Chicago Dermatological Society

September 2021 Educational Conference

Program & Speaker Information
CME Certification
Case Presentations

Wednesday, September 15, 2021
ONLINE Conference

Conference Host:
Division of Dermatology
Loyola University Medical Center

LOYOLA MEDICINE
We also treat the human spirit.®

Program

Host: Loyola University
Wednesday, September 15, 2021
Online Conference

9:00 a.m.	**Welcome & Introduction** *Jordan Carqueville, MD - CDS President*
9:05 a.m. - 9:50 a.m.	**Morning Lecture** "High-Yield Dermoscopy" *Elizabeth V. Seiverling, MD*
9:50 a.m. - 10:00 a.m.	**Questions & Answers**
10:00 a.m. - 11:00 a.m.	**Resident Case Presentations & Discussion; MOC Self-Assessment Questions** *Loyola University Residents*
11:00 a.m. - 11:45 a.m.	**Keynote Guest Presentation** “Dermoscopy Case Review” *Elizabeth V. Seiverling, MD*
11:45 a.m. - 12:00 p.m.	**Questions & Answers**
12:00 p.m.	**Meeting adjourns** Closing Comments – *Jordan Carqueville, MD*

Mark the Date!

Next CDS meeting will be on Wednesday, October 13th
We are planning for an IN-PERSON conference at the Gleacher Center!
Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

ELIZABETH V SEIVERLING, MD

Practicing Dermatologist at MMP Dermatology and Maine Medical Center, Portland, ME

Dr. Seiverling cares for patients with all aspects of skin disease. She has a special interest in skin cancer using dermoscopy and confocal microscopy to assist with the early detection of melanoma and other types of skin cancer. She teaches dermoscopy to dermatologists and primary care physicians with the hope of improving skin cancer detection and reducing melanoma death rates in Maine.

Dr. Seiverling graduated from medical school in 2006 at Pennsylvania State College Of Medicine. Following an internship at Massachusetts General Hospital, she completed residencies in nephrology and dermatology in 2010 at the University of California-San Francisco. Her primary practice location is the MMP Dermatology Clinic in South Portland, as well as the Maine Medical Center in Portland.

CME Information

September 15, 2021

Overview

The Chicago Dermatological Society was established in 1901 and has strived to provide meaningful educational opportunities to dermatologists in the Chicago area for more than a century. Guest speakers from across the country share their expertise with CDS members, as well as residents in training medical students doing their dermatology rotation. CDS schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. Two lectures are given by the guest speaker, and the residents of the host institution present cases which are offered for audience discussion. During the coronavirus pandemic, CDS has continued to organize our regular educational conferences, but these are providing in a somewhat shorter “virtual” setting.

Target Audience

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

Learning Objectives

At the conclusion of the 2019/20 series of meetings, the participant should be able to:
1. Explain the principles of dermoscopy and techniques to obtain the best results using this examination tool.
2. Discuss diagnostic methods which employ dermoscopy in a dermatological setting.
3. Discuss a range of dermatological conditions which are identified when utilizing dermoscopy.

Physician Accreditation Statement

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

Credit Designation for Physicians – IAO designates this live activity for a maximum of 3 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form in order to receive credit. Each attendee eligible for CME credit will receive a link to an online claim for and an evaluation form. Thank you for your attention to this important item.

Disclosure of Conflicts of Interest

The IAO and CDS require instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by IAO and CDS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are asked to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk. None of the participants in this conference have disclosed any relevant potential conflicts of interest.

Continued next page

Contact Information

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

Americans with Disabilities Act

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

Disclaimer

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

Dislosure of Unlabeled Use

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

Loyola Resident Case Reports

Chicago Dermatological Society **Case 1**

[1]Joy Tao, MD, [1]Mathew Joseph, MD, [1]Adam Vaudreuil, MD, [2]Madhu Dahiya, MD, [1,3]David Eilers, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Edward Hines Jr. VA Hospital
[3]Section of Dermatology, Edward Hines Jr. VA Hospital

Patient 1:

HISTORY OF PRESENT ILLNESS

A 75-year-old Caucasian male presented to dermatology clinic with two new lesions of concern on the abdomen that had been present for several months. The lesions have been stable in size, and the patient denied any associated pain, burning, pruritus, drainage, or bleeding. The patient was otherwise well.

PAST MEDICAL HISTORY

Umbilical hernia that was surgically repaired in 2016, hypertension, chronic obstructive pulmonary disease, hyperlipidemia, complex kidney cysts, adrenal hyperplasia, lumbar stenosis, osteoporosis, allergic rhinitis, gastroesophageal reflux disease, choledocholithiasis treated with biliary dilations and stents, prediabetes, portal vein thrombosis

MEDICATIONS

Carvedilol, aspirin, pregabalin, montelukast, methadone, omeprazole, simvastatin, alendronate, albuterol, theophylline, amlodipine, prednisone, meclizine

ALLERGIES

No known allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Previous smoker (quit in 2013), no alcohol use, no illicit drug use

PHYSICAL EXAMINATION

The patient was well-appearing. The periumbilical abdomen had two well-defined 0.5 cm bright, mammillated, erythematous papules

DERMATOPATHOLOGY

Shave biopsy of the lesions showed epidermal acanthosis with foci of gastrointestinal-like mucosa (columnar and apocrine) in the dermis and epidermis with some foci opening up to the epidermis. The gastrointestinal mucosal cells are cytologically bland.

ADDITIONAL STUDIES

A complete metabolic panel was significant for a magnesium of 1.4 (1.7 - 2.2 mg/dL). A complete blood count, thyroid stimulating hormone, lipid panel, amylase, and lipase were unremarkable.

DIAGNOSIS

Cutaneous intestinal metaplasia

TREATMENT AND COURSE
The patient opted to have the remaining lesion removed via shave removal. The patient reported resolution of the lesions after shave removal without any complications.

Patient 2:

HISTORY OF PRESENT ILLNESS
A 90-year-old Caucasian male presented with a peristomal lesion of several months duration. The patient reported significant drainage from the lesion and difficulty managing his ostomy pouch. The patient denied any pain, pruritus, or bleeding. The patient had a biopsy of the lesion at an outside institution which showed a primary adenocarcinoma, but it was unclear where the biopsies were taken. Patient presented to Edward Hines VA Hospital for further management after moving to the area to be closer to family.

PAST MEDICAL HISTORY
Ulcerative colitis resulting in a total colectomy with an end ileostomy approximately 70 years ago, coronary artery disease with a recent myocardial infarction, type 2 diabetes mellitus, chronic kidney disease stage 3, peripheral vascular disease

MEDICATIONS
Aspirin, atorvastatin, clopidogrel, hydrochlorothiazide, isosorbide mononitrate, metoprolol

ALLERGIES
No known allergies

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
Non-smoker, no alcohol use, no illicit drug use

PHYSICAL EXAMINATION
The patient was well-appearing. The peristomal abdomen had a well-defined, large, moist, red papillomatous plaque circumferentially around the ileostomy site.

DERMATOPATHOLOGY
Histologic sections from the punch biopsies showed intraepidermal growth of intestinal glandular tissue and dense reactive chronic inflammation and scattered acute inflammation with intramucosal neutrophils. There were no dysplastic changes or features of malignancy.

ADDITIONAL STUDIES
A complete blood count showed a decreased red blood cell count at 3.75 (4.20 - 5.80 M/µL), decreased hemoglobin of 10.7 (13.0 - 17.5 gm/dL), and decreased hematocrit of 34.7 (38.0 - 54.0%). A complete metabolic panel was significant for an increased creatinine of 1.9 (0.6 - 1.4 mg/dL), calcium of 8.3 (8.9 - 10.3 mg/dL), and magnesium of 2.5 (1.7 - 2.2 mg/dL).

DIAGNOSIS
Cutaneous intestinal metaplasia

TREATMENT AND COURSE

Due to the patient's recent myocardial infarction, the patient was not a candidate for surgical intervention. The patient and family reported that the peristomal lesion led to difficulties in managing the ostomy pouch due to significant leakage resulting in remarkably decreased wear time. They wanted a procedure to improve the patient's quality of life. Palliative curettage and electrodesiccation of the affected skin was offered to the patient, and he accepted. Silver nitrate was also applied to a small test area, but the patient did not tolerate the pain for any additional applications. Approximately three weeks later, the treated tissue started to epithelialize, and he reported significantly improved wear time of the ostomy pouch and decreased leakage. At follow up three months later, the patient noticed regrowth of part of the lesion at the medial portion of the stoma. The patient did endorse some pain at the site of the regrowing mass. The patient was still able to keep his ostomy bag on for three days at a time. The patient opted for repeat biopsies of the mass and palliative treatment with curettage and desiccation of the affected skin for symptomatic relief. One of the biopsies showed adenocarcinoma, and the patient is scheduled to follow up to discuss further management.

DISCUSSION

Intestinal metaplasia is the development of intestine-like epithelium in abnormal locations, traditionally the stomach and esophagus where squamous cells transform into columnar mucosal cells. It is considered a precancerous condition that is attributed to chronic inflammation. There are a combination of factors that are believed to contribute to chronic inflammation within the stomach and esophagus including genetics, Helicobacter pylori infections, diet, and environmental factors. Chronic mucosal inflammation leads to a cascade of events starting with gastritis and gastric atrophy. Over time, intestinal metaplasia may develop, then dysplasia, and eventually adenocarcinoma. There is a debate on which stage is the "point of no return", but intestinal metaplasia is widely believed to be irreversible.

Symptoms of intestinal metaplasia in the gastrointestinal tract are usually nonspecific and may include dyspepsia, bloating, and diarrhea. Diagnosis is usually confirmed with a biopsy via upper endoscopy. These patients are at a higher risk of developing a gastrointestinal malignancy. Treatment of intestinal metaplasia in the esophagus or stomach includes eradicating Helicobacter pylori or any other causes of inflammation as well as regular cancer surveillance.

Cutaneous intestinal metaplasia is rare, but it is likely an underreported entity. At least 70% of patients with a stoma have skin related issues, most commonly irritant or allergic contact dermatitis, excess granulation tissue, psoriasis, seborrheic dermatitis, infection, or even pyoderma gangrenosum in select patients. The etiology for cutaneous intestinal metaplasia is unknown but there are several theories. Firstly, mechanical pressure and local trauma from dressings and the stoma itself can lead to ulceration and chronic inflammation that may induce metaplasia. It is unclear if peristomal overgranulation is related. Another theory is direct seeding of intestinal mucosal cells into the peristomal skin during surgical procedures. Additionally, bile salts may also play a role. In the esophagus, bile salts can increase cell migration as well as damage the epithelium leading to metaplasia; therefore, it is possible that bile salts in feces can promote intestinal mucosal cells to migrate into the adjacent skin. Finally, it is postulated that secreted materials from the glands can destroy the epidermis, leading to metaplasia.

There are at least nine reported cases of cutaneous intestinal metaplasia. Almost all of the patients are over the age of 50 and typically develop the lesions decades after an abdominal surgical procedure. However, presently, there is one case of primary idiopathic cutaneous

intestinal metaplasia found on the elbow of a 25-year-old patient with a history of epidermolysis bullosa simplex but no personal history of any gastrointestinal disorders. Clinical presentation of intestinal metaplasia ranges from few pink or red discrete papules near a stoma or previous surgical site to larger plaques surrounding a stoma. Symptoms vary from no symptoms to burning, tenderness, bleeding, and drainage. Treatments for cutaneous intestinal metaplasia include surgical stomal revision, electrosurgery, and clinical monitoring. Treatments that were unsuccessful in individual case reports include topical and intralesional steroids. The rate of transformation into malignancy is unknown. Nonetheless, destruction of affected tissue if possible and screening for development of a primary malignancy is recommended.

REFERENCES

Call E, Cizenski J, Griffin J. Ulcerated draining plaque below stoma. *International Journal of Dermatology*. 2016; 56(1):27-28.

