Chicago Dermatological Society

September 2018 Educational Conference

Program & Speaker Information
CME Certification
Case Presentations

Wednesday, September 12, 2018
Stephens Convention Center – Rosemont, IL

Conference Host:
Division of Dermatology
Loyola University Medical Center

LOYOLA MEDICINE
We also treat the human spirit.®

Program

Host: Loyola University
Wednesday, September 12, 2018
Stephens Convention Center, Rosemont

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *Ballroom #42 & 41*
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** Slide viewing and posters - *Ballroom 41* Patient viewing - *Room 55*
9:00 a.m. - 10:00 a.m.	**Basic Science/Residents Lecture** - *Ballroom 42* "Creative Closure Tips for the Skin Cancer Surgeon" *Ronald Moy, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors** - *Ballroom 41*
10:30 a.m. - 12:15 p.m.	**Resident Case Presentations & Discussion;** **MOC Self-Assessment Questions** - *Ballroom 42*
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors** - *Ballroom 41*
12:55 p.m. - 1:00 p.m.	**CDS Business Meeting** - *Ballroom 42*
1:00 p.m. - 2:00 p.m.	**General Session** - *Ballroom 42* “Surgical Tips for Dermatologists” *Ronald Moy, 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, October 17th at the Gleacher Center downtown.

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

Guest Speaker

RONALD MOY, MD
Beverly Hills, CA

Dr. Ronald Moy earned his medical degree at Albany Medical College and Renssalaer Polytechnic Institute (Albany, NY) Combined Program in 1981. He then completed his dermatology residency training at UCLA and a Facial Cosmetic and Mohs Micrographic Surgery Fellowship at the University of Pittsburgh Center for Health Services.

A Fellow of the American Academy of Cosmetic Surgery, Dr. Moy has served as President of the American Society for Dermatologic Surgery (2004-2005), President of the Division of Medical Quality, Medical Board of California (2005) and President of the American Academy of Dermatology (2011-2012). He also has been a professor at the David Geffen School of Medicine at the University of California-Los Angeles, is a former Co-Chief of the UCLA division of Dermatology, is a former Chief of Dermatologic Surgery, served on the Editorial Board of the Archives of Facial Plastic Surgery, is a former president of Los Angeles County Medical Association Bay District, and is past Editor-in-Chief of the Dermatologic Surgery Journal. He is on the Editorial Board of Aesthetic Surgery, the leading cosmetic surgery publication for facial plastic surgeons.

Dr. Moy is a fellow of the American College of Mohs Surgery and the American Society for Dermatologic Surgery and is a member of the American Academy of Facial Plastic Surgery. He has published more than 200 scholarly articles on cosmetic and dermatologic surgery. Dr. Moy's most common lecture invitations include facelifts, eyelifts and neck lifts. He has written books and chapters on advanced facelifts and blepharoplasties. Dr. Moy has operated on more than 30,000 cases of Mohs micrographic surgery and facial plastic surgery over the past 25 years.

Chicago Dermatological Society
Patient Privacy and HIPAA Compliance

APPROVED
June 3, 2015

Purpose

The purpose of this policy is to reaffirm the intent of the Chicago Dermatological Society (CDS) to appropriately safeguard patient privacy with respect to CDS conferences, publications and its website, and also to adhere to HIPAA requirements. All CDS members are expected to be aware of and conform to all regulations concerning patient privacy when attending a conference or utilizing any materials produced by CDS which contains any form of patient information which could be considered to be Protected Health Information.

Background

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) and its implementing regulations restrict health care providers and others to use and disclose protected health information (PHI). Protected health information means information that is created or received by an entity and relates to the past, present, or future physical or mental health condition of a patient; the provision of health care to a patient; or the past, present, or future payment for the provision of health care to a patient; and that identifies the patient or for which there is a reasonable basis to believe the information can be used to identify the patient. Protected health information includes information of persons living or deceased.

Some examples of PHI are:
- Patient's medical record number
- Patient's demographic information (e.g. address, telephone number)
- Information doctors, nurses and other health care providers put in a patient's medical record
- Identifiable images of the patient
- Conversations a provider has about a patient's care or treatment with nurses and others
- Information about a patient in a provider's computer system or a health insurer's computer system
- Billing information about a patient at a clinic
- Any health information that can lead to the identity of an individual or the contents of the information can be used to make a reasonable assumption as to the identity of the individual

Policy

The CDS takes seriously compliance with HIPAA regulations and safeguards concerning protected health information. Accordingly, the Chicago Dermatological Society has adopted the following provisions:

1. Case descriptions included in clinical conference "protocol books" and posters may not include information that could potentially identify a particular patient.

2. Photos of patients will not be published in clinical conference handout materials, including the protocol book.

3. To the extent possible, posters, slide presentations and videos displayed at CDS clinical conferences should avoid using photos that display a patient's full face or other features that could identify a particular patient. When a full-face photo must be used for clinical/educational reasons, the photo must be altered as much as possible to disguise the identity of the patient.

4. At all times, all attendees of CDS clinical conferences must adhere to appropriate behavior that respects the patient's right to privacy. Taking personal photos of posters or other displays, images included in general session lectures/presentations, and live patients at CDS conferences is strictly prohibited. Making audio recordings of any session at a CDS conference also is prohibited.

5. Attendees may not share materials distributed by CDS as part of the clinical conference or on its website with others who are not participating in the conference or who are not members of the CDS.

6. It is the responsibility of the "host" department partnering with CDS for a clinical conference to obtain all appropriate patient waivers and/or informed consent regarding the patient's participation in the CDS conference, including presentation of their case and display of posters or photos.

7. CDS will include a copy of its patient privacy policy in every meeting packet, and it will display a poster reiterating this policy at the entrance to live patient and poster viewing areas.

CME Information

September 12, 2018

This educational activity is jointly provided by the Chicago Dermatological Society in partnership with the Indiana Academy of Ophthalmology

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. In addition to two lectures given by the guest speaker, the residents of the host institution present cases which are offered for audience discussion. In addition, live patients, posters and microscopic slides 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 2018/19 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 and for cosmetic 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 4.5 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form 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.

Neither the guest speaker, Ronald Moy, MD, nor any of the planning committee members have any relevant conflicts of interest to disclose.

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.

Division Director
Rebecca Tung, MD

Program Directors
David Eilers, MD
Wendy Kim, DO – Assistant Program Director

Faculty
James Swan, MD
Robert Signore, DO
Monika Kaniszewska, MD
Kelly Park, MD
Eden Lake, MD
Kristin Lee, MD
Kirsten Carly Webb, MD
Jodi Speiser, MD
Kumaran Mudaliar, MD
Madhu Dahiya, MD

Residents
PGY4
Ashish Arshanapalli, MD
Jayla Gray, MD
Adam Whittington, MD

PGY3
Jeave Reserva, MD
David Surprenant, MD
Brooke Vasicek, MD

PGY2
Ada Agidi, MD
Lauren Moy, MD
David Rosenfeld, MD
Adam Vaudreuil, MD

TABLE OF CONTENTS

NOTES

Chicago Dermatological Society **CASE #1**

Presented by Jeave Reserva[1] MD, Jodi Speiser[2] MD, Kumaran Mudaliar[2] MD, and Kristin Lee[1] MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 47-year-old female with seizure disorder was referred to dermatology in consultation for a persistent and slowly enlarging indurated plaque on her left cheek of two years duration. She was initially evaluated by a community otorhinolaryngologist (ENT) for left nasal swelling and pain and was found to have radiologic findings consistent with chronic sinusitis. Her symptoms persisted despite several courses of oral antibiotics and oral corticosteroids. She underwent sinus endoscopy and biopsy which showed benign sinonasal mucosa with acute and chronic inflammation and was started on outpatient intravenous antibiotics for chronic nasal osteomyelitis. Given high suspicion for lymphoma, Loyola ENT then performed an open sinus surgery and incisional biopsy. Pathology showed a Grenz zone with underlying superficial and deep inflammation composed of a mixture of B- and T-cells, reactive follicle formation and a negative microbiologic work-up. Differential diagnosis included granuloma faciale and pseudolymphoma. She was given a presumptive diagnosis of periorbital pseudotumor and underwent another course of high-dose oral corticosteroid without improvement.

Because of progressive nasal pain, epistaxis, and epiphora, she underwent septoplasty and endoscopic dacryocystorhinostomy with left nasolacrimal duct probing and stent placement. Nasal sidewall biopsy revealed fragments of respiratory mucosa with dense lymphoplasmacytic inflammation admixed with neutrophils, goblet cell metaplasia, and submucosal fibrosis consistent with reactive lymphoid infiltrate, with no evidence of lymphoma on immunohistochemistry and flow cytometry. Due to the prominence of plasma cells and associated fibrosis, the possibility of IgG4-related disease was considered but no significant increase in IgG4-staining plasma cells was noted.

After undergoing intensity modulated radiation therapy to the periorbital/nasal bridge area, her disease stabilized for almost a year but she subsequently developed more frequent epistaxis and infraorbital pain with imaging findings showing interval increased size of the left nasal mass. Repeat biopsy again showed a reactive lymphoid infiltrate. Rheumatology was consulted and found no laboratory evidence for granulomatous polyangiitis (Wegener's granulomatosis), lupus, sarcoidosis, or IgG4-related disease.

Extensive review of patient's past medical history revealed seizures that began after developing cerebritis thought to be a complication of mastoidectomy performed for recurrent mastoiditis. Her review of systems was positive for ongoing epistaxis and left nasal and infraorbital pain but was negative for fever, night sweats, or weight loss.

PAST MEDICAL HISTORY

Seizures
Mastoidectomy 2012 due to mastoiditis complicated by cerebral edema requiring craniotomy
Benign lung nodule status post wedge resection 2010
Hysterectomy
Asthma
Gastroesophageal reflux disorder
Diabetes mellitus

MEDICATIONS

Hydrocodone-acetaminophen 5mg-325mg
Lamotrigine 200 mg daily
Topiramate 100 mg twice daily
Metformin 500mg daily

Fluticasone furoate-vilanterol 100mg-25mg
Montelukast 10mg daily
Pantoprazole 40mg daily

ALLERGIES
Tramadol

FAMILY HISTORY
Diabetes
Hypertension

SOCIAL HISTORY
Works as a clinical laboratory personnel. No alcohol consumption, smoking, no illicit drug use.

