FIP1L1-PDGFRA* translocation that can be detected by FISH. These patients are often treated with imatinib, a tyrosine kinase inhibitor.

***L*-HES**: The lymphocytic variant of HES (L-HES) is characterized by polyclonal eosinophil expansion due to over-production of IL-5 by dysregulated T cells, which are detected by abnormal surface phenotypes (CD3−CD4+ and CD3+CD4−CD8−). Newer treatment modalities have emerged and include janus kinase inhibitors (tofacitinib and ruxolitinib) and benralizumab.

***i*HES:** Idiopathic HES (iHES) represents the majority of HES patients where the etiology remains unclear. These patients typically have hypercellular marrow characterized by an increase in eosinophils and eosinophilic precursors, however lack any of the typical translocations. Janus kinase inhibitors and dapsone have proven successful.

Skin involvement, specifically pruritus, is a common finding among these patients, however there is no characteristic cutaneous manifestation of HES. In our patient, the skin lesions manifested as an EGR-type eruption, thus prompting a thorough malignancy screening to completely rule out the possibility of malignancy. Her hyperpigmentation was thought to be a reactive process and underlying causes of diffuse bronzing such as Addison's disease were also ruled out. In general, prognosis for these patients is promising given absolute eosinophil counts can remain under control. Constant monitoring is necessary and often a multidisciplinary approach with hematology/oncology, dermatology, allergy and other specialties is required.

KEY POINTS

1. HES is diagnosed by having an AEC of greater than 1.5 x 10^9/L on two occasions separated by two weeks plus signs of end organ damage.
2. EGR is typically considered a paraneoplastic figurate erythema, but can occur in the absence of malignancy. Our case highlights the ability for EGR to occur as a cutaneous manifestation of HES, as described only by one other group in the literature.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 9**

Presented by Liza Siegel, MD[1], and Anthony J. Mancini, MD[1,2,3]

1. Department of Dermatology, Feinberg School of Medicine, Northwestern University
2. Department of Pediatrics, Feinberg School of Medicine, Northwestern University
3. Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago

HISTORY OF PRESENT ILLNESS

An eight-year-old Caucasian male with a history of eczema, penile chordee and macrocephaly was referred to Dermatology by Urology for evaluation of skin integrity in preparation for upcoming urologic surgery. The patient had undergone two prior surgeries for repair of the penile chordee with recurrence of ventral curvature. His parents denied a history of easy bruising or bleeding.

PAST MEDICAL AND SURGICAL HISTORY

The patient was born at 33.5 weeks gestational age due to placental abruption. He was born with penile chordee and underwent two surgical repairs, at ages one and six years, both followed by recurrence of ventral curvature. He had a history of four lipomas on the trunk, first noted at 18 months of age, which were excised by pediatric surgery. He was born with an isolated cafe au lait patch on his right arm. Due to family history of type 1 neurofibromatosis, he was evaluated by Ophthalmology at 18 months of age, without evidence of Lisch nodules or retinal astrocytomas. His history was also notable for mildly delayed acquisition of developmental milestones as an infant and macrocephaly, with the patient's head circumference tracking at the 90th percentile as an infant and subsequently crossing to >99th percentile at eight months of age.

FAMILY AND SOCIAL HISTORY

The patient's paternal aunt has type 1 neurofibromatosis.

MEDICATIONS

None

PHYSICAL EXAM

The patient was well-appearing and in no apparent distress. He had both macrocephaly and dolicocephaly. He had scattered ephelides on the cheeks. There were well-healed, white linear surgical scars on the left mid and right upper back, left flank, and inferior to the umbilicus. On the right forearm, there was a uniform, tan, well-demarcated patch. Genital exam was notable for thin, fibrous adhesion bands from the ventral penis to the upper scrotum and an overall curved appearance to the penis. There were no erosions, ulcerations, keloid scars, ecchymoses, capillary malformations or molluscoid pseudotumors present. No lentigines were present on the penile shaft or glans penis.

LABS/IMAGING

PTEN sequencing and deletion/duplication analysis: Pathogenic mutation of c.138C>A (Tyr46Ter). This substitution creates a nonsense variant, which changes a Tyrosine to a premature stop codon (TAC>TAA) and is predicted to cause loss of normal protein function.

Thyroid ultrasound: 11 x 5 x 6 mm hypoechoic mass in the right thyroid which appeared both solid and cystic. Follow up ultrasound six months later revealed a stable mass as well as an additional 9 x 3 x 5 mm hypoechoic lesion on the right, which appeared solid and cystic. Results of fine-needle aspiration of both masses were benign.