Correa P, Piazuelo MB, Wilson KT. Pathology of Gastric Intestinal Metaplasia: Clinical Implications. *American Journal of Gastroenterology.* Mar 2010;105(3):493-498.

Correa P. The biological model of gastric cancer. *IARC Scientific Publications*. 2004;(157):301-10.

Fernandez-Flores A, Cassarino D. Primary Idiopathic Cutaneous Intestinal Metaplasia: First Case. *American Journal of Dermatopathology*. July 2021. Online ahead of print.

Golubets K, Radu OM, Ho J, et al. Ostomy associated cutaneous colonic metaplasia. *Journal of the American Academy of Dermatology*. 2014 Jan;70(1):e18-19.

Iwamoto M, Kawada K, Hida K, et al. Adenocarcinoma arising at a colostomy site with inguinal lymph node metastasis: report of a case. *Japanese Journal of Clinical Oncology.* 2015;45(2):217-20.

Miida H, Wakaki K, Shimoda S, et al. A rare skin disorder associated with a stoma: intestinal metaplasia and adenoma occuring in a skin ulcer around a colostomy site. *International Journal of Dermatology*. Sept 2019; 58(9):e173-e175.

Ona R, Oka M, Sakaguchi M, et al. Peristomal skin ulcer with intestinal metaplasia. *British Journal of Dermatology*. Jan 2012;161(1):204-206.

Patel A, Kulkarni, K, Perkins W. A friable peristomal lesion. *Clinical and Experimental Dermatology*. Mar 2014; 39(3):420-422.

Prouty M, Patrawala S, Vogt A, et al. Benign colonic metaplasia at a previous stoma site in a patient without adenomatous polyposis. *Journal of Cutaneous Pathology.* 2016*:* 43: 276-279.

Tinker D, Roberts S, Hurley MY, et al. Cutaneous intestinal metaplasia: An unusual cause of peristomal complication with malignant potential. *Journal of Cutaneous Pathology.* Dec 2019; 47)5):479-480.

Udechukwu NS, Selim MA, Nicholas MW. A case of periostomy intestinal metaplasia without adenomatous or dysplastic changes in an ulcerative colitis patient. *Clinical Case Reports*. Mar 2020; 8(3):535-537.

Uedo N, Ishihara R, Iishi H, et al. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy.* Aug 2006;38(8):819-24.

[1]Laryn Steadman, MD, [1]Erin Garfield, MD, [2]Jodi Speiser, MD, [1]Eden Lake, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 37-year-old male patient with a history of juvenile idiopathic arthritis and uveitis presented to our outpatient dermatology clinic for follow-up of a 3-year history of stasis dermatitis with lipodermatosclerosis and recurrent ulcerations as well as a 3-month history of an asymptomatic dermatosis affecting the ventral forearms, chest, back, and abdomen. The patient started clobetasol 0.05% ointment BID, but his lesions remained asymptomatic and stable without progression or improvement. Due to lack of improvement with topical steroids, an area on the upper back was biopsied for histological examination.

His stasis with associated dermatitis and induration had been treated with daily compression stockings (20-30 mmHg), clobetasol 0.05% ointment BID, mupirocin 2% ointment BID to open areas, pentoxyfylline 400 mg BID and vitamin C supplementation. Despite patient adherence to treatment, he continued to have progressive ulceration and pain. The patient was also evaluated by vascular surgery and underwent right great saphenous vein ablation 8 months prior.

Patient has been followed by Rheumatology for many years for juvenile idiopathic arthritis (diagnosed at age 2) with previous treatments including methotrexate and oral corticosteroids. The patient has been on and off adalimumab for over 10 years. Patient also follows with ophthalmology for chronic uveitis and chronic iridocyclitis.

PAST MEDICAL HISTORY

Polyarticular juvenile rheumatoid arthritis, chronic iridocyclitis, myopia, uveitis, cataract, iron deficiency anemia, lipodermatosclerosis, left inguinal hernia, hydrocele, great saphenous vein ablation

MEDICATIONS

Clobetasol 0.05% ointment BID, difluprednate ophthalmic, ferrous sulfate, Humira 40 mg SQ q10 days, mupirocin 2% ointment, pentoxifylline 400 mg ER tablet TID, triamcinolone acetonide 0.1% cream BID, Vitamin C supplement

ALLERGIES

No known drug allergies

FAMILY HISTORY

Mother with cataracts, stroke, blindness, hypertension, and juvenile rheumatoid arthritis

SOCIAL HISTORY

Never smoker, social alcohol use

PHYSICAL EXAMINATION
The patient was well-appearing. On the ventral forearms, chest, back, and abdomen, there were numerous pink/yellow grouped papules without scale. The left lower leg had slightly indurated hyperpigmented erythematous plaques. The right lower leg had indurated violaceous plaques with ulceration medially. Areas of ulceration were surrounded by purpura.

DERMATOPATHOLOGY
Histologic sections from tangential shave biopsy of the upper back showed a superficial portion of skin with noncaseating, well-formed dermal granulomas with relatively sparse lymphocytic inflammation and Langhans-type giant cells suggesting granulomatous dermatitis. Periodic Acid Schiff was negative for fungal organisms. Acid Fast Bacilli stain was negative.

ADDITIONAL STUDIES
A complete metabolic panel demonstrated elevated total protein at 8.8 (6.5-8.3 gm/dL). A complete blood count demonstrated a low hemoglobin at 11.7 (13.0-17.5 gm/dL), low hematocrit at 36.0 (38.0-54.0 %), low mean corpuscular volume at 75.6 (82.0-99.0 fl), low mean corpuscular hemoglobin at 24.6 (27.0-34.0 pg), and high red cell distribution width at 17.9 (1.0-15.0 %). C-reactive protein was elevated at 78.8 (<8.1 mg/L). Serum protein electrophoresis demonstrated high protein at 8.5 (6.2-8.0 gm/dL), high Alpha 1 at 0.3 (0.1-0.2 gm/dL), and high gamma at 2.6 (0.6-1.5 gm/dL). Thyroid stimulating hormone and lactate dehydrogenase were within normal limits. Ankle Brachial Index was within normal limits bilaterally. Right lower extremity venous reflux duplex demonstrated no acute deep vein thrombosis but showed evidence of chronic superficial venous thrombosis of the greater saphenous vein status post ablation and multiple varicosities.

DIAGNOSIS
Blau syndrome

TREATMENT AND COURSE
Given the patient's family history and classic triad of symptoms he was referred for genetic testing, which is currently pending. He continued management of his inflammatory arthritis with Rheumatology. His adalimumab dosing was increased to 40 mg subcutaneous injection every 10 days instead of every 2 weeks due to worsening joint symptoms. No additional treatment of asymptomatic skin lesions on the trunk and upper extremities was pursued.

For his lower extremity dermatitis and ulceration, he was continued on daily compression, clobetasol 0.05% ointment BID to indurated areas until smooth, mupirocin 2% ointment BID to open areas, pentoxifylline 400 mg BID, and Vitamin C supplementation. Follow-up with vascular surgery revealed no obvious vascular etiology to explain the right lower extremity wound.

DISCUSSION
Blau syndrome (BS) is a rare, inherited autoinflammatory disorder characterized by a clinical triad of granulomatous dermatitis, symmetric polyarthritis, and uveitis. It is caused by a gain of function mutation in the NACHT domain of Nucleotide-binding oligomerization domain 2 (NOD2). NOD2 is an intracellular pathogen recognition receptor which typically recognizes a bacterial cell wall component muramyl dipeptide (MDP) and, upon binding, activates NF-kB leading to upregulation of inflammatory cytokines. Mutations due to BS cause ligand-independent activation of NF-kB, predictably resulting in exuberant autoinflammation.

The majority of patients with BS exhibit cutaneous findings of disease at 4 years of age or younger and this is often the first disease manifestation. However, the rash may sometimes go

unnoticed or be misdiagnosed as atopic dermatitis or even ichthyosis vulgaris. And, in one review of 50 cases of BS in Japan, only 63% of patients had skin rash as their first symptom. Early cutaneous manifestations include pinpoint erythematous to yellow non-confluent grouped lichenoid papules on the trunk and extremities. They are characteristically asymptomatic. Additional reported cutaneous manifestations include intractable leg ulcerations, erythema nodosum, and leukocytoclastic vasculitis.

Patients then typically develop symmetric polyarthritis later in childhood primarily affecting the wrists, hands, ankles, and elbows. It is classically non-erosive on radiographs but may result in joint contracture and deformity over time. Ophthalmologic findings encompass a panuveitis with chronic iridiocyclitis with significant morbidity including blindness. Given the early onset of arthritic symptoms, accompanying uveitis, and its rarity, BS is often misdiagnosed as systemic juvenile idiopathic arthritis (sJIA). Several factors may help distinguish BS from sJIA: arthritis in BS is typically “boggy” with prominent swelling; uveitis in sJIA is typically limited to the anterior segment, whereas it is a panuveitis in BS; lastly, one study found serum VEGF and S100A12 to be significantly elevated in sJIA compared to BS. Ultimately, genetic analysis can definitively distinguish the two.

Extra-triad manifestations of disease are relapsing-remitting or persistent low-grade fever (in >50% of patients), large vessel vasculitis, pulmonary and systemic hypertension, cranial neuropathies, normocytic anemia due to chronic inflammation, and glomerulopathy.

Histologic findings include large granulomas with multinucleated giant cells and comma-shaped bodies in epithelioid cells on electron microscopy. Treatment is most often with anti-Tumor Necrosis Factor-alpha (TNF-a) medications such as adalimumab and is aimed at preventing ocular and joint morbidity. High dose steroids may be needed for acute flares and topical ocular steroids may be needed throughout the disease course. Methotrexate was commonly used as a steroid-sparing agent prior to the wide availability of biologics and can still be an important adjunct to biologic treatment. Newer therapies for which only case reports exist include tocilizumab (IL-6 Receptor inhibitor), anakinra (IL-1 Receptor inhibitor), and canakinumab (IL-1B inhibitor). Dermatologic manifestations have been successfully treated in two patients with oral erythromycin, but is anecdotally not effective for ocular or joint disease.

Our patient has a near life-long history of symmetric polyarthritis and chronic panuveitis, which had previously been treated as sJIA. His more recent history of leg ulcerations and granulomatous dermatitis as well as a family history of similar findings in his mother, present a strong case for misdiagnosed BS. This case highlights the importance of considering BS in all children with a history of arthritis and uveitis, especially those with skin findings.

REFERENCES

Caso F, Costa L, Rigante D, Vitale A, Cimaz R, Lucherini OM, Sfriso P, Verrecchia E, Tognon S, Bascherini V, Galeazzi M, Punzi L, Cantarini L. Caveats and truths in genetic, clinical, autoimmune and autoinflammatory issues in Blau syndrome and early onset sarcoidosis. *Autoimmun Rev*. 2014;*13*(12):1220–1229.

Imayoshi M, Ogata Y, Yamamoto S. A case of sporadic blau syndrome with an uncommon clinical course. *Case Rep Rheumatol*. 2018;2018:1–5.

Kamio Y, Kanazawa N, Mine Y, Utani A. Intractable leg ulcers in Blau syndrome. *J Dermatol*. 2016;*43*(9):1096–1097.

Kitagawa Y, Kawasaki Y, Yamasaki Y, Kambe N, Takei S, Saito MK. Anti-TNF treatment corrects IFN-gamma-dependent proinflammatory signatures in Blau syndrome patient-derived macrophages. *J Allergy Clin Immunol.* 2021;article in press.

Lu L, Shen M, Jiang D, Li Y, Zheng X, Li Y, Li Z, Zhang L, Tang J, Guo Y, Liu S, Zheng Z, Gao G, Kan Q. (2018). Blau syndrome with good reponses to Tocilizumab: A case report and focused literature review. *Semin Arthritis Rheum.* 2018;47(5):727–731.

Matsuda T, et al. Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the NOD2 mutation. *Ann Rheum Dis*. 2020;*79*(11):1492–1499.