PHYSICAL EXAMINATION
Solitary well-demarcated indurated, bound-down firm violaceous tender plaque on the left medial and infraorbital cheek extending to the nasal bridge. Slight hypertrophy noted on area just inferior to medial canthus where prior biopsies were obtained.

DERMATOPATHOLOGY
Sections revealed an unremarkable epidermis and a Grenz zone above a dense infiltrate of small and intermediate-sized mature-appearing lymphocytes occupying the deep and superficial dermis. Perivascular neutrophils, eosinophils, and numerous plasma cells were noted without evidence of vasculitis or granulomatous foci. Immunohistochemical findings and clonality assays (see Table) confirm a mixed population of lymphocytes with plasma cells and no evidence of lymphoma.

Immunohistochemistry	**Other special studies**
*Equal number of T-cells (CD3/CD5 positive) and B-cells (CD20 positive). *CD4:CD8 ratio ~10:1 *CD7 positive in <50% mononuclear cell infiltrate. *Scattered CD30 (Ki-1) positive large cells *IgG positive plasma cells with no increase in IgG4 positive plasma cells *CD56 negative **T. pallidum* negative	Negative results: *EBV-encoded RNA (EBER) in-situ hybridization (ISH) *Bacteria, fungal, & mycobacterial PCR assay *T-cell receptor gamma gene rearrangement assay *Immunoglobulin H gene rearrangement assay

DIAGNOSIS (PRESUMPTIVE)
Granuloma faciale with coexistent sinonasal eosinophilic angiocentric fibrosis (IgG4-related disease)

TREATMENT AND COURSE
A trial of monthly intralesional triamcinolone acetonide (10mg/ml) injections (0.3ml – 0.5ml) was performed on the lateral aspects of the plaque without clinical improvement after four months. Patient was also started on oral dapsone titrating up to 100mg twice daily with minimal clinical improvement after 3 months. Daily application of topical tacrolimus 0.1% ointment was started but had to be discontinued due to development of pre-ictal sensations and a partial motor seizure episode despite preemptive addition of clonazepam, in collaboration with patient's neurologist. Patient is currently in the process of getting insurance approval to undergo intravenous rituximab infusion (2 doses of 1000mg separated by 15 days).

DISCUSSION

IgG4-related diseases (IgG4-RD) are a group of fibroinflammatory conditions affecting almost any organ and sharing particular pathologic, serologic, and clinical features. Proposed diagnostic criteria require inclusion of a combination of the following: (1) Diffuse or focal enlargement or mass lesions in one or more organs; (2) Elevated levels of serum IgG4 (more than135 mg/dl); and (3) Specific histologic findings including prominent infiltration of lymphocytes and plasmacytes with fibrosis, abundant infiltration of IgG4-positive plasmacytes (more than 10/hpf) and/or a ratio of IgG4/IgG-positive cells of more than 40%, storiform fibrosis, and obliterative phlebitis. A detailed review of past medical problems often reveals unrecognized manifestations of IgG4-RD. Thorough clinicopathologic correlation must be performed as many conditions may mimic IgG4-RD both clinically and pathologically. Glucocorticoids induce remission in many patients within days to weeks and is the first line treatment for active, untreated IgG4-RD.

Eosinophilic angiocentric fibrosis (EAF) is an uncommon IgG4-related disease, initially named as "intranasal granuloma faciale" due to its histologic similarity to granuloma faciale (GF). EAF is considered a mucosal variant of GF and most often affects the nasal mucosa, orbit, and, rarely, the subglottis. Its most common presenting signs and symptoms include nasal obstruction, nasal dorsum swelling or change in external appearance, epistaxis, or epiphora. The histology of EAF is pathognomonic and is characterized by perivascular inflammatory cell infiltration with progressive fibrosis around small vessels, leading to a characteristic 'onion-skin'-type pattern. Reports of this rare condition show surgical resection as a common treatment modality, but disease recurrence rate is extremely high, with persistence of disease seen following most nasal resections.

In a recent literature review by Heft Neal et al., 20% of EAF cases in the literature were associated with a diagnosis of GF, either prior to, during, or after diagnosis of EAF. GF presents as reddish-brown to violaceous plaques, often with follicular accentuation (peau d'orange appearance) and superficial telangiectasias. Plaques are situated almost solely on the face, but occasionally may appear on the trunk, and extremities.

Early stage GF is seldom biopsied and is characterized by a neutrophil-rich infiltrate with scant nuclear dust and fibrin in the vessel walls. Fully developed GF lesions feature a dense inflammatory infiltrate comprising neutrophils, eosinophils, lymphocytes, and plasma cells, with formation of perivascular concentric fibrosis. The inflammation is restricted to the mid-dermis and spares the subepidermal or periadnexal adventitial dermis, leaving a Grenz zone.

Topical corticosteroids, either locally applied or as intralesional injections, are frequently used for treatment of GF, with varying results (up to 42% of cases showing no improvement). Tacrolimus 0.1% ointment applied twice daily appears to be the most effective treatment option. Treatment with pulse-dye laser have also shown complete resolution of some cases. Other reported treatments include cryotherapy and both topical and oral dapsone. Regarding the present case, seizures are listed among adverse reactions identified during post-approval use of topical tacrolimus ointment.

Because some GF cases are associated with an abnormal content of IgG4-positive plasma cells, as well as morphologic changes typically found in IgG4-RD, such as obliterative vascular inflammation and storiform sclerosis, it is thought that GF may represent a localized form of IgG4-RD. Recently, favorable outcomes have been reported for cases of steroid-refractory IgG4-RD treated using off-label use of rituximab. Significant reduction in serum IgG4 levels and blood plasmablast concentrations are noted after rituximab infusion, the latter being considered as a marker of active IgG4-RD. CD4+ cytotoxic T cells are thought to play a central role in IgG4-RD by releasing pro-fibrotic cytokines after activation by B cells and plasmablasts through continuous antigen presentation. By CD20 signaling depletion in B cells and plasmablasts, rituximab is believed to halt the sustained activation of these cytokine-secreting effector CD4(+) T cells that orchestrate IgG4-RD.

We present this challenging case to identify additional probable diagnostic considerations as well as other therapeutic interventions.

REFERENCES

Carruthers MN, Stone JH, Khosroshahi A. The latest on IgG4-RD: a rapidly emerging disease. Curr Opin Rheumatol. 2012 Jan;24(1):60-9.

Cesinaro AM, Lonardi S, Facchetti F. Granuloma faciale: a cutaneous lesion sharing features with IgG4-associated sclerosing diseases. Am J Surg Pathol. 2013 Jan;37(1):66-73.

Chen VH, Grossniklaus HE, DelGaudio JM, Kim HJ. A Concomitant Case of Orbital Granuloma Faciale and Eosinophilic Angiocentric Fibrosis. Ophthalmic Plast Reconstr Surg. 2017 Mar/Apr;33(2):e47-e49.

Ebbo M, Grados A, Samson M, Groh M, et al. Long-term efficacy and safety of rituximab in IgG4-related disease: Data from a French nationwide study of thirty-three patients. PLoS One. 2017 Sep 15;12(9): e0183844.

Fernández-Codina A, Pinilla B, Pinal-Fernández I, López C, et al. Spanish Registry of IgG4 Related Disease (REERIGG4) investigators; Autoimmune Diseases Group (GEAS); Spanish Internal Medicine Society (SEMI). Treatment and outcomes in patients with IgG4-related diseaseusing the IgG4 responder index. Joint Bone Spine. 2018 Feb 13. pii: S1297-319X(18)30017-4.

Heft Neal ME, Rowan NR, Willson TJ, Wang EW, Lee SE. A Case Report and Systematic Review of Eosinophilic Angiocentric Fibrosis of the Paranasal Sinuses. Ann Otol Rhinol Laryngol. 2017 May;126(5): 415-423.

Jain R, Robblee JV, O'Sullivan-Mejia E, Lea J, Heller A, Faquin WC, Powers CN. Sinonasal eosinophilic angiocentric fibrosis: a report of four cases and review of literature. Head Neck Pathol. 2008 Dec;2(4):309-15.

Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, et al. Second International Symposium on IgG4-Related Disease. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis Rheumatol. 2015 Jul;67(7):1688-99.

LeBoit PE. Granuloma faciale: a diagnosis deserving of dignity. Am J Dermatopathol. 2002 Oct;24(5): 440-3.

Lindhaus C, Elsner P. Granuloma Faciale Treatment: A Systematic Review. Acta Derm Venereol. 2018 Jan 12;98(1):14-18.2.

Martínez-Valle F, Fernández-Codina A, Pinal-Fernández I, Orozco-Gálvez O, Vilardell-Tarrés M. IgG4-related disease: Evidence from six recent cohorts. Autoimmun Rev. 2017 Feb;16(2):168-172

Mattoo H, Mahajan VS, Maehara T, Deshpande V, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. J Allergy Clin Immunol. 2016 Sep;138(3):825-838.

Stelini RF, Moysés MD, Cintra ML, Soares TC, Souza EM, Altemani AM, Teixeira F. Granuloma Faciale and Eosinophilic Angiocentric Fibrosis: Similar Entities in Different Anatomic Sites. Appl Immunohistochem Mol Morphol. 2017 Mar;25(3):213-220.

Presented by Adam Vaudreuil[1] MD, Daniel Schlessinger[3] BA, Jodi Speiser[2] MD, Kumaran Mudaliar[2] MD, and Eden Lake[1] MD
[1]Department of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center
[3]Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 50-year-old Hispanic man with a history of chronic myelogenous leukemia presented with a pruritic rash affecting the trunk and bilateral upper extremities. The rash had been present for 3 months, initially starting on the right flank and slowly progressing despite treatment with topical steroids and antifungal creams by the patient's primary care provider.

The patient was originally diagnosed with chronic myelogenous leukemia in 2014, achieved remission on imatinib, but relapsed in 2016. He was treated with short trials of desatinib and nilotinib but these were discontinued due to inadequate disease control and intolerable side effects (pain). He was ultimately started on ponatinib with good disease control. At the time of first visit he had been on this medication for 2 years without interruptions in treatment or other cutaneous adverse effects.

PAST MEDICAL HISTORY

Chronic Myelogenous Leukemia
Anemia

MEDICATIONS

Ponatinib 45mg Daily
Sennosides with docusate
Vitamin D-3

ALLERGIES

Lorazepam

FAMILY HISTORY

Father with Diabetes
Mother with Hypertension

SOCIAL HISTORY

No alcohol, tobacco, or illicit drug use.
Married, lives in New Mexico, works part time in landscaping.