DIAGNOSIS
Bannayan-Riley-Ruvalcaba syndrome (BRRS), a *PTEN* hamartoma tumor syndrome (PHTS)

TREATMENT AND COURSE
The patient was advised to follow the same cancer surveillance guidelines as individuals with Cowden syndrome, another disorder within the spectrum of PHTS. For a pediatric patient this includes yearly thyroid ultrasound from the time of diagnosis, and yearly dermatology follow up.

DISCUSSION
Bannayan-Riley-Ruvalcaba syndrome (BRRS) is an autosomal dominant multiple hamartoma syndrome caused by mutations in the *PTEN* gene. *PTEN* hamartoma tumor syndrome (PHTS) is the terminology used to describe a collection of syndromes including BRRS, Cowden syndrome (CS) and Lhermitte-Duclos syndrome, which result from germline mutations in the tumor-suppressor gene *PTEN*.

Phosphatase and tensin homolog (PTEN) is a protein encoded by the *PTEN* gene. PTEN plays a role in cell-cycle regulation and apoptosis by downregulating the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, which promotes cellular proliferation and survival. A mutation in PTEN results in unregulated cellular proliferation and the formation of hamartomas, particularly in tissues with high physiologic proliferation, such as the epidermis, oral and GI mucosa, as well as thyroid and breast epithelium.

The most common clinical feature of BRRS is macrocephaly. Other common clinical findings include multiple subcutaneous and visceral lipomas (75%), pigmented macules of the penis (50%), vascular malformations, oral papillomas, acral keratoses, acanthosis nigricans, joint hyperextensibility, scoliosis, pectus excavatum, hamartomatous intestinal polyps, and down-slanting palpebral fissures. There is significant overlap in the clinical findings of CS and BRRS, and identical mutations have been found in patients with these syndromes. In some families, both BRRS and CS have been observed. Pigmented macules of the penis and lipomatosis are the two findings that are common in BRRS and rarely seen in patients with CS.

Lipomas present primarily in adults over 30 years of age, and in children are rare and should prompt investigation into a possible underlying syndrome. BRRS, encephalocraniocutaneous lipomatosis (ECCL), CLOVES syndrome, and congenital symmetrical circumferential skin creases (aka Michelin tire baby syndrome) are four childhood syndromes that include lipomas or lipomatous overgrowths as a feature. ECCL is a rare neurocutaneous syndrome characterized by cognitive delay, unilateral skin lipomas (which are typically limited to the scalp with overlying alopecia, and termed nevus psiloliparus), skin tags, and ocular lesions with ipsilateral cerebral malformations. CLOVES syndrome is a rare overgrowth syndrome caused by somatic activating mutations in PIK3CA, and is characterized by congenital lipomatous overgrowths, vascular anomalies, epidermal nevi, and skeletal abnormalities. Congenital symmetrical circumferential skin creases is a rare disorder of excessive subcutaneous fat in newborns, resulting in numerous cutaneous folds and nevus lipomatosus. These patients may have multiple extracutaneous manifestations including developmental delay, facial dysmorphism, microcephaly, musculoskeletal abnormalities, hemihypertrophy, abnormal ears, and neurologic abnormalities.

Treatment for all patients under the umbrella of PHTS consists of cancer surveillance. This includes annual thyroid ultrasound beginning at diagnosis, annual breast screening beginning at age 30 (or 5-10 years prior to the earliest breast cancer diagnosis in the family), colonoscopy every 5 years beginning at 35 (or 5 years prior to the earliest cancer diagnosis in the family), and renal imaging every one to two years beginning at age 40. Yearly dermatologic evaluation is recommended to screen for and manage mucocutaneous manifestations. Pediatric patients

should receive close neurodevelopmental follow up with consideration for neurocognitive evaluation, if indicated. Because the individual features of PHTS are frequently present in the general population, many affected individuals go undiagnosed and thus do not undergo the recommended malignancy screening.

KEY POINTS

1. Lipomas in children are rare and should prompt further investigation into a possible underlying syndrome.
2. Lipomas in conjunction with macrocephaly should suggest the possible diagnosis of Bannayan-Riley-Ruvalcaba syndrome.
3. Children with Bannayan-Riley-Ruvalcaba syndrome should be followed neurodevelopmentally and undergo yearly skin and thyroid evaluations, with further cancer surveillance once they reach adulthood.

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