Papatesta EM, Kossiva L, Tsolia M, Maritsi D. Persistent Tenosynovitis, Steroid dependency and a Hyperpigmented Scaly Macular rash in a child with Juvenile Idiopathic Arthritis. *Cureus*. 2020;12(10):e11208.

Paç Kısaarslan A. Blau syndrome and early-onset sarcoidosis: A six case series and review of the literature. *Arch Rheumatol*. 2020;*35*(1):117–127.

Sfriso P, Caso F, Tognon S, Galozzi P, Gava A, Punzi L. Blau syndrome, clinical and genetic aspects. *Autoimmun Rev*. 2012:12(1):44–51.

Wouters CH, Maes A, Foley KP, Bertin J, Rose CD. Blau syndrome, the prototypic auto-inflammatory granulomatous disease. *Pediatric Rheumatology*. 2014;12:33.

Yamasaki Y, Takei S, Imanaka H, Kubota T, Nonaka Y, Takezaki T, Kawano Y. S100A12 and vascular endothelial growth factor can differentiate Blau syndrome and familial Mediterranean fever from systemic juvenile idiopathic arthritis. *Clin Rheumatol*. 2018;*38*(3):835–840.

Chicago Dermatological Society **Case 3**

[1]Michael Knabel, MD, [2]Madhu Dahiya, MD, [1,3]David Eilers, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Edward Hines Jr. VA Hospital
[3]Section of Dermatology, Edward Hines Jr. VA Hospital

HISTORY OF PRESENT ILLNESS

An 84-year-old Caucasian male presented with a pruritic, blistering rash that started in the groin and buttocks which progressed to involve the trunk, bilateral axilla, forearms, and neck. He denied any systemic symptoms concerning for infection or malignancy. Six weeks prior to this eruption, he developed a rash on the bilateral legs with different morphology that was presumed to be a phototoxic eruption secondary to oral doxycycline. Topical nystatin applied at home prior to presentation was ineffective. Punch biopsy with H&E and DIF were performed. A culture was taken from a superficial vesicle.

PAST MEDICAL HISTORY

Rheumatoid arthritis, cardiac amyloid, atrial fibrillation, congestive heart failure, macrocytic anemia.

MEDICATIONS

Hydroxychloroquine 200mg twice daily, Methotrexate 12.5mg weekly, Folic Acid 1mg daily, Prednisone 5mg (as needed for RA flares), Pregabalin 100mg three times daily, Torsemide 60mg daily, Spironolactone 50mg daily, Potassium 40meq daily, Simvastatin 40mg daily, Apixaban 5mg twice daily, Tamsulosin 0.4mg nightly.

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Nonsmoker and denied alcohol or illicit drug use. Enjoyed sitting in direct sunlight while on his outdoor patio.

PHYSICAL EXAMINATION

The patient was stable and in no acute distress but appeared uncomfortable. Over the buttocks, lower back, abdomen, bilateral axilla, chest and extending to the bilateral cervical and nuchal neck there were scattered, annular, superficial erosions with central serous to yellow crusting and peripheral vesiculation coalescing into a circinate pattern. Notably, there was no involvement of the mucous membranes.

DERMATOPATHOLOGY

Histologic sections from punch biopsy of lesional skin on the abdomen showed subcorneal pustules and mild acantholysis with epidermal neutrophilic infiltrate on H&E. Additionally, there was a mixed superficial dermal infiltrate of predominantly neutrophils with lymphocytes and scattered eosinophils. Direct immunofluorescence of perilesional skin revealed intercellular IgA deposition in the upper parts of the epidermis and focally throughout the epidermis. Staining for

IgG, IgM, C3 and fibrinogen was non-specific. PAS, GMS and Gram staining were negative for organisms.

ADDITIONAL STUDIES

A complete blood count demonstrated a decreased hemoglobin at 10.9 (11.5-15.5 g/dL) with an MCV elevated to 100.9 (80-100 fl). The remainder of the complete blood count, complete metabolic panel and lipid studies were within normal limits. G-6-PD was within normal limits at 19.3 (5.5-20.5 u/gHb). Urine analysis was unremarkable (notably negative for bilirubin and protein). Serum protein electrophoresis (SPEP) revealed a slightly elevated $alpha_1$ protein to 0.5 (0.1-0.4 g/dL). $Alpha_2$ and beta were within normal limits at 0.5 (0.4-1.0 g/dL) and 0.6 (0.5-1.0 g/dL) respectively. Gamma decreased to 0.5 (0.6-1.5 gm/dL). Total protein and albumin were decreased to 5.0 (6.2-8.0 gm/dL) and 2.9 (3.7-4.8 gm/dL) respectively.
Bacterial culture grew methicillin sensitive *staphylococcus aureus*

DIAGNOSIS

IgA Pemphigus, subcorneal pustular dermatosis (SPD) type

TREATMENT AND COURSE

Our patient was empirically started on cephalexin 500 mg three times daily and ketoconazole 2% cream twice daily while awaiting the biopsy results due to concern for secondary infection of his erosions. When his skin lesions continued to progress he was transitioned to topical triamcinolone 0.1% ointment three times daily. Once the diagnosis of IgA pemphigus was made, multiple treatment options were discussed with the patient given his prior comorbidities including cardiac amyloid, anemia and rheumatoid arthritis. He elected to start low dose dapsone with plans to uptitrate as tolerated. No evidence of a monoclonal gammopathy was observed on serum protein electrophoresis and after completion of the initial workup, he was started on dapsone 25 mg daily which was increased to 50 mg daily leading to complete clearance of his skin. After 3 months of therapy his hemoglobin had downtrended to 8.9 gm/dL, but he was asymptomatic at his follow up visit. Several days after being seen in clinic he began to endorse dizziness and weakness so the patient dapsone was discontinued. His symptoms resolved and hemoglobin recovered to pre-treatment baseline. He remains free of disease 9 months after cessation of dapsone.

DISCUSSION

IgA pemphigus represents a group of autoimmune blistering conditions with overarching features including a neutrophilic infiltrate, mild acantholysis and deposition of IgA in the epidermis. First described by Vargas et al in 1979 and later Wallach et al in 1982, numerous terms have been used to describe this entity including *subcorneal pustulosis with IgA, subcorneal pustular dermatosis and monoclonal IgA, intraepidermal neutrophilic IgA dermatosis, IgA pemphigus foliaceus,* among others. Eventually the simplified term *IgA pemphigus* gained prevalence following the discovery of two distinct patterns of epidermal IgA deposition. The Subcorneal Pustular Dermatosis (SDP) type is favored when IgA deposition is confined to the upper part of the epidermis, as opposed to the Intraepidermal Neutrophilic Dermatosis (IEN) type when IgA is deposited diffusely across the entire epidermis. The primary antigen target for SPD-type is desmocollin 1 (Dsc1), which is an essential component of keratinocyte desmosomes. Alternative desmosomal proteins have been implicated in the disease pathophysiology to a lesser degree, therefore it is suspected that epitope spreading may play a role in disease progression. Although there has been speculation that the IgA antibodies in IEN-type target nondesmosomal cell surface proteins present throughout the epidermis, the exact antigen target is still unknown.

Classically the rash presents as a subacute eruption of tense bulla or flaccid vesicles that may develop into pustules. Lesions coalesce into annular or circinate patterns with central crusting and erosions on an erythematous base. SPD-type typically forms more superficial, subcorneal pustules while IEN-type has been described as “sunflower-like” plaques with pustules forming deeper within the epidermis. The condition itself is exceptionally rare with only 137 reported cases from 26 different countries (roughly one quarter of these coming from Japan) as of 2019. There is a slight female predominance but age ranges widely from infants to late adulthood. The trunk and extremities are most frequently involved, followed by intertriginous areas and the scalp. Mucous membrane involvement is uncommon. Histological examination displays mild acantholysis with a predominantly neutrophilic infiltrate in the epidermis. The dermal infiltrate is often mixed with prevalent neutrophils but also lymphocytes and occasional eosinophils. Hallmark features include subcorneal pustules in SPD-type and suprabasilar pustules in IEN-type. Direct immunofluorescence of perilesional skin shows “net-like” intercellular deposition of IgA that is restricted to the upper epidermis in SPD-type while present diffusely throughout the epidermis in IEN-type. There have been several reported cases of concomitant IgG and C3 deposition in addition to IgA, which is termed IgA/IgG pemphigus.

Oral dapsone is highly effective for IgA pemphigus and considered the treatment of choice with a target dose of 100mg daily, although complete clearance has been reported at lower daily doses. Other effective treatments include oral corticosteroids, isotretinoin, acitretin and colchicine but are not considered first line therapy. Topical steroids are used in limited skin disease or concomitantly with systemic medications. Alternative immunosuppressants such as cyclophosphamide, mycophenolate mofetil, azathioprine, adalimumab, and infliximab have been reported infrequently or in patients refractory to other medications.

Various malignancies and inflammatory conditions have been associated with IgA pemphigus. Hematological malignancies are most prevalent, specifically IgA monoclonal gammopathy, IgA type multiple myeloma, and peripheral T-cell lymphoma. IgA monoclonal gammopathy is the most common systemic association. Diagnosis typically occurs after onset of IgA pemphigus, thus routine screening upon initial evaluation of IgA pemphigus is recommended. Other associated diseases include solid organ malignancy and autoimmune conditions including ulcerative colitis, Crohn’s disease, Sjogren syndrome, myasthenia gravis and rheumatoid arthritis. IgA pemphigus represents a rare autoimmune bullous condition with characteristic intraepidermal IgA deposition that typically responds well to first line therapy with oral dapsone as was seen in this case. We did not identify an underlying gammopathy or malignancy in our patient although he did have a history of long-standing rheumatoid arthritis. Given the timeline, it was also hypothesized that our patient’s exposure to doxycycline and subsequent phototoxic reaction may have played a role in triggering this eruption.

REFERENCES

Düker I, Schaller J, Rose C, Zillikens D, Hashimoto T, Kunze J. Subcorneal pustular dermatosis-type IgA pemphigus with autoantibodies to desmocollins 1, 2, and 3. *Arch Dermatol*. 2009 Oct;145(10):1159-62.

Gruss C, Zillikens D, Hashimoto T, Amagai M, Kroiss M, Vogt T, Landthaler M, Stolz W. Rapid response of IgA pemphigus of subcorneal pustular dermatosis type to treatment with isotretinoin. *J Am Acad Dermatol*. 2000 Nov;43(5 Pt 2):923-6.

Hashimoto T. Immunopathology of IgA pemphigus. *Clin Dermatol*. 2001 Nov-Dec;19(6):683-9.

Hashimoto T, Kiyokawa C, Mori O, Miyasato M, Chidgey MA, Garrod DR, Kobayashi Y, Komori K, Ishii K, Amagai M, Nishikawa T. Human desmocollin 1 (Dsc1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. *J Invest Dermatol*. 1997 Aug;109(2):127-31.

Howell SM, Bessinger GT, Altman CE, Belnap CM. Rapid response of IgA pemphigus of the subcorneal pustular dermatosis subtype to treatment with adalimumab and mycophenolate mofetil. *J Am Acad Dermatol*. 2005 Sep;53(3):541-3.

Ishii N, Ishida-Yamamoto A, Hashimoto T. Immunolocalization of target autoantigens in IgA pemphigus. *Clin Exp Dermatol*. 2004 Jan;29(1):62-6.

Kridin, K, Patel PM, Jones VA, Cordova A, Amber KT. IgA pemphigus: A systematic review. *J Am Acad Dermat*ol. 2020 Jun; 82(6): 1386-1392.

Nishikawa T, Hashimoto T. Dermatoses with intraepidermal IgA deposits. *Clin Dermatol*. 2000 May-Jun;18(3):315-8.

Porro AM, Caetano LV, Maehara LS, Enokihara MM. Non-classical forms of pemphigus: pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. *An Bras Dermatol.* 2014 Jan-Feb; 89(1): 96-106

Ruiz-Genao DP, Hernández-Núñez A, Hashimoto T, Amagai M, Fernández-Herrera J, García-Díez A. A case of IgA pemphigus successfully treated with acitretin. *Br J Dermatol*. 2002 Nov;147(5):1040-2.