REVIEW OF SYSTEMS

Patient denies nausea, vomiting, fevers, chills, diarrhea, joint pain, weight loss, fatigue, cough, dizziness, weakness, depression, headaches, blood in stool or urine, visual disturbance, decreased appetite.

PHYSICAL EXAMINATION

Well-developed Hispanic man. Bilateral flanks from the upper thigh to shoulder with diffuse, erythematous, scaly papules coalescing into annular plaques in a symmetric distribution sparing the axillae. The groin, central abdomen, back, and buttocks are also spared.

DERMATOPATHOLOGY

Biopsy, Left Back (4/4/2018):

- Mild alternating orthokeratosis and parakeratosis, hypergranulosis, and mild follicular plugging.
- No fungal organisms identified on PAS stain.

ADDITIONAL STUDIES

Complete blood count with differential, complete metabolic panel, c-reactive protein, and erythrocyte sedimentation rate were all unremarkable

DIAGNOSIS

Pityriasis rubra pilaris-like delayed drug eruption to ponatinib

TREATMENT AND COURSE

The patient was started on daily tretinoin 0.025% cream. Unfortunately, the patient moved to Texas for family concerns, and thus was lost to physical follow up. However, he reported almost completed resolution of the rash within 9 days of starting treatment, and photo documentation of clearance was obtained. He was also continued on ponatinib without further complication.

DISCUSSION

Ponatinib is a multikinase inhibitor approved for the treatment of multidrug-resistant, Philadelphia chromosome-positive leukemia. Low-grade rash was reported in 32% and 38% of phase-I and phase-II clinical trial subjects, respectively, and reported in up to 47% of patients at 5-years. In the last few years, however, other authors have reported cases of pityriasis rubra pilaris (PRP) and papulosquamous eruptions generally occurring between 2 and 12 weeks after initiation of ponatinib. Given ponatinib's ability in preclinical trials to inhibit VEGF, PDGF, FGF, KIT, FLT3, and the SRC families, in addition to mutant and wild-type Abl clones, the pathogenesis may involve downstream effects of kinase inhibition on inflammation and epidermal growth pathways, but this has not yet been verified.

As with many drug reaction cases, we cannot prove that ponatinib caused our patient's PRP-like eruption without cessation and reintroduction of the drug, but several factors support this drug-related etiology. First, the eruption completely resolved with topical therapy as Alloo et al suggested, while primary PRP can be much more resistant to therapy. Second, the circumferential, symmetric axillary involvement and frank sparing of the axillary concavity is an unusual morphology for primary PRP, but it is nearly identical to 3 of the previously published cases of ponatinib-related PRP.

Unlike other reported cases, our patient experienced a delayed-onset reaction, with the rash occurring nearly 2 years after initiating ponatinib. He had not been previously sensitized to ponatinib nor experienced gaps in his treatment course. Importantly, this case highlights the effective and safe treatment of this drug eruption with topical retinoids, allowing continued treatment without cessation of the necessary medication. As more targeted chemotherapeutic agents are discovered, the ability to characterize and treat cutaneous adverse events without interruption of life prolonging treatment is increasingly important.

We present this case for clinical interest, and to demonstrate an easy and effective, topical treatment for a specific drug eruption to a multikinase inhibitor.

REFERENCES

Alloo, A., et al. Ponatinib-Induced Pityriasiform, Folliculocentric and Ichthyosiform Cutaneous Toxicities. Br J Dermatol. 2015:574-7.

Cortes, J. E., et al. A Phase 2 Trial of Ponatinib in Philadelphia Chromosome-Positive Leukemias. N Engl J Med. 2013:1783-96.

Cortes, J. E., et al. Ponatinib in Refractory Philadelphia Chromosome-Positive Leukemias. N Engl J Med. 2013:2075-88.

Cortes J. E., et al. A pivotal phase 2 trial of ponatinib in patients with chronic myeloid leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph1 ALL) resistant or intolerant to dasatinib or nilotinib, or with the T315I BCR-ABL mutation: a 12-month follow-up of the PACE trial. Blood. 2012;120:163.

Cortes, J. E., et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018:393-404

Eber, A. E., et al. Ichthyosiform Pityriasis Rubra Pilaris-Like Eruption Secondary to Ponatinib Therapy: Case Report and Literature Review. Drug Saf Case Rep. 2017:19.

Gozgit, J. M., et al. Potent Activity of Ponatinib (Ap24534) in Models of Flt3-Driven Acute Myeloid Leukemia and Other Hematologic Malignancies. Mol Cancer Ther. 2011:1028-35.

Jack, A., M. J. Mauro, and B. D. Ehst. Pityriasis Rubra Pilaris-Like Eruption Associated with the Multikinase Inhibitor Ponatinib. J Am Acad Dermatol. 2013:e249-e50.

Krygier, J., et al. "[A New Case of Pityriasis Rubra Pilaris-Like Eruption Associated with Ponatinib, a Tyrosine Kinase Inhibitor]." [In fre]. Ann Dermatol Venereol. 2018.

Orenay, O. M., et al. Lamellar Ichthyosis-Like Eruption Associated with Ponatinib. Acta Dermatovenerol Alp Pannonica Adriat. 2016:59.

Patel, A. B., et al. Unique Cutaneous Reaction to Second- and Third-Generation Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia. Dermatology 232, no. 1 (2016): 122-5.

NOTES

Chicago Dermatological Society **CASE #3**

Presented by Lauren Moy[1] MD, Jayla Gray[1] MD, Joy Tao[1] BS, Jodi Speiser[2] MD, Wendy Kim[1] DO
[1]Department of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 3-month-old otherwise healthy infant male was admitted to the hospital for a 1-month history of scattered tense clear to yellow vesicles and bullae on a pink base on the bilateral hands and feet. The week prior to admission he began to develop pink papules coalescing into thin plaques on the trunk. He was previously treated with hydrocortisone cream and oral antibiotics without improvement. The patient was otherwise healthy and his parents denied any fevers, chills, nausea, vomiting, upper respiratory symptoms, recent illnesses, or sick contacts.

PAST MEDICAL HISTORY

Full term birth
Small ventricular septal defect
Immunizations up-to-date

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

No family history of childhood diseases or skin diseases

SOCIAL HISTORY

Does not attend daycare

PHYSICAL EXAMINATION

Well-appearing male infant with a cutaneous examination notable for scattered tense clear to yellow vesicles and bullae with a pink base of the bilateral dorsal hands and feet. Some of the vesicles and bullae were hemorrhagic and others were unroofed with an overlying serosanguinous crust. There were also thin pink papules coalescing into plaques and few pinpoint clear vesicles mostly on the chest and abdomen with some scattering on the back and thighs. No oral or genital lesions were seen and the face and diaper area were spared.

DERMATOPATHOLOGY

Biopsy from left foot showed sub-epidermal split with eosinophils and linear IgG/C3 at the dermal epidermal junction consistent with bullous pemphigoid.
Salt-split skin showed localization of antibodies to the blister roof.

LABORATORY RESULTS

A complete blood count was notable for an elevated white blood count at 18.9 (3.5-10.5 K/UL) and elevated eosinophils 4.4 (0.0-0.7 K/MM3). A C-reactive protein, Sjogren's antibodies (SS-A and SS-B), and ANA levels were within normal limits. Antibodies to BP 180 were elevated at 157 units. Respiratory panel was negative and an aerobic culture showed a negative Gram stain and one colony of coagulase-negative Staphylococcus

DIAGNOSIS

Bullous pemphigoid of childhood

TREATMENT AND COURSE

The patient was discharged on topical steroids. He was given triamcinolone 0.1% ointment twice daily for affected areas of the body, mometasone 0.1% ointment twice daily for affected areas of the hands and feet, aclometasone 0.05% ointment twice daily for affected areas of the face and scalp. At his follow up appointment, 75% of his body surface area was involved. Therapy with oral prednisolone at a dose of 1 mg/kg/day, and erythromycin at a dose of 40 mg/kg/day (divided BID) was initiated. We recommended daily dilute bleach baths to reduce the risk of secondary infection. He responded well to treatment with clearing of the skin within 3 weeks. Prednisolone was then tapered over 3 weeks. During the taper, his skin flared in limited areas. Clobetasol ointment was prescribed. His skin was well controlled until 3 weeks after his last dose of prednisolone, when the skin on his face, scalp, and diaper area flared. A repeat course of prednisolone and initiation of mycophenolate mofetil was discussed. His parents wished to wait as the topical medications were helping. Within two weeks, his skin cleared. The patient's parents continue to apply topical steroids intermittently to small discrete areas as needed.

DISCUSSION

The differential diagnosis for acquired blisters on acral sites in infants includes infectious and noninfectious etiologies. Scabies, herpes simplex virus (HSV), bullous impetigo, incontinentia pigmenti, dermatitis herpetiformis, Langerhans cell histiocytosis, linear IgA dermatosis, acropustulosis of infancy, and erythema multiforme should be considered. Bullous pemphigoid (BP) is an autoimmune blistering skin disorder which rarely presents in infants. To date, there have been a little over 100 cases reported. Infantile bullous pemphigoid differs from the adult presentation in its distribution – there is acral involvement with predominantly palmoplantar lesions and sparing of the mucosa and genital area in infants.

BP of childhood is based on clinical, histological and immunologic criteria. Nemeth et al proposed that the criteria for childhood BP was 1) age 18 or younger, 2) clinical appearance of tense bullae, 3) histopathologic findings of a subepidermal blister with eosinophilia, and 4) direct immunofluorescence with linear deposition of IgG or C3 at the basement membrane zone or a positive indirect immunofluorescence with IgG antibasement membrane zone autoantibodies. Specific criteria for bullous pemphigoid of infancy do not exist.

There are reports of immunizations and viral infections triggering bullous pemphigoid in children. Reported associations include HSV-1, cytomegalovirus, Epstein-Barr virus, and hepatitis B and C. However, the true association of childhood BP and vaccination is thought to be more of a coincidental finding. Given the low number of reported BP cases compared to the high rate of vaccinations in the first year of life, a temporal association is not difficult to find in this time frame.

Treatment options include topical steroids, oral corticosteroids at a dosage of 1 to 2 mg/kg per day, dapsone, sulfapyridine, cloxacillin sodium, erythromycin ethylsuccinate, mycophenolate mofetil, cyclosporine, and IVIG. Our patient responded well to oral prednisolone, but flared within 3 weeks its discontinuation. This flare was ultimately controlled with topical medications, and his skin is currently clear. Unlike adult BP, affected children usually have rapid resolution of their skin disease after initiation of treatment, with rare relapses.