Szturz P, Adam Z, Klincová M, Feit J, Krejčí M, Pour L, Zahradová L, Vašků V, Hájek R, Mayer J. Multiple myeloma associated IgA pemphigus: treatment with bortezomib- and lenalidomide-based regimen. *Clin Lymphoma Myeloma Leuk*. 2011 Dec;11(6):517-20.

Tsuruta D, Ishii N, Hamada T, Ohyama B, Fukuda S, Koga H, Imamura K, Kobayashi H, Karashima T, Nakama T, Dainichi T, Hashimoto T. IgA pemphigus. *Clin Dermatol*. 2011 Jul-Aug;29(4):437-42.

Wallach D. Intraepidermal IgA pustulosis. *J Am Acad Dermatol*. 1992 Dec;27(6 Pt 1):993-1000.

Zaraa I, Kerkeni N, Sellami M, Chelly I, Zitouna M, Makni S, Mokni M, Ben Osman A. IgG/IgA pemphigus with IgG and IgA antidesmoglein 3 antibodies and IgA antidesmoglein 1 antibodies detected by enzyme-linked immunosorbent assay: a case report and review of the literature*. Int J Dermatol*. 2010 Mar;49(3):298-302.

[1]Adam Souchik, MD, [1]Wendy Kim, DO
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS
A 17-year-old male presented to Loyola Dermatology at age 9 after immigrating from Iraq for depigmented patches of the forehead and knees. Both in Iraq and at Loyola, topical therapy trials including calcitriol, calcipotriene, clobetasol, betamethasone diproprionate, triamcinolone, fluocinonide, tacrolimus, and pimecrolimus as well as nb-UVB and excimer laser led to incomplete response. His lesions initially spread to include the lower back and left malleolus but then stabilized in size.

PAST MEDICAL HISTORY
No other medical conditions

MEDICATIONS
None

ALLERGIES
No known drug allergies.

FAMILY HISTORY
Maternal grandfather and maternal aunt both with vitiligo

SOCIAL HISTORY
Student. Lives with mother, father, and one sibling. Denies smoking, drinking, and recreational drug use.

PHYSICAL EXAMINATION
The patient was well appearing. Depigmented patches were noted on the left forehead, glabella, right upper forehead, left medial malleolus, and lower midline back.

DERMATOPATHOLOGY
N/A

ADDITIONAL STUDIES
At the initial visit, normal values were noted for TSH at 3.77 uU/mL (0.5-4.3 uU/mL), free T4 at 1.2 ng/dL (0.8-1.7 ng/dL), anti-thyroid peroxidase antibodies at 0.6 iU/mL (<9.0 iU/mL) and anti-thyroglobulin antibodies at 2.0 iU/mL (<4.1 iU/mL).

DIAGNOSIS
Vitiligo

TREATMENT AND COURSE
On four occasions over the course of 2.5 years, the patient underwent punch grafting for depigmented patches of the lower back and forehead with the following technique. After cleansing with chlorhexidine and anesthetic infiltration with 1% lidocaine with epinephrine, 1 mm punch grafts scored to the depth of the upper dermis were taken from unaffected skin of cosmetically inconspicuous areas. These grafts were transferred to the effected vitiliginous skin

also scored to the level of the upper dermis and secured with dermabond. Grafts were harvested with the use of toothless bishop clamps and gradle scissors. There was initial partial repigmentation of each site, which has advanced to over 90% repigmentation of the initial procedure site, the lower back, at the 1-year mark. This area was complicated by hypertrophic scarring of the recipient site. The forehead procedures were performed more recently and have resulted in >50% repigmentation as of his last office visit.

DISCUSSION

Vitiligo is a chronic acquired depigmenting autoimmune condition in genetically predisposed individuals affecting between 0.5% and 2.0% of the world's population, resulting in a significant impact on quality of life. Prevalence is equal among all races and sexes, and 50% develop the disease before age 20. It is associated with other auto-immune diseases including most commonly thyroid disease, T1DM, pernicious anemia, RA, Addison's disease, and Guillane-Barre syndrome.

Pathophysiology is not completely elucidated, but appears to be 2-fold with predisposed individuals having intrinsic melanocyte defects as well as an autoimmune process. The inciting event is related to IFNγ over signaling, with resultant activation of JAK/STAT pathways and CXCL9/10 chemokines. This leads to increased melanocyte activation, oxidative stress, and activation of the innate immune system by the melanocytes. Melanocyte antigens including gp100, MART1, tyrosinase, and tyrosinase associated proteins 1 and 2 are then further targeted by CD8+ cytotoxic T cells, leading to melanocyte depletion in effected skin.

Mainstays of treatment include topical corticosteroids, oral corticosteroids, topical calcineurin inhibitors, topical vitamin D analogues, immunosuppressives, light therapy, and depigmentation in cases of high body surface area involvement. Surgical intervention is reserved for those with poor response to medical therapies and stable disease, which is defined as between 3 months and 2 years of constant lesion size without signs of inflammation, keobnerization, tricombing, or confetti macules.

Surgical therapies include mini-punch grafting, epidermal or suction blister grafting, thin skin grafting, and cellular grafting including cultured or non-cultured melanocyte cell suspensions and cultured follicular cell suspensions. In a recent meta-analysis comparing surgical techniques for vitiligo, punch grafting resulted in >90% repigmentation in 45.76 % (95CI 30.67-60.85), >75% repigmentation in 56.78% (45.35-68.22), and >50% repigmentation in 71.02% (62.23-79.80) of patients undergoing the procedure. Thin skin grafting, cultured and non-cultured melanocytes suspensions, and blister grafting each resulted in higher repigmentation rates across all categories when compared to punch grafting. However, of these methods, punch grafting offers moderate efficacy with the lowest cost, shortest procedure time, greatest technical ease, and importantly can be safely performed in most office settings without specialized equipment or training.

To perform, 0.8 to 2.5 mm punch grafts are harvested to the depth of the upper dermis from a cosmetically inconspicuous area and placed onto recipient sites also punched out to the level of the upper dermis. Grafts are immobilized with sutures or a non-adherent dressing and an overlying pressure bandage which is removed in 2 weeks. Post-surgical light therapy, either PUVA or nbUVB, may be utilized, but has not to date been conclusively shown to make a significant impact on regimentation. Repigmentation will spread on average 6.5 mm from the graft sites, beginning around 3 months after the procedure and reaching the highest level of repigmentation after around 1 year.

Adverse effects include most commonly a cobblestone appearance, milia, and color mismatch, with less commonly occurring mottled pigmentation, marginal halos, scarring, and Koebnerization of the donor site. Some authors suggest that recipient sites be made 1 mm deeper than graft height or 0.5 mm narrower than graft size to lower the risk of cobblestoning. Adverse effects have been shown to be significantly reduced using emerging techniques, such as motorized micropunch grafting. This also decreases the time to treat of larger surface area lesions.

For stable, medically resistant vitiligo, punch grafting offers a viable treatment option that can be performed in most community dermatology offices without specialized surgical training or equipment.

REFERENCES

Bae JM, Lee SC, Kim TH, et al. Factors affecting quality of life in patients with vitiligo: a nationwide study. *Br J Dermatol*. 2018;178(1):238-244.

Boersma BR, Westerhof W, Bos JD. Repigmentation in vitiligo vulgaris by autologous minigrafting: result in nineteen patients. *J Am Acad Dermatol* 1995; 33: 990–995.

Ju HJ, Bae JM, Lee RW, et al. Surgical Interventions for Patients With Vitiligo: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2021;157(3):307–316.

Lahiri K, Malakar S, Sarma N, Banerjee U. Repigmentation of vitiligo with punch grafting and narrow-band UV-B (311 nm)—a prospective study. *Int J Dermatol*, 2006; 45:649–55.

Majid I. Grafting in vitiligo: how to get better results and how to avoid complications. *J Cutan Aesthet Surg*. 2013 Apr;6(2):83-9.

Njoo MD, Westerhof W, Bos JD et al. A systematic review of autologous transplantation methods in vitiligo. *Arch. Dermatol*. 1998; 134: 1543–1549.

Parsad D, Gupta S. Standard guidelines of care for vitiligo surgery. *Indian J. Dermatol*. Venereol. Leprol. 2008; 74 (Suppl.): S37–45.

Patel N, Paghdal KV, Cohen GF. (2012). Advanced Treatment Modalities for Vitiligo. *Dermatologic Surgery*, 38, 381–391.

Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE. New discoveries in the pathogenesis and classification of vitiligo, *Journal of the American Academy of Dermatology*, Volume 77, Issue 1, 2017, Pages 1-13.

Rusfianti, M. and Wirohadidjodjo, Y.W. (2006), Dermatosurgical techniques for repigmentation of vitiligo. *International Journal of Dermatology*, 45: 411-417.

Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. Pigment. *Cell Res*. 2007; 20: 27–35.

Chicago Dermatological Society **Case 5**

[1]Kyle Bhatia, MD, [1]Michael Knabel, MD, [2]Jodi Speiser, MD, [1]Eden Lake, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 29-year-old male patient presented to the Loyola dermatology clinic with a rash in his bilateral inguinal creases for 6 months. He had been following with an outside oncologist for a history of Langerhans cell histiocytosis who suspected that the rash was fungal. The patient had been using nystatin powder to the area without improvement. He endorsed pruritus and burning that worsened with sweat and warm weather. The rash did not spread or involve other areas of the body. He had no bleeding or discharge from the affected area. He was otherwise well.

PAST MEDICAL HISTORY

Hyperlipidemia
Langerhans cell histiocytosis (LCH)

- Diagnosed with LCH at age 21
- Underwent induction chemotherapy with vinblastine and prednisone
- Maintenance with vinblastine, 6-mercaptopurine, prednisone for 1 year (completed 2014)
- Excellent response without evidence of residual disease
    - Colon and bone marrow biopsy negative
- Due to residual diffuse cystic changes leading to worsening pulmonary symptoms, patient underwent right-sided single lung transplantation in 2018

MEDICATIONS

Nystatin powder BID, Mycophenolate mofetil 1000mg BID, Tacrolimus 3mg qAM and 2mg qPM, Prednisone 2.5mg BID, Trimethoprim-sulfamethoxazole, Pravastatin, Gabapentin, Folic acid, Ergocalciferol

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

He previously smoked 3 cigarettes per day but quit in 2014. He denied alcohol or illicit drug use.

PHYSICAL EXAMINATION

The patient was well-appearing. Cutaneous examination revealed well-demarcated, beefy red plaques in the bilateral inguinal creases. The skin folds themselves were spared. There were no erosions, scale, weeping, or drainage appreciated.

DERMATOPATHOLOGY

Shave biopsy of the right inguinal crease revealed dermal infiltration of large ovoid cells with eosinophilic cytoplasm and reniform nuclei. Immunostaining for CD1a and S100 was positive.

ADDITIONAL STUDIES

Complete blood count, complete metabolic panel, and urinalysis were unremarkable.

DIAGNOSIS
Recurrence of adult-onset Langerhans cell histiocytosis

TREATMENT AND COURSE
Due to the patient's history of lung transplant, the case was discussed with both oncology and transplant pulmonology. Systemic therapy was deferred, and the patient was started on fluocinonide 0.05% solution twice daily to the affected areas. The patient continued to feel well without any systemic symptoms. Six months later, he was admitted with a headache and nuchal rigidity. Workup for meningitis was negative, but imaging demonstrated a left infraorbital mass on imaging. He was also found to have an abnormally enhancing left kidney with perinephric and peripelvic infiltration concerning for malignancy. These findings are currently being worked up as an outpatient.

DISCUSSION
Langerhans cell histiocytosis (LCH) is a neoplasm of myeloid origin characterized by a clonal proliferation of CD1a, S100 and CD207 positive cells. Characteristic Birbeck granules can be appreciated on electron microscopy. The disease is rare, with an estimated incidence of three to five cases per one million children, and one to two cases per one million adults. It is named for its morphological resemblance to skin Langerhans cells, though the LCH cells themselves originate from the myeloid dendritic cell lineage. The name Langerhans cell histiocytosis has traditionally comprised multiple diseases, including Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma, and congenital self-healing reticulohistiocytosis.

The pathogenesis of LCH is poorly understood, though a study in 2010 identified a gain-of-function mutation in *BRAF* (V600E) in 35 of 61 studied cases of LCH. In another study of 315 patients, the BRAF V600E mutation was found to be associated with a more severe clinical presentation, a greater likelihood of resistance to initial therapy with vinblastine and prednisone, and higher reactivation rates.

Clinically, the disease is characterized most frequently by bone and skin involvement, with lymph nodes, liver, spleen, oral mucosa, lung, and the central nervous system as other potential sites of involvement, though at lower rates. The skin is involved in 30-40% of LCH cases, and skin rash is the most common presenting symptom in adults. Skin findings are variable but typically include erythematous or skin-colored papules and plaques on the scalp or in the intertriginous areas. These may become scaly, crusted, or petechial. The eruption is often more tender rather than pruritic, and may be confused with seborrheic dermatitis, eczema, scabies, varicella, or intertrigo. Diagnosis was previously determined by observation of Birbeck granules on electron microscopy, though this has now been replaced by immunohistochemical staining of CD1a, S100, and/or CD207 of biopsy specimens.

The disease is classified into single-system or multisystem LCH. Of note, 40% of cases of skin LCH have multisystem disease. Thus, patients with skin disease as the presenting symptom warrant an extensive laboratory and imaging workup, typically including a whole-body PET/CT, to evaluate the skeletal, hematologic, pulmonary, hepatic, and renal systems.

For treatment of mild disease limited to the skin, current NCCN guidelines recommend clinical monitoring, topical nitrogen mustard, topical or injected corticosteroids, or PUVA. Imiquimod has been effective in case reports. For more extensive, refractory, or relapsed skin disease, systemic therapy with methotrexate, hydroxyurea, or thalidomide should be considered.

Patients with multisystem disease who are asymptomatic without impending organ dysfunction may be clinically monitored. Patients who are symptomatic or who have impending organ dysfunction may require chemotherapy and/or radiotherapy. Vemurafenib may be used in *BRAF* V600E mutated disease. A small portion of patients with reactivation of LCH have undergone treatment with etanercept, cyclosporine, 2-chlorodeoxyadenosine, imatinib mesylate, or bone marrow transplant. Of note, an increased incidence of solid organ tumors and leukemia have been seen in patients treated for LCH, thought to be secondary to treatment with chemotherapy, radiotherapy, or both.

REFERENCES

Badalian-Very G, Vergilio JA, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919-1923.

Carstensen H, Ornvold K. The epidemiology of Langerhans cell histiocytosis in children in Denmark, 1975-1989. *Med Pediatr Oncol*. 1993;21:387-388.

Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014;124(19):3007-3015.

Fronek LF, Grubbs H, Dorton DW, Miller R. Isolated Cutaneous Langerhans Cell Histiocytosis Presenting in an Adult Male. *Cureus*. 2020;12(8):e9861.

Go R, Jacobsen E, Baiocchi R, et al. Histiocytic Neoplasms. *NCCN Clinical Practice Guidelines in Oncology.* 2021; version 1.2021.

Goyal G, Shah MV, Hook CC, et al. Adult disseminated Langerhans cell histiocytosis: incidence, racial disparities and long-term outcomes. *Br J Haematol*. 2018;182(4):579-581.

Imashuku S, Kobayashi M, Nishii Y, Nishimura K. Topical Imiquimod for the Treatment of Relapsed Cutaneous Langerhans Cell Histiocytosis after Chemotherapy in an Elderly Patient. *Case Rep Dermatol Med*. 2018;2018:1680871.

Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. *Cancer Sci*. 2018;109(12):3707-3713.

Krooks J, Minkov M, Weatherall AG. Langerhans cell histiocytosis in children: History, classification, pathobiology, clinical manifestations, and prognosis. *J Am Acad Dermatol*. 2018;78(6):1035-1044.

Monsereenusorn C, Rodriguez-Galindo C. Clinical Characteristics and Treatment of Langerhans Cell Histiocytosis. *Hematol Oncol Clin North Am*. 2015;29(5):853-873.

Stierman SC, Spicknall KE. Dermatology diagnosis. Langerhans cell histiocytosis. *Cutis*. 2013;91(2):64-69.

Chicago Dermatological Society **Case 6**

[1]Blanca Estupiñan, MD, [1]Wendy Kim, DO
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 22-year-old Caucasian female presented to our clinic with periorificial dermatitis. She was prescribed tacrolimus 0.1% ointment twice daily, and subsequently reported five distinct episodes of facial flushing after alcohol consumption. She denied burning sensation, pain, bleeding, discharge, blisters, fever, chills, and lip or tongue swelling.

PAST MEDICAL HISTORY

Asthma, environmental allergies, anxiety, supraventricular tachycardia, migraine headaches

MEDICATIONS

Tacrolimus 0.1% ointment BID, montelukast, albuterol, rizatriptan

ALLERGIES

Latex

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Occasional alcohol use, no recreational drug use, non-smoker/vaper

PHYSICAL EXAMINATION

The patient was well-appearing. On the bilateral alar creases and lower cutaneous lip there were scattered monomorphic pink papules. Patient-provided photos of the alcohol-induced reactions that occurred after topical tacrolimus application showed brightly erythematous patches involving the forehead, bilateral cheeks, and chin.

ADDITIONAL STUDIES

None

DIAGNOSIS

Disulfiram-like reaction to topical tacrolimus

TREATMENT AND COURSE

She had marked improvement of the periorificial dermatitis with the addition of metronidazole 0.75% cream and doxycycline 50mg twice daily. Topical tacrolimus 0.1% ointment was discontinued. The periorificial dermatitis cleared and she no longer experienced facial flushing with alcohol consumption.

DISCUSSION

Disulfiram is an oral medication used to treated alcohol use disorders by irreversibly inhibiting hepatic aldehyde dehydrogenase. When alcohol is consumed, acetaldehyde rapidly accumulates in the blood. Patients can experience warmth and flushing of the skin, sweating, nausea, vomiting, and tachycardia. At higher blood alcohol levels, blurred vision, dyspnea, chest pain, hypotension, arrhythmias, seizures, and syncope can occur.

There are a number of medications known to cause such disulfiram-like reactions to varying degrees. Those relevant to dermatology include topical calcineurin inhibitors, cephalosporins, griseofulvin, isoniazid, oral ketoconazole, oral metronidazole, topical sulfiram, and sulfonamides.

Around 50% of pateints experience burning with topical tacrolimus application, which improves with continued use. Disulfiram-like reactions to topical tacrolimus are uncommon, affecting an estimated 3-7% of users. An open-label study assessing the safety and efficacy of topical tacrolimus patients defined “alcohol intolerance” as facial flushing or irritation after consumption of alcoholic beverages. There were 12 cases involving the application site only, 4 cases only involving areas outside of the application site, and 3 cases involving both treated and non-treated areas. Disulfiram-like reactions have also been reported with topical pimecrolimus cream, though this is rare.

Typically, facial flushing occurs 5-30 minutes after consumption of alcohol and resolves in under 60 minutes. The mechanism of action is unknown. It has been hypothesized that aldehyde dehydrogenases expressed by keratinocytes are inhibited by topical calcineurin inhibitors, causing local accumulation of acetaldhyde in the skin after alcohol consumption, similar to disulfiram. Alternatively, some have suggested that topical calcineurin inhibitors cause neuropeptide release with resultant capsaicin-mediated vasodilation enhanced with alcohol use. One study found that aspirin inhibited facial flushing, suggesting prostaglandins may play a role.

Patients should be counseled about this potential side effect, considering an unexpected disulfiram-like reaction can be distressing and socially disconcerting. Alternative treatment options, such as topical steroids for atopic dermatitis or oral doxycycline for periorificial dermatitis, should be considered. Aspirin 325mg twice daily was shown inhibit flushing in one small study of two participants. Finally, topical brimonidine 0.33% gel could be used prior to events to prevent flushing, though rebound erythema has been reported.

REFERENCES

Borja-Oliveira CR. Alcohol-Medication Interactions: The Acetaldehyde Syndrome. *J Pharmacovigilance*. 2014; 2(5):145-150.

Ehst BD, Warshaw EM. Alcohol-induced application site erythema after topical immunomodulator use and its inhibition by aspirin. Arch Dermatol 2004;140(8):1014–1015.

Karamanakos PN, Pappas P, Boumba VA, et al. Pharmaceutical agents known to produce disulfiram-like reaction: effects on hepatic ethanol metabolism and brain monoamines. *Int J Toxicol*. 2007;26(5):423-432.

Knight AK, Boxer M, Chandler MJ. Alcohol-induced rash caused by topical tacrolimus. Ann Allergy Asthma Immunol 2005;95(3):291–292.

Milingou M, Antille C, Sorg O, Saurat JH, Lübbe J. Alcohol intolerance and facial flushing in patients treated with topical tacrolimus. *Arch Dermatol*. 2004;140(12):1542-1544.

Muzio G, Maggiora M, Paiuzzi E, Oraldi M, Canuto RA. Aldehyde dehydrogenases and cell proliferation. *Free Radic Biol Med*. 2012;52(4):735-746.

Ogunleye T, James WD. Ethanol-induced flushing with topical pimecrolimus use. *Dermatitis*. 2008;19(2):E1-E2.

Reitamo S, Wollenberg A, Schöpf E, et al. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol*. 2000;136(8):999-1006.

Sabater-Abad J, Matellanes-Palacios M,Millán Parrilla F. Image gallery: interaction between alcohol and topical tacrolimus as a cause of facial flushing. *Br J Dermatol.* 2019;180(5):e144.

Soter NA, Fleischer AB, Webster GF *et al*. Tacrolimus ointment for the treatment of atopic dermatitis in adult patients: part II, safety. *J Am Acad Dermatol.* 2001;44(1 Suppl.): S39– 46.

Chicago Dermatological Society **Case 7**

[1]Zisansha Zahirsha, MD, [2]Lauren E Watchmaker, BA, [3]Jodi Speiser, MD, [1]Mariam Mafee, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]School of Medicine and Public Health, University of Wisconsin
[3]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

An 18-year-old Caucasian female initially presented to an outside facility with progressively worsening bilateral foot and ankle joint pain inhibiting ambulation. The patient received IV vancomycin and piperacillin-tazobactam for presumed sepsis without improvement. The patient subsequently developed painful, non-pruritic bulla, initially appearing on her left foot, prompting transfer to Loyola University Medical Center. She endorsed worsening pain, redness, and swelling of the bilateral feet and hands. In addition, the patient reported bullae appearing on her right foot, and brown, purulent fluid draining from the bullae. She endorsed concomitant fevers of 103F, chills, abdominal pain, weight loss, hematochezia, and arthralgias.

PAST MEDICAL HISTORY

No pertinent past medical history

MEDICATIONS

Inpatient: Enoxaparin, hydrocodone-acetaminophen, pantoprazole

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Denied alcohol, tobacco, or illicit drug use

PHYSICAL EXAMINATION

The patient was ill-appearing. The left anterolateral, left posterior, and right lateral ankle had tense bullae with purulent drainage and surrounding ill-defined erythema and edema. The left dorsal foot, right plantar foot, left dorsal hand, and left wrist had ill-defined, pink, erythematous plaques with surrounding soft tissue edema and were exquisitely tender. The right ventral forearm had a pink, erythematous, tender, indurated nodule, and the right hand and fingers were markedly edematous with an associated tender and erythematous plaque. The oral mucosa, nail folds and cuticles were unremarkable. A notable expulsion of copious purulent drainage occurred during the acquisition of a 4mm punch biopsy at the right foot.