We present this case to highlight a rare case of bullous pemphigoid of an infant.

REFERENCES

Amos B, Deng J, Flynn K, et al. Bullous Pemphigoid in Infancy: Case Report and Literature Review. Ped Derm 1998; Vol 15;2:108-111

Baroero L, Coppo P, Bertolino L, et al. Three case reports of post immunization and post viral Bullous Pemphigoid: looking for the right trigger. BMC Pediatr. 2017;17(1):60.

Bean SF, Good RA, Windhorst DB. Bullous pemphigoid in an 11 year old boy. Arch Dermatol 1970; 102:205-8

Ister M, Pouessel G, Ythier H, et al. Postvaccinal, corticosteroid-resistant bullous pemphigoid in infancy: treatment with intravenous immunoglobulin. Pediatr Dermatol. 2014;31(4):e94-5.

Korman NJ. Bullous pemphigoid: the latest in diagnosis prognosis, and therapy. Arch Dermatol 1998; 134:1137-41

Martinez-De Pablo M, Gonzale Ensenat M, et al. Childhood Bullous Pemphigoid Clinical and Immunological Findings in a Series of 4 Cases. Arch Dermatol. 2007;143(2):215-220

Nemeth AJ, Klein AD, Gould EW, et al. Childhood bullous pemphigoid: clinical and immunologic features, treatment, and prognosis. Arch Dermatol 1991; 127:378-86

NOTES

Presented by David Surprenant[1] MD, Ashish Arshanapalli[1] MD, Madhu Dahiya[2] MD, David Eilers[1] MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Hines VA Medical Center

HISTORY OF PRESENT ILLNESS
A 38-year-old man presented to our dermatology clinic with a two-month history of slightly pruritic and minimally draining lesions in his left inguinal fold. The lesions began as a single, nickel-sized, pink bump. Subsequently, multiple lesions arose and coalesced into one large plaque. The patient denied any other skin issues or systemic symptoms. He had not been sexually active for two years and had no history of genital warts or sexually transmitted infections. The patient was adopted with no known family history.

PAST MEDICAL HISTORY
Type II Diabetes Mellitus, Hyperlipidemia

MEDICATIONS
Metformin

ALLERGIES
No known drug allergies

FAMILY HISTORY
Unknown

SOCIAL HISTORY
No tobacco, alcohol, or illicit drug use. No other significant social history.

PHYSICAL EXAMINATION
In the left inguinal fold there was a large pink to violaceous vegetative plaque with a slightly atrophic hyperpigmented center along with scattered satellite pink to violaceous papules. The rest of the exam was unremarkable.

LABS
Laboratory testing including complete blood count and complete metabolic panel were unremarkable. HIV and hepatitis C serologic tests were negative.

DERMATOPATHOLOGY
Punch biopsies were obtained for histological analysis. Light microscopy revealed pseudoepitheliomatous hyperplasia, inflammatory cell infiltrate with eosinophilic microabscesses, eosinophilic spongiosis, and subtle acantholysis with follicular involvement. Direct immunofluorescence staining (DIF) of perilesional skin revealed an intercellular (chicken-wire) IgG staining pattern.

DIAGNOSIS
Pemphigus vegetans

TREATMENT AND COURSE
The patient was initially treated with doxycycline 100 mg twice a day, niacinamide 500 mg three times per day, and twice daily application of hydrocortisone valerate 0.2% cream. The patient self-discontinued all medications after three weeks due to complete resolution of symptoms as well as medication side effects, namely gastrointestinal upset. Exam at eight-week follow-up revealed only a hyperpigmented patch with one small pink papule in the left inguinal fold. Despite understanding the risk of recurrence

without therapy, the patient opted to proceed with no additional intervention given his lack of significant symptoms. Three months later the patient's condition flared, this time with more widespread disease involving not only the inguinal folds, but also the alar-facial sulcus, umbilicus, scalp, oral mucosa, and penis. The patient was re-started on doxycycline, niacinamide, and topical corticosteroids. However, his now more widespread disease ultimately required more aggressive treatment. He was started on 60 mg/day (~0.5 mg/kg/day) of oral prednisone as well as 100 mg/day of dapsone. He had rapid improvement in symptoms within days of starting this regimen. After several weeks of remaining symptom free, without the development of new lesions, a gradual steroid taper was initiated (50 mg/day x14 days followed by a decrease of 5 mg/day every 14 days). The patient is currently on 40 mg/day of prednisone and remains symptom free.

DISCUSSION

Pemphigus vegetans (PVeg) is a rare variant of pemphigus vulgaris (PV), representing only about 1-2% of all PV cases. Clinically, PVeg presents with vegetating, mamillated plaques located primarily in areas of occlusion and friction, particularly intertriginous folds and the oral mucosa. These plaques can become quite large and often have irregular, polycyclic margins. While involvement of the inguinal and axillary folds (i.e. large folds) is most common, involvement of nasolabial, labial, and umbilical folds (i.e. small folds) also occurs. The vegetated plaques are often wet, weepy, and malodorous. While less common, non-flexural plaques can occur and often appear more dry and verruciform. Oral involvement is exceedingly common, occurring in as many as 80% of individuals. The majority of these individuals (~75%) have oral involvement at disease onset.

There are two main subtypes of PVeg: Hallopeau and Neumann type. While both subtypes present with vegetating plaques, Neumann type begins with pustules while Hallopeau type initially presents as more classic PV, with vesicles or bullae. While the significance of these subtypes is largely historical, Hallopeau type PVeg may have a more benign disease course.

As a variant of PV, pathogenesis involves autoantibody formation to desmoglein 3 (Dsg3) and frequently desmoglein 1 (Dsg1), the binding of which results in suprabasilar acantholysis. Given its rarity, the pathogenesis underlying the unique clinical appearance of PVeg is poorly understood. Friction, maceration, and microorganism colonization are hypothesized to play a role in PVeg given disease predilection for intertriginous fold areas. However, involvement of vegetating plaques outside these areas in select individuals challenges this thinking. Additional uncharacterized antibodies have been identified in PVeg patients, which may account for the unique clinical presentation. One study found a predominance of IgG2 and IgG4 autoantibodies in lesional skin of PVeg patients, verses a predominance of IgG1 and IgG4 autoantibodies in PV patients. These authors hypothesize that the IgG subclass, particularly complement-activating IgG2, may play a role in generating the unique clinical and histological features of PVeg.

Histologically, PVeg is characterized by epidermal hyperplasia with eosinophilic microabscesses and suprabasilar acantholysis with follicular extension. Compared with PV, acantholysis in PVeg is often very subtle and difficult to detect, especially in more mature lesions. Immunofluorescence findings are identical to those found in PV, with lesions displaying intercellular 'chicken wire' deposition of IgG and C3.

Several important diagnoses should be considered in the differential for PVeg. Pyostomatitis vegetans-pyodermatitis vegetans (PSV-PDV) is a rare inflammatory disorder often associated with inflammatory bowel disease, particularly ulcerative colitis. Clinical and histological findings in PSV-PDV are similar to PVeg; however, immunofluorescence studies will be negative in PSV-PDV. Pemphigoid vegetans is an exceedingly rare vegetating variant of bullous pemphigoid with a clinical presentation similar to PVeg. Histological analysis of bullous pemphigoid tissue will demonstrate subepidermal blister formation and direct immunofluorescence will show linear deposition of IgG and C3.

Treatment of PVeg is similar to PV, with first line therapy often involving oral corticosteroids (~1 mg/kg/day) and frequently a non-steroidal immunosuppressive agent. The most common steroid sparing immunosuppressant agents used are azathioprine, methotrexate, mycophenolate mofetil, dapsone, cyclophosphamide, and cyclosporine. Mild disease may be controlled with doxycycline and niacinamide combination therapy. Adjuvant use of topical corticosteroids is especially helpful for PVeg. Lastly, destruction of recalcitrant plaques with surgery or ablative CO2 laser has been described in the literature. The treatment goals for PVeg mirror those of PV, to induce and maintain remission with the ultimate goal of complete remission in the absence of medications.

This case of pemphigus vegetans highlights an exceedingly rare clinical variant of pemphigus vulgaris.

REFERENCES

Elston, Dirk, et al. Dermatopathology. Elsevier Health Sciences, 2013.

Hashimoto, Koji, et al. "Detection of anti-desmocollins I and II autoantibodies in two cases of Hallopeau type pemphigus vegetans by immunoblot analysis." Journal of Dermatological Science 7.2 (1994): 100-106.

Kim, Jinah, et al. "Pemphigoid vegetans: a case report and review of the literature." Journal of Cutaneous Pathology 35.12 (2008): 1144-1147.

Lin, Ming-Hsien, Chao-Kai Hsu, and Julia Yu-Yun Lee. "Successful treatment of recalcitrant pemphigus vulgaris and pemphigus vegetans with etanercept and carbon dioxide laser." Archives of Dermatology 141.6 (2005): 680-682.

McCarty, Morgan, and David Fivenson. "Two decades of using the combination of tetracycline derivatives and niacinamide as steroid-sparing agents in the management of pemphigus: Defining a niche for these low toxicity agents." Journal of the American Academy of Dermatology 71.3 (2014): 475-479.

Parodi, Aurora, et al. "Epidermal antigens in pemphigus vegetans. Report of a case." British Journal of Dermatology 119.6 (1988): 799-802.

Ruocco, Vincenzo, et al. "Pemphigus vegetans of the folds (intertriginous areas)." Clinics in Dermatology 33.4 (2015): 471-476.

Zaraa, I., et al. "Pemphigus vegetans: a clinical, histological, immunopathological and prognostic study." Journal of the European Academy of Dermatology and Venereology 25.10.(2011): 1160-1167

NOTES

Presented by Ada Agidi[1] MD, Alison Bailey[1] MS4, Adam Whittington[1] MD, Jodi Speiser[2] MD, Kumaran Mudaliar[2] MD, and Rebecca Tung[1] MD.
[1]Department of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 42-year-old male was referred to our clinic because of a non-healing ulcer on his right lateral ankle. The lesion initially began as a "scab" that appeared two months prior to presentation and later fell off while he was removing his socks. This ulcerated lesion was persistent and occasionally bled. Other symptoms included mild local tenderness and pruritus. He did not recall any trauma or injuries to the area. Of note, he had a longstanding history of hypertrophic cardiomyopathy with de novo MYH7 gene mutation complicated by end stage renal disease. One month preceding the onset of the cutaneous lesion, he underwent a combined heart and kidney transplantation and was started on an immunosuppressive regimen.