DERMATOPATHOLOGY

Histologic sections from the initial punch biopsy demonstrated epidermal, dermal, and subcutaneous mixed perivascular and interstitial inflammation with neutrophils. Gram, PAS, GMS, AFB, and Fite special stains were negative for bacterial, fungal, or acid-fast organisms.

ADDITIONAL STUDIES

A complete blood count demonstrated an elevated white blood count of 19.4 (3.5 - 10.5 k/μL), decreased hemoglobin of 9.2 (11.5 – 15.5 gm/dL), decreased hematocrit of 27.2 (34.0 – 46.5%),

decreased mean corpuscular volume of 80.5 (82.0-99.0 fl), elevated granulocyte number of 16.0 (1.5-7.0 K/mm^3), elevated percent granulocyte of 81%, and elevated platelet count of 810 (150-400 k/µL). C Reactive protein was elevated at 287.5 (<8.1 mg/L) and sedimentation rate was elevated at 102 (0-20 mm). An infectious work up including aerobic, anaerobic, AFB, and fungal cultures of splenic abscess fluid, pleural fluid, blood, and tissue were unremarkable. Flow cytometry was negative for a monoclonal B or T-cell population. An extensive rheumatology work up was only notable for atypical p-ANCA positivity with a 1:40 titer.

IMAGING

CT Chest/Abdomen/Pelvis with intravenous contrast demonstrated splenomegaly with numerous large fluid collections consistent with splenic abscesses. In addition, a left lower lobe lung consolidation with a large left pleural effusion was visualized. Magnetic resonance imaging of bilateral feet (MRI bilateral feet) without intravenous contrast demonstrated multiple, mildly complex T2 hyperintense collections tracking along tendons concerning for an intraosseous infectious process. In addition, in the right foot, numerous T2 hyperintense lesions predominantly at the plantar aspect of the right forefoot were present, possibly reflecting pyomyositis with numerous abscesses and tenosynovitis. Given her history of hematochezia, gastroenterology was consulted, and the patient underwent a colonoscopy demonstrating chronic active colitis without granulomas, histologically favorable for Crohn's colitis.

DIAGNOSIS

Bullous and subcutaneous Sweet's syndrome with extracutaneous manifestations

TREATMENT AND COURSE

After diagnosing the patient with Sweet's syndrome, the patient was started on IV prednisolone 50mg daily for 3 days while inpatient. She had rapid clinical improvement of her abscesses on her bilateral feet, resolution of her fever, and marked improvement of her inflammatory markers. The patient was transitioned to oral prednisone 40mg daily for the remainder of her hospital course. The patient was discharged on topical triamcinolone 0.1% ointment to be applied twice daily to affected areas and oral prednisone 40mg daily after a 15-day hospital course with close dermatology, rheumatology, gastroenterology, podiatry, and physical therapy follow up. At her 1-week dermatology follow up, the patient had evidence of fibrin deposition at superficial ulcerations without soft tissue edema and was counseled to continue topical triamcinolone 0.1% ointment twice daily to wound edges and start mupirocin 2% ointment daily to the center of wounds. The patient was initiated on adalimumab 40mg subcutaneous every 2 weeks by gastroenterology approximately 1 month after discharge. She was tapered off prednisone within 4 months of discharge with repeat colonoscopy demonstrating no active colonic inflammation. Repeat MRI of the left foot demonstrated interval decrease in surrounding marrow edema consistent with healing intraosseous inflammation.

DISCUSSION

Sweet's syndrome, or acute febrile neutrophilic dermatosis, is characterized by painful erythematous papules or plaques and a generalized inflammatory state. This inflammatory state, possibly caused by cytokine cascades, manifests as pyrexia, malaise, arthralgias, myalgias, elevated inflammatory markers, and leukocytosis with prominent neutrophilia in many patients. Several etiologies for Sweet's syndrome have been reported including idiopathic, pregnancy, drug-induced, malignancy, and inflammatory conditions. The disease is classically

described as affecting 30- to 50-year-old females. However, cases have been reported in ages as young as 7-weeks-old and in both genders without racial predilection. Our patient's presentation meets all 6 (2 major and 4 minor) diagnostic criteria for Sweet's syndrome not associated with a medication:

Table 1. Diagnostic criteria of Sweet's syndrome

Major criteria (2)	Minor criteria (4)
1. Abrupt onset of painful erythematous plaques or nodules	1. Pyrexia > 38 degrees C (100.4 degrees F)
	2. An associated malignancy, infection, or inflammatory condition
2. Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis	3. An excellent clinical response to systemic corticosteroids
	4. Abnormal lab values (3 of the 4) (elevated sedimentation rate, positive C reactive protein, and leukocytosis with a neutrophilic predominance)

The additional cutaneous manifestations of subcutaneous edema, erythematous indurated nodules, and tense bullae seen in our patient are consistent with the subcutaneous and bullous variants of Sweet's syndrome reported in literature. Histologically, classical Sweet's syndrome is characterized by a mature neutrophilic infiltrate in the upper dermis with associated papillary dermal edema. However, the subcutaneous variant of Sweet's syndrome demonstrates neutrophilic infiltrate that is either exclusively in the subcutis or partially affecting both the subcutis and dermis, such as our case.

Extracutaneous manifestations of Sweet's syndrome have been reported including involvement of bone, central nervous system, eyes, kidneys, intestines, liver, heart, bronchi, lungs, muscles, and spleen. The involvement can be highly concerning for infectious etiologies but will have a negative infectious work up. Our patient's presentation with Crohn's colitis and extensive extracutaneous manifestations, including splenic, lung, bone, and muscle involvement, required a multidisciplinary approach with gastroenterology, rheumatology, podiatry, physical therapy, pulmonology, and infectious disease to appropriately manage. The subsequently culture-negative splenic abscesses and left pleural effusion initially visualized on CT are consistent with previous reports of Sweet's syndrome, including bullous Sweet's syndrome, and Sweet's syndrome associated with Crohn's disease. In addition, our patient had evidence of high signal intensities suspicious for myositis and osteomyelitis seen on MRI of her bilateral feet. Although no culture or infectious work up was performed, the clinical improvement of the patient and improvement of the intensities on a subsequent MRI without antibiotics suggest sterile myositis and osteomyelitis, which have been reported as presentations of extracutaneous Sweet's syndrome.

Dermatologists should be aware of the cutaneous manifestations of the bullous and subcutaneous variants of Sweet's syndrome in order to expedite diagnosis and treatment. In addition, dermatologists should be mindful of the variety of extracutaneous manifestations of

Sweet's syndrome and the multidisciplinary approach necessary to appropriately care for these patients.

REFERENCES

Andre M, Aumaitre O, Papo T, et al. Disseminated aseptic abscesses associated with Crohn's disease: a new entity? *Dig Dis Sci*. 1998;43: 420–428

Andre MF, Piette JC, Kemeny JL, et al. Aseptic abscesses: a study of 30 patients with or without inflammatory bowel disease and review of the literature. *Medicine*. 2007;86:145–161.

Attias D, Laor R, Zuckermann E, et al. Acute neutrophilic myositis in Sweet's syndrome: late phase transformation into fibrosing myositis and panniculitis. *Hum Pathol* 1995; 26: 688 – 690.

Berro S, Calas A, Sohier P, Darbord D, Dupin N. Sweet's Syndrome Three Weeks after a Severe COVID-19 Infection: A Case Report. *Acta Derm Venereol*. 2021;(c):0. doi:10.2340/00015555-3850

Burrows NP. Sweet's syndrome in association with Crohn's disease [Letter]. *Clin Exp Dermatol* 1995; 20: 279 – 281.

Choonhakarn C, Chetchotisakd P, Jirarattanapochai K, et al. Sweet's syndrome associated with non-tuberculous mycobacterial infection: a report of five cases. *Br J Dermatol* 1998; 139: 107 – 110.

Christ E, Linka A, Jacky E, et al. Sweet's syndrome involving the musculoskeletal system during treatment of promyelocytic leukemia with all-trans retinoic acid. *Leukemia* 1996; 10: 731 – 734.

Cohen PR, Kurzrock R. Extracutaneous manifestations of Sweet's syndrome: steroid-responsive culture-negative pulmonary lesions [Letter]. *Am Rev Respir Dis* 1992; 146: 269.

Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol.* 2003 Oct;42(10):761-78.

Cohen PR, Kurzrock R. Sweet's syndrome. a neutrophilic dermatosis classically associated with acute onset and fever. *Clin Dermatol* 2000; 18: 265 – 282.

Cohen PR. Sweet's syndrome - A comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet *J Rare Dis*. 2007;2(1):1-28. doi:10.1186/1750-1172-2-34

Dunn TR, Saperstein HW, Biederman A, et al. Sweet's syndrome in a neonate with aseptic meningitis. *Pediatr Dermatol* 1992; 9: 288 – 292.

Fett DL, Gibson LE, Su WPD. Sweet's syndrome: systemic signs and symptoms and associated disorders. *Mayo Clin Proc* 1995; 70: 234 – 240

Fortna RR, Toporcer M, Elder DE, Junkins-Hopkins JM. A case of sweet syndrome with spleen and lymph node involvement preceded by parvovirus B19 infection, and a review of the

literature on extracutaneous sweet syndrome. *Am J Dermatopathol*. 2010;32(6):621-627. doi:10.1097/DAD.0b013e3181ce5933

Going JJ, Going SM, Myskow MW, et al. Sweet's syndrome: histological and immunohistochemical study of 15 cases. *J Clin Pathol* 1987; 40: 175 – 179.

James WD, Berger TG, Elston DM. Erythema and urticaria: reactive neutrophilic dermatoses. In: James WD, Berger TG, Elston DM, editors. Andrews' Diseases of the Skin: Clinical Dermatology. 10th ed. Philadelphia, PA: Saunders/Elsevier; 2006:144–147.

Jordaan HF. Acute febrile neutrophilic dermatosis: a histopathological study of 37 patients and a review of the literature. *Am J Dermatopathol* 1989; 11: 99 – 111.

Kemmett D, Hunter JAA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. *J Am Acad Dermatol* 1990; 23: 503 – 507.

Klinger S, Mathis N, Jackson S. Bullous sweet syndrome associated with an aseptic splenic abscess. *Cutis*. 2009;84(5):255-258.

Liang, Yi, et al. "Sweet's Syndrome With Original Involvement of Lymph Node and Lung: A Case Report." *Chest*, vol. 149, no. 4, Elsevier Inc, 2016, pp. A466–A466, doi:10.1016/j.chest.2016.02.485.

Majeed HA, Kalaawi M, Mohanty D, et al. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet's syndrome in two siblings. *J Pediatr* 1989; 115: 730 – 734.

Marie I, Boyer A, Heron F, et al. Focal aseptic osteitis underlying neutrophilic dermatosis [Letter]. *Br J Dermatol* 1998; 139: 744 – 745.

Marzano AV, Borghi A, Wallach D, Cugno M. A comprehensive review of neutrophilic diseases. *Clin Rev Allergy* Immunol 2018; 54: 114–130.

Peters FPJ, Drent M, Verhaegh M, et al. Myelodysplasia presenting with pulmonary manifestations associated with neutrophilic dermatosis. *Ann Hematol* 1998; 77: 135 – 138.

Quilichini R, Mazzerbop F, Baume D, et al. Syndrome de Sweet et abces aseptiqes de la rate. *Rev Med Interne.* 1996;17:1029–1031.

Sitjas D, Cuatrecasas M, De Moragas JM. Acute febrile neutrophilic dermatosis (Sweet's syndrome). *Int J Dermatol* 1993; 32: 261 – 268.

Thurnheer R, Stammberger U, Hailemariam S, et al. Bronchial manifestations of acute febrile neutrophilic dermatosis (Sweet's syndrome). *Eur Respir J* 1998; 11: 978 – 980.

Tuerlinckx D, Bodart E, Despontin K, et al. Sweet's syndrome with arthritis in a 8-month-old boy. *J Rheumatol* 1999; 26: 440 – 442.

Vaz A, Kramer F, Kalish RA. Sweet's syndrome in association with Crohn's disease. *Postgrad Med J* 2000; 76: 713 – 714.

Voelter-Mahlknecht S, Bauer J, Metzler G, Fierlbeck G, Rassner G. Bullous variant of Sweet's syndrome. *Int J Dermatol*. 2005;44; 946-947.

Von Den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol* 1994; 31: 535 – 556.

Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol*. 1996 May;34(5 Pt 2):918-23. doi: 10.1016/s0190-9622(96)90080-8. PMID: 8621829.

Chicago Dermatological Society **Case 8**

[1]Maureen Riegert, MD, [2]Kumaran Mudaliar, MD, [1]Eden Lake, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A thirty-five-year-old male presented to the outpatient dermatology clinic for evaluation of a rash on the back and arms for six months duration. The patient endorsed itching and night sweats for two weeks and fatigue for six months to one year. The patient also endorsed low-grade fever for one day. The patient tried Aveeno lotion with improvement of dryness but no improvement of the actual rash. The patient denied any clear triggers for the lesions; they were not rapidly growing or spreading. The patient reported he is otherwise healthy.

PAST MEDICAL HISTORY

Bronchitis, nephrolithiasis, syphilis previously treated with penicillin G

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

None pertinent

SOCIAL HISTORY

Smoking: Former smoker, quit fifteen years ago
Alcohol: Five drinks a week
Marital Status: Monogamous with male partner x two years

PHYSICAL EXAMINATION

The scalp, back, and bilateral upper and lower extremities had scattered erythematous to violaceous firm plaques with surrounding faint yellow hue.

DERMATOPATHOLOGY

Punch biopsy of two lesions showed slit-like compressed vessels throughout the dermis. Immunohistochemical stains showed that the vessels were highlighted by CD31 and that the endothelial cells show positivity for human herpesvirus 8 (HHV-8)

ADDITIONAL STUDIES

CBC was significant for a WBC of 3.9 (3.5 -10.5 K/uL), Hemoglobin 11.7 (13-17 gm/dL). Albumin was low at 3.1 (3.6-5.0 gm/dL) and total protein was elevated at 8.7 (6.5-8.3 gm/dL) for a protein gap of 5.6.

DIAGNOSIS

AIDS-associated Kaposi sarcoma

TREATMENT AND COURSE

Following his dermatology appointment, the patient went to urgent care and was diagnosed with pneumonia which was treated with azithromycin. He then continued to feel ill and presented to the ED and was admitted for further workup. His HIV test was positive. He was also diagnosed with cryptococcal pneumonia, giardia, toxoplasmosis, and syphilis. He was treated with amphotericin B, fluconazole, vancomycin, cefepime, metronidazole, and penicillin G. CT chest concerning for visceral involvement of the Kaposi sarcoma, with recurrent exudative pleural effusions which were treated with repeat thoracenteses. He has since established with oncology and will be starting doxorubicin for treatment of his Kaposi sarcoma.

DISCUSSION

Kaposi sarcoma (KS) is a malignant neoplasm of lymphatic endothelial origin. There is some discussion whether the condition is truly neoplastic or hyperplastic. It is triggered by HHV-8. There are four classic sub-types of KS: classic, African endemic, iatrogenic immunosuppression, and AIDS-related. The classic subtype is seen predominantly in individuals of Ashkenazi Jewish and/or Mediterranean/Eastern European descent. It is more common in males who are above fifty years of age. The African endemic subtype has an incidence in Africans ranging from 1-10% and accounts for 9% of all cancers in equatorial Africa. It is also associated with the lymphadenopathic variant in children. The iatrogenic immunosuppression subtype is seen in individuals on systemic immunosuppressants. Cyclosporine is associated with a higher incidence and more rapid onset of KS than other immunosuppressants. Immunosuppression-related KS may regress following cessation of immunosuppressant therapy. AIDS-related KS is usually seen in patients who are men who have sex with men (MSM) and 40% of men who have AIDS via homosexual contact develop KS. Occasionally, KS can be seen in those with HIV who are on chronic antiretroviral therapy and whom do not have active AIDS.

The classic clinical presentation of KS is the appearance of slowly growing, red to pink-violet macules on the distal lower extremities that may coalesce into large plaques, nodules or tumors. Early lesions may regress, while others can evolve. Patients with longstanding KS may develop oral and gastrointestinal lesions. The African endemic subtype usually presents with more nodular, florid, infiltrative and lymphadenopathic lesions. These lesions tend to be more biologically aggressive. The lymphadenopathic type affects children most commonly. The tumors involve lymph nodes primarily and tend to have a fulminant and fatal course. In AIDS-related KS, patients generally have a CD4 count less than 200. Presentation can range from a single lesion to many disseminated lesions with visceral involvement. The lesions range from faint erythematous macules, papules and plaques to purple-black tumors and nodules. Large plaques that are constricting can impair function and cause lymphedema. The most common sites of involvement are the trunk and midface. Tumors can ulcerate and be a source of infection. Frequently involved sites of visceral involvement include the gastrointestinal tract, lymph nodes, and lungs. The incidence of KS in the United States in people with HIV from 2000-

2015 decreased from 109 per 100,000 person years to 47 per 100,000 person years, a -6% annual percent change. 89% of affected individuals are MSM.

Treatment of KS can be difficult and recurrence rates are high. For AIDS- and HIV-associated cases anti-retroviral therapies are key. In immunocompetent patients with stable disease, observation and close follow up can be considered. Solitary lesions can be treated with surgical excision. For superficial patches and plaques treatment options include cryotherapy, laser surgery, photodynamic therapy, intralesional vinblastine or vincristine, and topical alitretinoin or imiquimod. In transplant patients, substituting sirolimus for cyclosporine can lead to resolution. Radiation therapy or total body electron beam can also be used. Patients with more extensive or aggressive disease and visceral involvement generally need systemic treatment with chemotherapy such as doxorubicin, paclitaxel, vincristine, or etoposide. Newer treatment options include bevacizumab, thalidomide or lenalidomide, bortezomib, and tyrosine kinase inhibitors.

REFERENCES

Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet*. 1990 Jan 20;335(8682):123-8. doi: 10.1016/0140-6736(90)90001-l. PMID: 1967430.

Bolognia J, Schaffer J, Cerroni L. *Dermatology.* 4th Edition. New York: Elsevier, 2017. Print

Etemad SA, Dewan AK. Kaposi Sarcoma Updates. *Dermatol Clin*. 2019 Oct;37(4):505-517. doi: 10.1016/j.det.2019.05.008. Epub 2019 Jul 10. PMID: 31466590.

Geraminejad P, Memar O, Aronson I, Rady PL, Hengge U, Tyring SK. Kaposi's sarcoma and other manifestations of human herpesvirus 8. *J Am Acad Dermatol*. 2002 Nov;47(5):641-55; quiz 656-8. doi: 10.1067/mjd.2002.128383. PMID: 12399755.

James, William D, Dirk M. Elston, Timothy G. Berger, and George C. Andrews. *Andrews' Diseases of the Skin: Clinical Dermatology*. London: Saunders/ Elsevier, 2020. Print.

Kaposi Sarcoma Incidence, Burden and Prevalence in United States People with HIV, 2000-2015. *Cancer Epidemiol Biomarkers Prev.* June 2021. Online ahead of print.

Régnier-Rosencher E, Guillot B, Dupin N. Treatments for classic Kaposi sarcoma: a systematic review of the literature. *J Am Acad Dermatol*. 2013 Feb;68(2):313-31. doi: 10.1016/j.jaad.2012.04.018. Epub 2012 Jun 12. PMID: 22695100.

Rigo R, Lee A, Minkis K. Nodular Endemic Kaposi Sarcoma Successfully Treated with Mohs Micrographic Surgery. *Dermatol Surg*. July 2021. Online ahead of print.

Schwartz RA, Micali G, Nasca MR, Scuderi L. Kaposi sarcoma: a continuing conundrum. *J Am Acad Dermatol*. 2008 Aug;59(2):179-206; quiz 207-8. doi: 10.1016/j.jaad.2008.05.001. PMID: 18638627.

Wang J, Reid H, Klimas N, Koshelev M. An unusual series of patients with Kaposi sarcoma. *JAAD Case Rep*. 2019 Jul 31;5(8):646-649. doi: 10.1016/j.jdcr.2019.05.016. PMID: 31388528; PMCID: PMC6677764.

Chicago Dermatological Society **Case 9**

[1]Erin Garfield, MD, [2]Madhu Dahiya, MD, [1,3]David Eilers, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Edward Hines Jr. VA hospital
[3]Section of Dermatology, Edward Hines Jr. VA Hospital

HISTORY OF PRESENT ILLNESS

A 57-year-old female patient presented for outpatient follow-up for hair loss of at least 10 years duration with associated scalp pruritus and burning. The patient was initially treated with ketoconazole shampoo and clobetasol 0.05% solution 3 years prior for suspected seborrheic dermatitis without improvement. The patient returned to clinic due to continued hair loss, predominantly on the vertex scalp and occiput.

PAST MEDICAL HISTORY

PTSD, migraine with aura, chronic low back pain, primary fibromyalgia, hyperlipidemia

MEDICATIONS

Sertraline, prazosin, bupropion, amlodipine, montelukast, atorvastatin, aspirin

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Non-smoker, no history of illicit drugs

PHYSICAL EXAMINATION

The patient was a well-appearing African American female. On examination of the scalp, there were few localized areas of scarring hair loss with loss of follicular ostia under trichoscopy as well as adjacent areas of perifollicular erythema and scaling. The patient's scalp was remarkably spongy on palpation, without fluctuance.

DERMATOPATHOLOGY

Two punch biopsies were submitted for vertical and horizontal sectioning in areas of perifollicular erythema and scaling. Vertical sectioning showed perifollicular fibrosis with prominent subcutaneous adipose tissue and infiltration of mature adipocytes into the lower to mid dermis. The epidermis was unremarkable. Horizontal sectioning showed chronic lymphocytic inflammation, perifollicular fibrosis in the isthmus region with surrounding lymphocytes appearing to "back away" from the follicles.

ADDITIONAL STUDIES

MRI brain without contrast from 6 months prior for evaluation of the patient's chronic headaches revealed a diffusely thickened subcutaneous fat layer on the scalp, most prominent on the vertex and occiput.

DIAGNOSIS
Lipedematous scalp with lichen planopilaris

TREATMENT AND COURSE
The patient started clobetasol 0.05% solution twice daily to the affected areas and hydroxychloroquine 200 mg twice daily for treatment of lichen planopilaris. There is no definitive treatment for lipedematous scalp. The patient has not yet presented for follow-up.

DISCUSSION
Lipedematous scalp is a condition characterized by the presence of a thickened, boggy, doughy, or spongy scalp due to a thickened subcutaneous fat layer. When associated with patchy hair loss, the condition is called lipedematous alopecia. Lipedematous alopecia was first described by Coskey et al. in 1965, who reported two cases of women with shortened hair and an increased subcutaneous fat layer on histology. Approximately 50 reports of lipedematous alopecia are presently cited in the literature.

Lipedematous scalp and lipedematous alopecia most frequently present in adult black women, but can occur in any race or age cohort. Scalp thickening is often most prominent on the vertex and occiput but may be diffuse. The thickness of the average human scalp is only 5-8 mm while lipedematous scalp thickness ranges from 9-19 mm. Increased scalp thickness can be visualized by ultrasound, x-ray, MRI or head CT. Lipedematous alopecia is a non-scarring hair loss and can be associated symptoms such as pruritus, pain, or paresthesia of the scalp.

Histopathology classically demonstrates expansion of the subcutaneous fat layer, sometimes with associated replacement of hair follicles with fibrous tracts without inflammation. Ectatic lymphatic vessels, dermal edema, perifollicular fibrosis, perifollicular lymphocytic infiltration, and dermal lymphocytic infiltration can also be seen.