PAST MEDICAL HISTORY

Hypertrophic cardiomyopathy with de novo MYH7 genetic mutation
End stage renal disease
Heart transplant (10/2016)
Kidney transplant (10/2016)
Atrial fibrillation
Hypertension
Pulmonary hypertension
Hyperlipidemia
Diabetes Mellitus II
Hypothyroidism

MEDICATIONS

Mycophenolate mofetil 1500 mg twice daily
Prednisone 10 mg twice daily
Tacrolimus 4.5 mg in the morning and 4 mg at night
Trimethoprim-Sulfamethoxazole 800-160 mg three times weekly
Valganciclovir 450 mg twice daily
Pravastatin
Lisinopril
Furosemide
Levothyroxine
Aspirin
Glipizide
Nystatin suspension
Sildenafil

ALLERGIES

Amlodipine

FAMILY HISTORY

Father: alive with hypertension and diabetes mellitus II
Mother: alive with no known medical problems

SOCIAL HISTORY
Drinks 1-2 glasses of wine per week.
No history of tobacco, illicit drug use or intravenous drug use.
Married with 2 children
Works as a construction project manager

REVIEW OF SYSTEMS
No nausea, vomiting, fevers, chills, diarrhea, joint pain, weight loss, fatigue, cough, dizziness, weakness, depression, headaches, blood in stool/urine, visual disturbances, decreased appetite.

PHYSICAL EXAMINATION
Well appearing Fitzpatrick type 2 male who was alert, afebrile with no respiratory distress.
Right lateral ankle with 3 cm x 2 cm well-circumscribed, friable, gray-red ulcerated plaque without surrounding cellulitis or edema.

DERMATOPATHOLOGY
Deep Shave Biopsy (1/31/2017): Pseudoepitheliomatous hyperplasia with underlying mixed inflammation and granulation tissue with multiple fungal organisms identified on GMS special stain.

ADDITIONAL STUDIES
Gram stain: few gram positive bacteria and normal skin flora. Moderate colonies of corynebacterium species. Moderate colonies of coagulase negative staphylococcus species.

Fungal smear: moderate true septate hyphae and moderate non-budding fungal forms seen
Acid fast bacilli blood culture negative

Fungal culture: moderate colonies of Alternaria species; sensitive to itraconazole, voriconazole and posaconazole.

DIAGNOSIS
Cutaneous Alternariosis

TREATMENT AND COURSE
Based on the susceptibilities of the Alternaria cultures, posaconazole was deemed to be the most appropriate treatment. Patient was started with posaconazole 300 mg every 12 hours for 3 days followed by daily posaconazole 300mg for a total of 9 months. His tacrolimus dose was decreased in order to adjust for drug interaction with posaconazole. Posaconazole and tacrolimus blood levels were monitored during the course of treatment. Patient responded well to treatment with resolution of ulceration at his 10 week follow up appointment. To date, he has not had any recurrence of the infection.

DISCUSSION
Alternaria is a very large and complex genus including hundreds of species, few of which are involved in human and animal infections. They are ubiquitous dematiaceous or phaeoid filamentous fungi found in the soil, air or necrotic plant material. They have also been identified as contaminants in fungal cultures through airborne spores and healthy human skin. *A. alternata* is the most common pathogen; other clinically relevant species include *A tenuissima, A infectoria, A dianthicola, A longipes, and A chartarum.*

Alternariosis occurs most often in immunocompromised individuals such as patients with solid organ transplant on immunosuppressant medications, AIDS and lymphoproliferative disorders. Cases of alternariosis have also been reported in patients with diabetes mellitus, Cushing syndrome and granulomatous disease. It can occur rarely in immunocompetent patients such as farmers or gardeners due to occupational exposure and usually has a less severe clinically course compared with immunocompromised patients. Cutaneous alternariosis can occur through two routes of transmission: 1)

inhalation of fungal conidia with subsequent systemic dissemination and secondary cutaneous involvement or 2) traumatic inoculation of the skin with fungal spores through injury with plant spine or colonization of traumatized skin. Other non-cutaneous conditions include ocular alternariosis due to ocular trauma, osteomyelitis of the maxilla, sinusitis, peritonitis, hypersensitivity pneumonitis, granulomatous pulmonary disease, soft palate perforation, onychomycosis, and disseminated disease.

Cutaneous alternariosis can present as a localized skin lesion or an invasive and disseminated infection. Clinically, it can manifest as painless verruciform, eczematous or ulcerating violaceous nodules, plaques, papules or macules, and most commonly occurs on bony prominences or areas predisposed to minor trauma such as the feet, knees, legs, dorsal hands and forearms. However, many patients do not recall any previous trauma to the infection site. Less frequently, Alternaria can occur on the face. While this fungal infection can happen at any time following organ transplantation, it has been found to occur within 1 year in 70% of cases.

Because of its ubiquitous nature in the environment, identifying Alternaria in both tissue culture and on histopathology is critical to rendering a definitive diagnosis. Histologic features include suppurative and granulomatous dermatitis or panniculitis with clustered pigmented broad, branching hyphae. The inflammatory reaction occurs mainly in the upper dermis but may reach the deep dermis. In some cases, hyperkeratosis, pseudoepitheliomatous hyperplasia and neutrophilic infiltration with intraepidermal microabscesses may be present. Pigmented hyphae may also be present on hematoxylin-eosin or with melanin staining.

Currently, there are no established treatment guidelines for cutaneous alternariosis. In some cases, resolution of the lesion has been achieved by reduction of immunosuppression. In patients with few, small lesions, surgical excision can be considered. When the disease is extensive due to size or number, systemic antifungals can be curative. Itraconazole is the first line for antifungal therapy due to low toxicity. Unfortunately, because this medication inhibits the CYP3A system which can lead to toxic drug levels of calcineurin inhibitors, it is not ideal for transplant recipients taking this type of immunosuppressant. Posaconazole has been considered superior to itraconazole in some studies because of its better bioavailability, lower inhibitory effects of the cytochrome P450 system and overall fewer drug-drug interactions. Other treatment options include fluconazole, terbinafine, amphotericin B and voriconazole. The best treatment option often involves a combination of surgical excision and systemic antifungals. Cryosurgery in addition to systemic antifungals is a good option when multiple lesions are present and surgical excision is not feasible. Some recalcitrant cases have been successfully treated with a combination of Mohs surgery and systemic antifungals. Relapses can occur even after prolonged treatment therefore long term follow up is essential.

REFERENCES

Bajwa, R., Wojciechowski, A. L., Hsiao, C. B. (2017). Cutaneous alternariosis in a renal transplant patient successfully treated with posaconazole: Case report and literature review. Medical mycology case reports, 15, 16-20.

Essabbah, N., Gorsane, I., Youssef, M., et. al. (2014). Cutaneous alternariosis in a renal transplant recipient. Cutis, 93(5), 237-240.

González-Vela, M. C., Armesto, S., Unda-Villafuerte, F., et. al. (2014). Cutaneous infection with Alternaria triticina in a bilateral lung transplant recipient. Actas Dermo-Sifiliográficas (English Edition), 105(8), e51-e54.

Hsu, C. C., Chang, S. S., Lee, P. C., et. al. (2015). Cutaneous alternariosis in a renal transplant recipient: a case report and literature review. Asian journal of surgery, 38(1), 47-57.

Kleker, B., Endo, J., Bennett, D., et. al. (2013). Mohs micrographic surgery for the treatment of localized cutaneous alternariosis. Journal of the American Academy of Dermatology, 68(2), e55-e56.

Lopes, L., Borges-Costa, J., Soares-Almeida, L., et. al. (2013). Cutaneous alternariosis caused by Alternaria infectoria: three cases in kidney transplant patients. In Healthcare (Vol. 1, No. 1, pp. 100-106). Multidisciplinary Digital Publishing Institute.

Osmond, G. W., Walters, R. W., & Puri, P. K. (2011). Cutaneous alternariosis microscopically mimicking blastomycosis. Journal of cutaneous pathology, 38(11), 923-925.

Sečníková, Z., Jůzlová, K., Vojáčková, N., et. al. (2014). The rare case of A lternaria alternata cutaneous and pulmonary infection in a heart transplant recipient treated by azole antifungals. Dermatologic therapy, 27(3), 140-143.

Simpson, C. L., Craig-Muller, S., Sobanko, J. F., et. al. (2016). Refractory cutaneous alternariosis successfully treated with Mohs surgery and full-thickness skin grafting. Dermatologic Surgery, 42(3), 426-429.

Presented by Ashish Arshanapalli[1] MD, Reeba Omman[2] MD, Jodi Speiser[2] MD, Kumaran Mudaliar[2] MD, and Wendy Kim[1] DO
[1]Department of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

Dermatology was consulted by the newborn nursery to evaluate a lesion on the right cheek of an otherwise healthy one-day-old male newborn. The lesion was present at birth, but per mom, it was initially slightly darker and had lightened over the first day of life. The lesion did not appear to be painful or bothersome to the patient, and he was feeding well. The primary team was concerned for a congenital hemangioma, however an ultrasound did not show any evidence of increased vascularity indicating a hemangioma. No treatments had been attempted yet on the lesion.

PAST MEDICAL HISTORY

Born at 38 weeks gestation at 7 lbs 11 oz by spontaneous vaginal delivery to a 33 year-old G5P2 mother
Apgar scores 9/9/9 at 1, 5, and 10 minutes
Prenatal course was complicated by type II diabetes mellitus in mother
Maternal prenatal screening was negative for Group B Streptococci, Rubella, HIV, RPR, Hepatitis B
No history of HSV in mother

MEDICATIONS

None

ALLERGIES

NKDA

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Mom denied tobacco, alcohol, or illicit drug use during pregnancy. No history of intravenous drug use.

PHYSICAL EXAMINATION

Well appearing, healthy newborn male
Right malar cheek with an 8 x 4 mm reddish-brown, firm papulonodule with a central white crusted papule
No lymphadenopathy, no hepatosplenomegaly.

DERMATOPATHOLOGY

A punch biopsy showed a diffuse dermal infiltrate composed of ill-defined nodular collections of histiocytoid cells with surrounding lymphocytic inflammation and an area of overlying epidermis with erosion/ulceration. The histiocytoid cells are immunohistochemically positive for CD1a, S-100, and CD68 and are consistent with Langerhans cells.

ADDITIONAL STUDIES

Newborn metabolic screen, complete blood count, C-reactive protein: within normal limits

Ultrasound right cheek: Heterogenous, predominantly hypoechoic lesion in the right cheek without increased vascularity, nonspecific with differentials including sebaceous cyst/neonatal acne. No sonographic features of hemangioma.

DIAGNOSIS
Langerhans cell histiocytosis

TREATMENT AND COURSE
Based on clinical and histologic features, a diagnosis of Langerhans cell histiocytosis (LCH) was made. Workup including a complete blood count with differential, complete metabolic panel, a skeletal survey, ultrasound of the abdomen, and coagulation studies which were all within normal limits. He was referred to pediatric hematology oncology, and their evaluation did not identify any other signs of multisystemic disease. His skin lesion resolved spontaneously within weeks.

The patient had a 3 month appointment scheduled with dermatology that the patient's mother cancelled; however, he did follow-up with hematology oncology and a repeat skeletal survey and abdominal ultrasound were performed 3 months after the original studies. At that time, abdominal ultrasound was within normal limits, and the repeat skeletal survey showed soft-tissue swelling in the right posterior parietal skull concerning for LCH bone involvement. Hematology oncology recommended starting prednisone and vinblastine at that time, but the patient's parents declined treatment and sought a second opinion from an outside hospital. At the outside hospital, they were told that the skeletal survey was not conclusive for LCH, and he is now being closely monitored there for multisystem disease.

DISCUSSION
Langerhans cell histiocytosis is a rare inflammatory myeloid neoplasia that can have a wide variety of clinical manifestations and affect many different organ systems including the skin. Langerhans cells are derived from the monocyte-macrophage cell lineage, and in LCH there is a pathologic clonal collection of Langerhans cells proliferating from immature myeloid precursor cells. These pathologic cells have the same immunohistologic staining profile of normal skin Langerhans cells. The pathogenesis of LCH appears have both inflammatory and neoplastic components to it (hence the term inflammatory myeloid neoplasia), and all cases of LCH have upregulation of the RAS-RAF-MEK-ERK-MAP kinase molecular pathway. The BRAFV600E mutation plays a role in this pathway and has been identified in up to 69% of cases of LCH in previously published studies.

LCH is a rare condition that typically affects children, but it has been reported in people of all ages. Incidence is approximately 4 to 5 children per million each year, with a slight male predominance in pediatric cases. The highest incidence of cases is reported in children less than 1 year of age, but the median age of diagnosis is about 3.5 years of age.

Historically, LCH was classified into four distinct clinical variants- Letterer-Siwe, Hand-Schüller-Christian, congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker), and eosinophilic granuloma. There is significant clinical overlap between these subtypes, so the term histiocytosis X has also been used in the past as an all-encompassing term for these conditions. As the pathologic cell types of origin were identified as Langerhans cells, the group was renamed Langerhans cell histiocytosis. Due to its variety of clinical presentations, LCH is currently classified based on the extent of involvement- single system single site, single system multisite, and multisystem. The presence of risk organ involvement including the liver, spleen, and bone marrow is an important prognostic factor and is also included in the classification.

LCH can affect a wide variety of organs including bone, skin, endocrine organs, lungs, liver, spleen, bone marrow, and lymph nodes. Of all, the skeletal system is the most commonly affected, which most often presents as a unifocal soft tissue mass with pain and swelling on the skull. The skin is eventually involved in about one-third to one-half of all cases of LCH, but cutaneous involvement is the most common presentation in children less than 2 years old. Due to limited study sizes and variations in reporting patterns, it is difficult to predict the rate at which isolated cutaneous disease will progress to multisystem disease with estimates ranging from 6% to 56%. More recent studies suggest a rate of

progression towards the lower end of that range. The cutaneous presentations of LCH can vary significantly from a seborrheic dermatitis-like rash to a recalcitrant diaper dermatitis to an isolated papule as seen in our patient. Other reported presentations include hypo- or hyperpigmented macules, varicella-like eruptions, eczematous rashes, lichenoid rashes, ulcers, and tumor-like lesions, amongst others. Cutaneous LCH can affect any part of the body, including rare oral or nail involvement, but the most commonly affected areas are the head, face, or trunk. Lesions are often pruritic, and cutaneous involvement may be associated with signs of systemic involvement including fevers, lymphadenopathy, bone pain, hepatosplenomegaly, and others.

The diagnosis of LCH requires one of the above clinical presentations in addition to consistent histologic and immunohistochemical findings. Histologic findings of LCH include a non-specific inflammatory infiltrate of eosinophils, macrophages, lymphocytes, and multinucleate giant cells in addition to the presence of Langerhans cells. These Langerhans cells are characterized by a round shape, “coffee-bean” cleaved nuclei, and an eosinophilic cytoplasm. Atypical mitoses and pleomorphism are generally not present. The immunohistochemical profile of the pathologic Langerhans cells is identical to that of normal epidermal Langerhans cells, staining positive for S100, CD1a, and CD207 (Langerin). Electron microscopy to identify Birbeck granules is no longer routinely performed.

After a diagnosis of cutaneous LCH is made, a thorough work-up must be initiated to rule out multisystem disease. Initial workup includes a detailed history and physical exam with special focus on the skin, lymph nodes, oral cavity, bones, thyroid, liver, spleen, and central nervous system. Laboratory evaluation with a complete blood count, electrolyte evaluation, and liver function tests is recommended. Patients should also undergo imaging including a chest radiograph, skeletal survey, and ultrasound of the liver and spleen. Additional imaging such as an MRI of the brain may be indicated in the presence of symptoms such as polyuria, polydipsia, or stunted growth which could indicate involvement of the hypothalamic-pituitary axis. Patients with single system cutaneous involvement should be followed closely, every 2-4 weeks until resolution of cutaneous disease and then every 6 months for 5 years after complete resolution.

Prognosis of LCH depends on the extent of disease involvement and response to therapy. Single system disease has a survival rate of nearly 100% with a low rate of recurrence or sequelae. Treatment is not indicated for limited single system cutaneous disease as lesions generally heal on their own, though they may heal with scarring, hypo- or hyperpigmentation. For symptomatic or progressive cutaneous disease, first line therapy is medium to high potency topical steroids possibly in conjunction with other treatments including nitrogen mustard, imiquimod, or phototherapy. If more aggressive therapy is required, combination therapy with systemic steroids and vinblastine may be initiated for 6-12 months. Multisystem disease is associated with greater rates of recurrence and sequelae. Survival in multisystem disease is greatly influenced by involvement of high risk organs (liver, spleen, and bone marrow) with 5-year survival rates of 98% without high risk organ involvement and less than 77% with high risk organ involvement. Within the high-risk disease group, initial response to therapy may help predict disease course. Those who respond to therapy within 6 weeks of initiation have lower mortality rates and higher rates of complete resolution that non-responders. For multisystem disease, first-line therapy is combination treatment with systemic steroids and vinblastine for 12 months. If high risk-organ involvement is present, mercaptopurine is added to the treatment regimen 6-12 weeks after initiation of therapy. Future treatments may include targeted therapies that block the RAS-RAF-MEK-ERK-MAP kinase molecular pathway, including Vemurafenib, which have demonstrated efficacy in isolated case reports.

REFERENCES

Alikhan A and Hocker T. Review of Dermatology. Elsevier. 2017.

Bolognia J, Jorizzo J, Schaffer J. Dermatology, 3rd Ed. Elsevier Saunders. 2012.

Badalian-Very G, Vergilio J, Degar B, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010; 116:1919-1923.

Gadner H, Grois N, Potschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood. 2008; 111:2556-2562.

Gadner H, Minkov M, Grois N, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013; 121:5006-5014.

Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. Pediatr Blood Cancer. 2008; 51:71-75.

Jezierska M, Stefanowicz J, Romanowicz G, et al. Langerhans cell histiocytosis in children – a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. Postępy Dermatol Alergol. 2018; 35(1):6-17.

Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical workup, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013; 60:175-184.

Krooks J, Minkov M, Weatherall A. Langerhans cell histiocytosis in children. J Am Acad Dermatol. 2018; 78(6):1035-1058.

Li Z, Yanqiu L, Yan W, et al. Two case report studies of Langerhans cell histiocytosis with an analysis of 918 patients of Langerhans cell histiocytosis in literatures published in China. Int J Dermatol. 2010; 49:1169-1174.

Minkov M, Prosch H, Steiner M, et al. Langerhans cell histiocytosis in neonates. Pediatr Blood Cancer. 2005; 45:802-807.

Morren, M, Vanden Broecke K, Vangeebergen L, et al. Diverse cutaneous presentations of Langerhans cell histiocytosis in children: a retrospective cohort study. Pediatr Blood Cancer. 2016; 63:486-492.

Salotti J, Nanduri V, Pearce M, et al. Incidence and clinical features of Langerhans cell histiocytosis in the UK and Ireland. Arch Dis Child. 2009; 94:376-380.

Satoh T, Smith A, Sarde A, Lu H, et al. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One. 2012; 7:e33891.

Chicago Dermatological Society **CASE #7**

Presented by Jayla Gray[1] MD, Daniel Schlessinger[3] BA, Kumaran Mudaliar[2] MD, Jodi Speiser[2] MD and Eden Lake[1] MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center
[3]Feinberg School of Medicine, Northwestern University

UNKNOWN

NOTES

Presented by Adam Whittington[1] MD, Jodi Speiser[2] MD, Kumaran Mudaliar[2] MD, Eden Lake[1] MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Division of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 41-year-old female with a history of acute myeloid leukemia (AML) was admitted as an inpatient for abdominal pain. Dermatology was consulted for blue-gray nodules on the back. Both the patient and her family were unaware of when the lesions first appeared, though they mentioned that a previous physician had noticed a bruise on her back 4 months ago. At that time, there was only one. The lesions were asymptomatic. The patient noted increasing fatigue, nausea, non-bloody/nonbilious vomiting and decreased appetite.

Relative to the patients AML, she was first diagnosed in 2014. She was induced with a cytarabine and anthracycline chemotherapy protocol and consolidated shortly after with multiple courses of high dose cytarabine.

PAST MEDICAL HISTORY

Acute Myeloid Leukemia (as above)
Obesity
Polycystic Ovarian Syndrome
Diabetes Mellitus, Type 2

MEDICATIONS

No pertinent medications other than the chemotherapy regimens as listed above

ALLERGIES

No pertinent allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

The patient was unemployed. She had a 52-pack year history of smoking but otherwise was without history of alcohol or illicit drug use.