The etiology of this condition is unknown, but several mechanisms have been suggested. It has been proposed that increased pressure on the hair follicles from the thickened subcutaneous fat layer results in decreased growth or shortening of the anagen phase. The majority of patients with lipedematous alopecia are female, suggesting a hormonal etiology, though no hormonal mechanism has been described. Ectatic lymphatic vessels are often seen on histology suggesting a role for lymphatic dilatation. Genetics and familial inheritance may also play a part; a mother and daughter both with lipedematous scalp and two sisters in their twenties with lipedematous alopecia have been reported in the literature. Lipedematous alopecia has been reported concurrently with androgenetic alopecia, psoriasis, mucinosis, and discoid lupus erythematosus. Some authors propose that lipedematous alopecia could represent a late consequence of discoid lupus erythematosus, though most cases of lipedematous alopecia lack mucin deposition, a characteristic pathologic feature of DLE. Some hypothesize that lipedematous alopecia represents a reactive pattern to chronic inflammation, as fatty changes have been seen in other lesions with chronic injury. Finally, some propose that dysregulation of leptin, a hormone that is involved with the distribution of adipose tissue, may contribute to the pathogenesis.

There is no definitive treatment for lipedematous scalp or lipedematous alopecia. Intralesional and topical steroids have shown little to no improvement per literature review. One study showed successful treatment with a 10-month course of mycophenolate mofetil 1 gram daily with marked increase in growth and hair density as well as decreased hypodermic thickening on follow up ultrasound. Another study showed success with surgical debulking.

REFERENCES

Cabrera R, Larrondo J, Whittle C, Castro A, Gosch M. Successful treatment of lipedematous alopecia using mycophenolate mofetil. *Acta Derm Venereol.* 2015 Nov;95(8):1011-2. doi: 10.2340/00015555-2114. PMID: 25881615.

Chen E, Patel R, Pavlidakey P, Huang CC. Presentation, diagnosis, and management options of lipedematous alopecia. *JAAD Case Rep*. 2018;5(1):108-109. Published 2018 Dec 17. doi:10.1016/j.jdcr.2018.10.012

Dhurat RS, Daruwalla SB, Ghate SS, Jage MM, Sharma A. Distinguishing Lipedematous Scalp, Lipedematous Alopecia, and Diffuse Alopecia Areata. *Skin Appendage Disord*. 2019;5(5):316-319. doi:10.1159/000495947

High WA, Hoang MP. Lipedematous alopecia: an unusual sequela of discoid lupus, or other co-conspirators at work? *J Am Acad Dermatol 2005;* 53: S157–161.

Kilinc E, Dogan S, Akinci H, Karaduman A. Lipedematous Scalp and Alopecia: Report of Two Cases with a Brief Review of Literature. *Indian J Dermatol*. 2018;63(4):349-353. doi:10.4103/ijd.IJD_2_17

Koç Yıldırım S, İğde B. Lipedematous alopecia: Report of two female siblings. *J Cosmet Dermatol.* 2021 May 19. doi: 10.1111/jocd.14235. Epub ahead of print. PMID: 34008886.

Palo S, Biligi DS. Utility of horizontal and vertical sections of scalp biopsies in various forms of primary alopecias. *J Lab Physicians*. 2018;10(1):95-100. doi:10.4103/JLP.JLP_4_17

Lee HE, Kim SJ, Im M, et al. Congenital lipedematous alopecia: adding to the differential diagnosis of congenital alopecia. *Ann Dermatol*. 2015;27(1):87-89. doi:10.5021/ad.2015.27.1.87

Peter CV, Jennifer A, Raychaudhury T, Chandrashekhar L, Merilyn S, Gowda S, Shyam G. Lipedematous scalp. *Indian J Dermatol Venereol Leprol.* 2014 May-Jun;80(3):270-2. doi: 10.4103/0378-6323.132266. PMID: 24823416.

Yaşar S, Mansur AT, Göktay F, Sungurlu F, Vardar Aker F, Ozkara S. Lipedematous scalp and lipedematous alopecia: report of three cases in white adults. *J Dermatol.* 2007 Feb;34(2):124-30. doi: 10.1111/j.1346-8138.2006.00231.x. PMID: 17239151.

Yip L, Mason G, Pohl M, Sinclair R. Successful surgical management of lipoedematous alopecia. *Australas J Dermatol.* 2008 Feb;49(1):52-4. doi: 10.1111/j.1440-0960.2007.00427.x. PMID: 18186851.

Chicago Dermatological Society **Case 10**

[1]Mathew Joseph, MD, [2]Dariusz Borys, MD, [1]Mariam Mafee, MD
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 68-year-old man presented with a mass on the posterior scalp. The patient believed the mass had been present for seven years but was a poor historian. His daughter and wife brought him in for evaluation due to increased bleeding and malodor in the past week. They report the mass had grown significantly in the past 6 months. The patient denied pain, tenderness, or numbness. He denied any recent weight loss or loss of appetite.

PAST MEDICAL HISTORY

Polysubstance (alcohol, cocaine, heroin) abuse complicated by withdrawal episodes, uncomplicated falls, anemia, and protein-calorie malnutrition for past 15+ years

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

He drinks 6-10 12-oz. beers daily, occasionally uses cocaine and heroin, and denies tobacco use. He is cared for by his wife and daughter.

PHYSICAL EXAMINATION

The patient was well-appearing, alert, and oriented to time, date, location, and purpose. On the vertex scalp there was a 13 x 12 x 9 cm exophytic, multilobulated, firm mass with areas of ulceration and active bleeding. The base was soft and mobile. No occipital, cervical, or supraclavicular lymphadenopathy was appreciated.

IMAGING

CT head with and without contrast was notable for a heterogeneously enhancing pedunculated mass left of midline vertex with solid and lipomatous components with punctate foci of calcification. The maximum dimension was 13 cm. There was no apparent osseous invasion or hyperostosis. There was no evidence of hemorrhage or extra-axial fluid collection. Comparative imaging from a head CT without contrast from 18 months prior show the maximum dimension at 5 cm at that time.

DERMATOPATHOLOGY

Histologic sections from punch biopsy showed a biphasic tumor composed of groups of poorly differentiated epithelioid cells with squamous cell features and prominent pleomorphism positive for AE1/AE3, CK 5/6, P40 and P63, and a second component of spindle cells with liposarcoma-like and pleomorphic sarcoma-like areas, positive for CK 5/6 and vimentin and negative for P40 and P63. Other immunohistochemical stains were negative including CD34, ALK1, S100, CD30, CD68, desmin, and SMA. Ki67 mitotic index was 20%.

ADDITIONAL STUDIES
No relevant studies

DIAGNOSIS
Primary cutaneous carcinosarcoma

TREATMENT AND COURSE
The patient underwent wide local excision of the mass by ENT with a 1.5 cm margin down to periosteum and a dermal matrix skin graft was applied. The wound was complicated by Pseudomonas aeruginosa infection five days post graft placement, which resolved with IV and PO antibiotics. Negative margins were confirmed. A second dermal skin graft matrix was applied without complication. The patient suffered no further complications, and no evidence of recurrence was noted at his last visit three months post-operatively. Further reconstruction was deferred.

DISCUSSION
Primary cutaneous carcinosarcoma (PCC) is a rare biphasic neoplasm consisting of both malignant epithelial and mesenchymal components. Carcinosarcoma is most common in the reproductive and gastrointestinal tracts, lung, breast, and thyroid but is uncommon as a primary neoplasm of the epidermis. PCC is more common in men and typically presents in the eighth to ninth decades. Patients often have a history of extensive sun or occupational radiation exposure, and the tumor favors sun-exposed regions, most often on the face and scalp.

Clinically, PCCs are typically exophytic, with frequent surface ulceration which easily bleeds with trauma. Patients often present with long-standing lesions that have undergone rapid growth preceding presentation. In this patient, the lesion grew significantly in the preceding 6 months. Frequently, PCC is clinically diagnosed as squamous cell carcinoma due to the morphologic similarity between these tumors. Histopathologically, PCC shows an epithelial component admixed with a sarcomatous component. The epithelial component is typically a basal or squamous cell carcinoma but may also consist of adnexal tumors such as porocarcinoma, proliferating trichilemmal cystic carcinoma and spiradenocarcinoma. The mesenchymal component of PCC often contains undifferentiated spindle cells with pleomorphic nuclei and cytoplasm, necrosis, and increased mitotic figures. Immunohistochemistry is useful in diagnosis. Staining for p63 can highlight cells of epithelial origin, while vimentin, desmin, or alpha-smooth muscle actin can highlight cells of mesenchymal origin.

Ultraviolet-induced p53 mutations are implicated in tumor formation for both epithelial and mesenchymal components. PCC is thought to arise from a single clonal origin that differentiate into distinct epithelial and mesenchymal components. Surgical excision via wide local excision or Mohs micrographic surgery is the most common treatment modality though radiation therapy has been employed. The survival rate of PCC is better than visceral carcinosarcomas, partly due to earlier diagnosis of visible lesions. Adnexal and squamous carcinosarcomas have poorer survival outcomes than basal carcinosarcoma. After treatment, PCC has a 70% 5-year disease-free survival rate, while visceral PCC has a 25% 5-year disease-free survival rate and is more common in younger patients. Local recurrence, lymphatic spread, and metastasis leading to death from PCC has been reported. Due to limited reports and likely underdiagnosis of PCC, long-term prognostic data remains unclear.

REFERENCES

Chung HJ, Wolpowitz D, Scott G, Gilmore E, Bhawan J. Squamous cell carcinoma with osteoclast-like giant cells: a morphologically heterologous group including carcinosarcoma and squamous cell carcinoma with stromal changes. *Journal of cutaneous pathology*. 2016 Feb;43(2):148-57.

Clark JJ, Bowen AR, Bowen GM, Hyngstrom JR, Hadley ML, Duffy K, Florell SR, Wada DA. Cutaneous carcinosarcoma: a series of six cases and a review of the literature. *Journal of cutaneous pathology*. 2017 Jan;44(1):34-44.

El Harroudi T, Ech-Charif S, Amrani M, et al. Primary carcinosarcoma of the skin. *J Hand Microsurg*. 2010;2:79-81.

García-Souto F, Pereyra-Rodriguez JJ, Cabrera-Perez R, Durán-Romero AJ, Escudero-Ordoñez J, Conejo-Mir J. Primary cutaneous carcinosarcoma: clinical, histological, and immunohistochemical analysis of eight cases. *International Journal of Dermatology*. 2021 Jan;60(1):93-8.

Hong SH, Hong SJ, Lee Y, et al. Primary cutaneous carcinosarcoma of the shoulder: case report with literature review. *Dermatol Surg*. 2013;39:338-340.

Lim Y, Byun HJ, Park CS, Lee JH, Park JH, Lee JH, Lee DY. Primary cutaneous carcinosarcoma developing after chronic C-arm radiation exposure. *JAAD case reports*. 2018 Mar;4(2):126.

Paniz Mondolfi AE, Jour G, Johnson M, et al. Primary cutaneous carcinosarcoma: insights into its clonal origin and mutational pattern expression analysis through next-generation sequencing. *Hum Pathol*. 2013;44:2853-2860

Patel NK, McKee PH, Smith NP. Primary metaplastic carcinoma (carcinosarcoma) of the skin: a clinicopathologic study of four cases and review of the literature. *Am J Dermatopathol*. 1997;19:363-372.

Syme-Grant J, Syme-Grant NJ, Motta L, et al. Are primary cutaneous carcinosarcomas underdiagnosed? five cases and a review of the literature. *J Plast Reconstr Aesthet Surg*. 2006;59:1402-1408.

Tran TA, Muller S, Chaudahri PJ, et al. Cutaneous carcinosarcoma: adnexal vs. epidermal types define high- and low-risk tumors. results of a meta-analysis. *J Cutan Pathol*. 2005;32:2-11.

Upjohn E, Braue A, Ryan A. Primary cutaneous carcinosarcoma: dermoscopic and immunohistochemical features. *Australasian journal of dermatology*. 2010 Feb;51(1):26-8.