PHYSICAL EXAMINATION

The patient appeared to be in no distress. She had multiple gray-blue patches and nodules on the back, chest, and extremities. Also, of note, she had right-sided submandibular lymphadenopathy.

DERMATOPATHOLOGY

A biopsy obtained from the left paraspinal back revealed a dense dermal infiltrate of large atypical cells with frequent mitoses. Immunohistochemistry confirmed the diagnosis of myeloid sarcoma.

LABORATORY STUDIES

The patient’s complete blood count and complete metabolic panel were stable relative to her recent past.

DIAGNOSIS

Myeloid sarcoma (MS)

TREATMENT AND COURSE

Given the patient's relapse, she was induced with chemotherapy and is currently undergoing consolidation therapy.

DISCUSSION

MS is a rare manifestation of extramedullary hematologic malignancies. It may be observed in isolation, in conjunction with a myeloproliferative neoplasm, as a component of myelodysplastic syndrome, in the blast phase of chronic myeloid leukemia, or as in this case, as a manifestation of relapsing AML. MS may be seen in 2-8% of patients with AML; it is most commonly seen in the active phase of the disease. MS may occur at any age and has a slight male predominance. The etiopathogenesis of integumentary MS is a result of extramedullary myeloid blast cells migrating to the skin. While MS is the most recent appellation for this condition, it was once called a chloroma due to its green color secondary to high amounts of myeloperoxidase (MPO) produced in blastic cells.

MS is characterized by the appearance and growth of any number of reddish to blue macules, patches, papules, plaques, and nodules. Of note, some authors have shown that diascopy to the lesion will result in a green hue. The lesions have no location preference, though lymphadenopathy is frequently observed. Diagnosis is often aided by radiologic studies but histologic evidence is crucial, especially in the easily accessible locations, such as the skin. Stains suggestive of myeloid sarcoma include MPO, CD43, CD68, and CD117. The recognition of myeloid sarcoma should prompt hematology and oncology referral. In the case of de novo MS, recognition allows for early intervention which is necessary given frequent transformation to AML within 1 years' time. In this patient who already had a diagnosis of AML, the recognition of MS does not change prognosis outside of heralding the onset of a relapse. The management of MS has relied upon similar regimens as AML. In conjunction with oncologists, treatment options include chemotherapy, radiation, targeted molecular therapies, and stem cell transplant.

We present this case to highlight myeloid sarcoma, a rare sign of AML relapse.

REFERENCES

Almond LM, Charalampakis M, Ford SJ, et al. Myeloid Sarcoma: Presentation, Diagnosis, and Treatment. Clin Lymphoma Myeloma Leuk. 2017; 5(17):263-7.

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia; Blood. 2016.

Avni B, Koren-Michowitz M. Myeloid sarcoma: current approach and therapeutic options. Ther Adv Hematol 2011; 2:309–16.

Hagen P, Singh C, Hart M, et al. Differential diagnosis of isolated myeloid sarcoma: a case report and review of the literature. Hematology Reports. 2015; 7:5709.

Sauter C, Jacky E. Chloroma in Acute Myelogenous Leukemia. NEJM. 1998; 338:969.

Schiffer CA, Gurbuxani S. Classification of acute myeloid leukemia. In: UpToDate, Larson RA, UpToDate, Waltham, MA, 2017.

Yilmaz AF, Saydam G, Sahin F, et al. Granulocytic sarcoma: a systematic review. Am J Blood Res. 2013;3(4):265–270.

Chicago Dermatological Society **CASE #9**

Presented by Brooke Vasicek[1] MD, Jayla Gray[1] MD, Kristin Lee[1] MD, Eden Lake[1] MD
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 60-year-old female presented from an outside facility with a brightly erythematous rash for 6 weeks. Days prior to the development of the rash she had completed a course of oral azithromycin for an upper respiratory infection. The rash started on her chest and spread to involve the trunk, extremities, palms, soles, and face. Associated symptoms included severe pruritus. She was treated with oral prednisone and oral terbinafine for 3 weeks with no improvement. She presented to an outside emergency department where she was treated with vancomycin for presumed septicemia due to staphylococcus aureus as well as methylprednisolone and diphenhydramine for suspected bullous drug eruption but continued to develop new lesions despite these treatments. Subsequently, she was transferred to the Loyola Burn Unit given concern for Stevens-Johnson syndrome. At the time of admission the patient denied pain with eating, swallowing, urination or defecation as well as ocular and genital symptoms. She reported swelling over areas affected by the rash but review of systems was otherwise negative.

PAST MEDICAL HISTORY

Cutaneous squamous cell carcinoma

MEDICATIONS

Azithromycin, prednisone, terbinafine - all prescribed for this acute episode

ALLERGIES

Penicillins

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Former smoker, social alcohol use, no illicit drug use

PHYSICAL EXAMINATION

The patient was well-appearing. The vermillion border of the upper and lower lips had thin red scaly plaques with overlying yellow crust. Over the face there were scattered erythematous papules. On the trunk and extremities were widespread red perifollicular and non-follicular papules coalescing into large plaques. Over the lateral thighs were few superficial, fragile vesicles. Palms were diffusely erythematous with desquamation over the palms and volar fingertips.

The patient volunteered photos of the rash from 3 weeks prior, which demonstrated large bright pink to red erythematous plaques with annular, thin, yellow-white scale and scattered erythematous papules primarily involving the inframammary folds and breasts.

DERMATOPATHOLOGY

Histologic sections from the initial punch biopsy by an outside provider showed epidermal spongiosis with a subcorneal pustule and focal neutrophilic inflammation in the stratum corneum.

ADDITIONAL STUDIES

A complete blood count demonstrated an elevated white blood count at 23.5 (3.5 - 10.5 K/µL), decreased red blood count at 3.61 (3.80 – 5.20 M/µL), decreased hemoglobin at 11.1 (11.5 – 15.5 gm/dL) and decreased hematocrit at 33.1 (34.0 – 46.5%). A serum protein electrophoresis (SPEP) was remarkable for decreased protein at 5.3 (6.2 - 8.0 gm/dL), elevated alpha 1 at 0.3 (0.1 - 0.2 gm/dL), decreased albumin at 3.0 (3.7 - 4.8 gm/dL) and gamma at 0.5 (0.6 - 1.5 gm/dL). Immunoglobulins demonstrated decreased IgG at 633 (694 - 1,1618 mg/dL) and decreased IgM at 39 (46 - 304 mg/dL). Blood culture, urine protein electrophoresis, immunofixation and G6PD were unremarkable.

DIAGNOSIS

Subcorneal pustular dermatosis (SPD) or Sneddon-Wilkinson disease

TREATMENT AND COURSE

The patient was started on dapsone 25 mg which was titrated up to 100 mg over 1 month with resolution after 2 weeks on a therapeutic dose. She followed-up with hematology-oncology for the abnormal SPEP and immunoglobulin studies, which normalized on repeat testing.

DISCUSSION

SPD is a relapsing, chronic, benign but rare neutrophilic dermatosis thought to be due to exaggerated neutrophilic processes, including activation and phagocytosis. The resultant tissue damage caused by neutrophils is responsible for causing the micropustules that are seen in SPD. SPD most commonly presents in middle-aged women with a 4:1 female to male ratio.

Classically, SPD presents with acute, superficial, sterile pustules with a symmetric distribution over the trunk, intertriginous regions, and flexor aspects of the extremities. Occasionally it may present with pruritic superficial papules which develop into pustules or vesicles. Pustules may progress over 1 or 2 days to form annular or serpiginous patterns with central clearing and pustules at the periphery. These pustules rupture easily leading to desquamation. Affected areas will then crust and may heal with hyperpigmentation. SPD is chronic in nature with exacerbations and remissions in disease activity which can go on for many years. The palms, soles, nails, face and mucosal surfaces are rarely involved. SPD may have associated pruritus or pain. Systemic symptoms are rarely seen but have been reported.

Histologically SPD appears as a subcorneal pustule filled with neutrophils and occasional eosinophils which appears to “sit” on the epidermis. Spongiosis and acantholysis are other diagnostic features which are rarely reported. The underlying dermis demonstrates a mixed superficial perivascular inflammatory cell infiltrate. Neutrophils are more prominent in early lesions. Unlike pustular psoriasis, mitotic figures are not often seen in the epidermis. Unlike IgA pemphigus, direct immunofluorescence is negative.

SPD has been associated with systemic conditions including connective tissue diseases, inflammatory bowel disease, hypothyroidism, hyperthyroidism, SAPHO syndrome, multiple sclerosis, and hematologic disorders. In cases of SPD associated with monoclonal gammopathies or multiple myeloma, IgA-type paraproteinemia is most common, rather than IgG. The time course between SPD and hematologic malignancies is not well established, thus initial and periodic screening for paraproteins has been suggested.

The differential diagnosis for SPD can be broad, but the most common entities include SPD-type IgA pemphigus, pustular psoriasis, acute generalized exanthematous pustulosis, and pemphigus foliaceus. SPD-type IgA pemphigus is an intraepidermal blistering disease that is clinically and histologically very difficult to distinguish from SPD. The main difference is circulating or tissue bound IgA autoantibodies directed at desmocollin 1, which are present in SPD-type IgA pemphigus and negative in SPD. Direct immunofluorescence (DIF) is the most sensitive test for detecting this antibody followed by indirect immunofluorescence. The patient declined repeat biopsy for DIF, given that the results would not change management, thus we cannot say with certainty this patient does not have SPD-type IgA pemphigus.

Dapsone at 50 to 200 mg daily is first-line treatment with most patients improving in 1-4 weeks. Maintenance therapy can often be continued at a lower dose. If treatment is discontinued relapses are common. For patients that are unable to tolerate, allergic to, or not improving with dapsone, other anti-neutrophilic drugs can be tried including colchicine, sulfapyridine, and sulfamethoxypyridazine. The use of oral retinoids, topical or systemic steroids or light therapy either alone or in combination with other treatments and TNF inhibitors have all been successfully reported. SPD in males and those outside of the typical age range of SPD are often less responsive to dapsone.

We present this case to highlight a rare neutrophilic dermatosis for clinical interest as well as effective treatment with systemic dapsone.

REFERENCES

Bordignon M, Zattra E, Montesco MC, Alaibac M. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) with absence of desmoglein 1 and 3 antibodies: case report and literature review. Amer J Clin Dermatol. 2008;9(1): 51-5.

Cheng S, Edmonds E, Ben-Gashir M, and Yu RC. Subcorneal pustular dermatosis: 50 years on. Clin Exp Dermatol. 2007;33: 229-33.

Cohen PR. Neutrophilic dermatoses: a review of current treatment options. Am J Clin Dermatol. 2009;10(5):301-12.

Lotery H, Eedy D, McCusker G. Subcorneal pustular dermatosis involving the face. J Eur Acad Dermatol Venereol. 1999;12(3): 230-33.

Lutz ME, Daoud MS, McEvoy MT, Gibson LE. Subcorneal pustular dermatosis: a clinical study of ten patients. Cutis. 1998;61(4): 203-8.

Naik HB, Cowen EW. Autoinflammatory pustular neutrophilic diseases. Dermatol Clinics. 2013;31(3):405-25.

Patterson J. The vesiculobullous reaction pattern. In: Patterson J. Weedon's Skin Pathology, 4th Ed. Philadelphia Elsevier. 2016:135-187.

Prat L, Bouaziz JD, Wallach D, Vignon-Pennamen MD, Bagot M. Neutrophilic dermatoses as systemic diseases. Clin Dermatol 2014;32(3): 376-88.

Sneddon IB, Wilkinson DS. Subcorneal pustular dermatosis. Brit J Dermatol. 1956;68:385-94.

van de Kerkhof P and Nestle F. Psoriasis. In: Bolognia J, Schaffer J, Cerroni L. Dermatology, 4th Ed. Philadelphia Elsevier. 2018:138-160.

Watts P and Khachemoune A. Subcorneal Pustular Dermatosis: A Review of 30 Years of Progress. Am J Clin Dermatol. 2016;17: 653-671.

NOTES

Presented by David Rosenfeld[1] MD, Brooke Vasicek[1] MD, Jayla Gray[1] MD, Jodi Speiser[2] MD, James Swan[1] MD and Eden Lake[1] MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 51-year-old female presented as a transfer from an outside hospital to the Loyola Burn Unit with a diffuse painful and pruritic rash. Two weeks prior to admission, the patient developed a sore throat and took ibuprofen. The next day when it did not improve, she went to work (patient is an emergency medicine physician) and took 10 mg of intramuscular dexamethasone. Over the next several days, she continued to worsen, developing generalized malaise and cervical lymphadenopathy. Five days later she went to an outside hospital ED, and a CT scan revealed purulent uveitis. She received IV ampicillin/sulbactam and was discharged on oral amoxicillin/clavulanate. Three days after starting the antibiotics she developed a “dark red patch” on her posterior left leg. The following day, she discontinued the amoxicillin, but the rash spread. She also had irritation of the eyes, mouth and significant swelling of the labia majora. She was then admitted to an inpatient service and was started on 60 mg prednisolone IV BID and received over six liters of fluid. After five days at the outside hospital, the patient was transferred to Loyola due to lack of improvement.

At the time of consultation, patient reported some cutaneous improvement, but new areas continued to appear. The rash was intermittently painful and pruritic. She denied skin sloughing, crusting or bleeding. She did endorse significant swelling of the skin. She had associated malaise, but denied any cough, rhinorrhea, post-nasal drip, fever or anorexia. She denied sick contacts but is an emergency physician.

PAST MEDICAL HISTORY

None

MEDICATIONS

IV ampicillin/sulbactam (as above)
Oral amoxicillin/clavulanate (as above)

ALLERGIES

None

FAMILY HISTORY

No known history of autoimmune or dermatologic disease

SOCIAL HISTORY

Drinks alcohol occasionally
Denies smoking or illicit drug use

PHYSICAL EXAMINATION

The patient was in moderate distress. Cutaneous examination revealed erythematous, blanchable papules coalescing into plaques on the scalp, face, abdomen and back, as well as tense vesicles overlying erythematous, blanching papules coalescing into plaques on the chest and bilateral arms and legs. The lesions had negative Nikolsky and Absoe-Hansen signs. There were also flaccid bullae filled with clear-yellow serous fluid and 2+ pitting edema on the bilateral lower posterior legs. The perioral skin was noted to have mild yellow honey-colored crusting. She had no mucosal or palmoplantar involvement.

DERMATOPATHOLOGY

Histopathology from the right distal inner arm demonstrated a subcorneal pustular and spongiotic dermatitis with underlying marked dermal edema and superficial and deep perivascular and interstitial mixed inflammation with neutrophils and eosinophils. Direct immunofluorescence studies using antibodies for IgG, IgA, IgM and C3 showed a negative or non-diagnostic staining pattern.

ADDITIONAL STUDIES

Routine laboratory tests included a complete metabolic panel and a complete blood count. The most significant abnormality was an elevated white blood count of 32.6 (3.5-10.5 K/uL). Marked leukocytosis was thought to be secondary to high-dose steroids. The patient self-reported two negative outside heterophile antibody tests in the prior two weeks. During admission we were contacted by the outside treating physician who informed us that the patient had positive CMV IgM and IgG antibodies suggestive of primary or reactivated CMV infection.

DIAGNOSIS

Ampicillin or amoxicillin hypersensitivity eruption in the setting of CMV mononucleosis

TREATMENT AND COURSE

The patient was treated with triamcinolone 0.1% ointment BID (extremities and trunk) and hydrocortisone 2.5% ointment BID (face, groin and axilla), mupirocin 2% ointment BID (to impetiginized areas on the face), wet wraps (over the topical steroids) and loratadine for pruritus. The patient's IV prednisolone was transitioned to a quick PO prednisone taper. She was discharged after two nights. The patient was seen in our dermatology clinic 11 days later with complete resolution.

DISCUSSION

Hypersensitivity eruption in the setting of infectious mononucleosis (IM) is relatively uncommon, most often seen in association with ampicillin or amoxicillin administration. IM often presents with a classic triad of fever, pharyngitis and lymphadenopathy preceded by a one- to two-week prodrome of low-grade fever, malaise and fatigue. Other symptoms include hepatosplenomegaly, tonsillar exudate, palatal petechiae and persistent fatigue. While roughly 90% of cases are caused by Epstein-Barr virus (EBV), 10% are caused by cytomegalovirus (CMV). The signs and symptoms of each are very similar, although CMV mononucleosis tends to be less severe. CMV mononucleosis is also reported less in children and is most commonly seen in women in the third decade of life. EBV is diagnosed by a Monospot test, which detects IgM heterophile antibodies. This is the most specific, rapid and cost-effective diagnostic test. CMV is diagnosed with CMV serologies (IgM and IgG). Rare complications include peritonsillar abscess, splenic rupture, Hodgkin's lymphoma and ampicillin or amoxicillin hypersensitivity reaction.

In immunocompetent patients, primary CMV typically presents as IM. Primary cutaneous manifestations of CMV are rare. A viral exanthem is reported in less than 10% of cases. Reports of a morbilliform eruption following the administration of ampicillin or amoxicillin in CMV mononucleosis have previously been described in greater than 90% of cases. Other aminopenicillins have been associated with these findings, including piperacillin/tazobactam and cephalexin. In recent literature, non-aminopenicillins have also been reported, including levofloxacin and azithromycin.

This type of hypersensitivity reaction usually produces a diffuse, symmetric morbilliform eruption, often indistinguishable from classic viral or drug exanthems, although they tend to be more pronounced and involve a more extensive surface area. Other skin lesions may also be present, including vesicles, pustules and palpable purpura. The eruption will often clear in one to two weeks.

The pathophysiology of this process is not well understood, although the activation of drug-specific T-cells is likely to be involved. One hypothesis suggests that CMV infection results in activation of ampicillin-specific T-cells that are otherwise silenced. TNF-alpha elevation has been observed preceding the symptoms of CMV mononucleosis, and this may play a synergistic role with other pro-inflammatory

cytokines in lowering the activation threshold for ampicillin-specific T-cells. The reaction itself is usually a transient and reversible delayed-type hypersensitivity reaction, although a subset of patients may develop a true and persistent allergy. One study suggested allergy testing of the implicated antibiotic following resolution of symptoms.

Diagnosis is clinical, although as noted, it can be indistinguishable from a traditional viral exanthem or morbilliform drug eruption. Treatment of this condition includes withdrawal of the offending antibiotic followed by symptomatic relief. This includes potent topical steroids, emollients and wet wraps. Antihistamines are often prescribed, but are usually not helpful.

We present a case of amoxicillin hypersensitivity eruption in the setting of CMV mononucleosis. The patient responded promptly to treatment with topical steroids and wet wraps. Of note, the patient endorsed having had a previous morbilliform eruption after taking ampicillin in the setting of IM as a young adult. The typical onset of rash is 7-9 days post-antibiotic exposure, but our patient's rash began at day 3. It has been hypothesized that the presence of memory T-cells to ampicillin may facilitate a faster and more severe eruption upon subsequent exposure. This phenomenon has been reported in other drug eruptions, but there have been no cases reported specifically in the setting of CMV or EBV.

REFERENCES

Bolognia, Jean, et al. "Human Herpesviruses." Dermatology. Elsevier, 2018:1417-1418.

Drago, Francesco, et al. "Cytomegalovirus Infection in Normal and Immunocompromised Humans." Dermatology. 2000; 200(3):189–195.

Kano, Yoko, and Tetsuo Shiohara. "Current Understanding of Cytomegalovirus Infection in Immunocompetent Individuals." Journal of Dermatological Science. 2000; 22(3):196–204.

Klemola, Erkki. "Hypersensitivity Reactions to Ampicillin in Cytomegalovirus Mononucleosis." Scandinavian Journal of Infectious Diseases. 1970;2(1):29–31.

Ónodi-Nagy, et al. "Amoxicillin Rash in Patients with Infectious Mononucleosis: Evidence of True Drug Sensitization." Allergy, Asthma & Clinical Immunology. 2015:1.

Ónodi-Nagy, et al. "Antibiotic Induced Cutaneous Rash in Infectious Mononucleosis: Overview of the Literature." Journal of Allergy & Therapy, vol. 06, no. 05, 2015

Thompson, Dennis F., and Carroll L. Ramos. "Antibiotic-Induced Rash in Patients With Infectious Mononucleosis." Annals of Pharmacotherapy. 2016;51(2):154–162.

Vancikova, Z., and P. Dvorak. "Cytomegalovirus Infection in Immunocompetent and Immunocompromised Individuals - A Review." Current Drug Target - Immune, Endocrine & Metabolic Disorders. 2001;1(2):179–187.

NOTES