PROTOCOL BOOK • SEPTEMBER 11, 2024

CHICAGO DERMATOLOGICAL SOCIETY

Monthly Meeting

Co-hosted by Loyola University Department of Dermatology

Chicago Dermatological Society

PROTOCOL BOOK
September 11, 2024

Co-hosted by
Loyola University Department of Dermatology

Guest Speaker: **Michelle Min, MD**
Director of Rheumatologic Dermatology at the
University of California Irvine School of Medicine

Chicago Dermatological Society
Serving dermatologists since 1901

INVITED GUEST LECTURER

Michelle Min, MD

Dr. Min is the Director of Rheumatologic Dermatology at the University of California Irvine School of Medicine. Prior to her career in medicine, she double majored in biochemistry and biology with a minor in history at the University of Pennsylvania. She graduated as a Vagelos Life and Molecular Life Sciences Scholar, researching with a Howard Hughes Medical Institution Investigator, with whom she earned her master's degree in chemistry. She then went on to complete her medical degree at Boston University School of Medicine. She completed her dermatology residency at the Icahn School of Medicine at Mount Sinai in New York as a chief resident. Ultimately, she pursued a fellowship in dermatology-rheumatology at the Brigham and Women's Hospital with the world-renowned expert in dermatomyositis, Dr. Ruth Ann Vleugels.

Dr. Min is currently on the executive board of the Rheum Derm Society and the Orange County Dermatologic Society. She specializes in psoriasis, lupus, systemic sclerosis, morphea, Raynaud's disease, and dermatomyositis. She has been invited to speak at several national and international conferences, recently with the distinctions of Emerging Thought Leader and Rising Derm Star.

Chicago Dermatological Society
Serving dermatologists since 1901

PROGRAM

Co-hosted by
Loyola University Department of Dermatology

September 11, 2024
Donald E. Stephens Convention & Conference Center

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors**
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** *Slide viewing/posters – ongoing through the early morning*
9:00 a.m.	**Welcome and Opening Comments** *Claudia Hernandez, MD - CDS President*
9:00 a.m. - 10:00 a.m.	**Morning Lecture: JAK-Inhibitors in Dermatology** *Michelle Min, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:00 p.m.	**Resident Case Presentations & Discussion**
12:00 p.m. - 12:30 p.m.	**Box Lunches & Visit with Exhibitors**
12:30 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**Afternoon Lecture: Cases from Rheum-Derm Clinic: Pearls for the Medical Dermatologist** *Michelle Min, MD*
2:00 p.m.	*Program adjourns*

Loyola University Department of Dermatology

Chicago Dermatological Society Meeting
September 11, 2024

Dermatology Residents

Third Year
Rachit Gupta
Adnan Ahmed
Vik Patel

Second Year
Lauren Watchmaker
Sarah Benton
Robin Wang

First Year
Megana Rao
Marisa Luck
Farinoosh Dadrass
Kathryn Franke

TABLE OF CONTENTS

Resident Case Presentations & Discussion

Chicago Dermatologic Society **Case #1**

[1]Viki Patel, [1]Kyle Bhatia, [2]Jodi Speiser, [3]Timothy Durso, [3]David Eilers
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center
[3]Section of Dermatology, Edward Hines Jr. VA Hospital

HISTORY OF PRESENT ILLNESS

A 68-year-old male presented to our Hines VA dermatology clinic for bilateral symmetric growths on his feet for over 20 years.

He reported his main goal was to wear normal shoes as the growths were severely impacting his quality of life. The patient's past medical history was notable for Graves hyperthyroidism and Graves ophthalmopathy. Various treatments for his eye disease including prednisone, tocilizumab, and teprotumumab, an insulin-like growth factor I receptor (IGF-IR) inhibitor for proptosis, had no effects on his lower leg and feet. He denied any notable family history. Other than difficulty wearing shoes, he denied any symptoms.

PAST MEDICAL HISTORY

Graves hyperthyroidism s/p radioiodine therapy
Graves ophthalmopathy

MEDICATIONS

Glipizide, Levetiracetam, Levothyroxine, Sertraline, Tamsulosin

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

No alcohol, smoking, or illicit drug use.

PHYSICAL EXAMINATION

The patient presented with numerous firm, polypoid and verrucous papules and nodules coalescing into large plaques on his bilateral dorsomedial feet. He had similar, focal findings on his bilateral ankles with firm induration of bilateral lower extremities.

DERMATOPATHOLOGY

Histologic sections from a shave biopsy and palliative debridement/excision demonstrated dermis expanded by myxoid material. The dermis was largely paucicellular with small, fibroblast-like cells embedded within myxoid areas. Alcian blue pH 2.50 and Colloidal iron stains highlight the myxoid/mucinous material. These findings are compatible with myxedema.

ADDITIONAL STUDIES

None

DIAGNOSIS

Elephantiasic pretibial myxedema

TREATMENT AND COURSE

The patient was initially treated with localized intralesional triamcinolone followed by an area of palliative debridement. The plan is to target areas of growth in a sequential manner to lessen the wound healing surface area and to maximize cosmetic and functional outcomes.

DISCUSSION

Pretibial myxedema (PTM), also known as thyroid dermopathy, is a known manifestation of Graves' disease and is the second most common extrathyroidal manifestation after exophthalmos. Typically, it is characterized by bilateral, nonpitting, scaly thickening and induration of the skin that most commonly occurs on the shins and dorsal feet. Pathophysiology is not fully understood, though it is likely multifactorial in nature. The most commonly proposed mechanism states that TSH receptor antibodies in the serum of patients with PTM act directly on skin fibroblasts by stimulating the synthesis of glycosaminglycans (GAGs), which are major constituents of mucin. Patients have very high serum concentration of TSH receptor antibodies and overexpressed TSH receptors on fibroblasts induced by certain cytokines or local factors such as interleukin-6 (IL-6) in pretibial tissues. Recent studies have also proposed that insulin-like growth factor-1 (IGF-1) receptor on fibroblasts interacts with Graves' disease immunoglobulins to cause upregulation of T-cell chemoattractants and activation of fibroblasts. Infiltrated thyroid-specific T-cells also release cytokines, including IL-1α and TGF-β, stimulating the synthesis of GAGs by fibroblasts.

The incidence of pretibial myxedema has been reported to be between 0.5% to 4.3% of patients with hyperthyroidism. Though the most common manifestation is the classic form as described above, it is important to mention rarer manifestations including plaque, nodular, and elephantiasic forms. Of note, the elephantiasic form, as seen in our patient, is the rarest manifestation and occurs in less than 1% of patients with PTM. This form is characterized by formation of fleshy, verrucous plaques and nodules, thickening of the skin, and induration. Most cases that have been described in the literature involve just the shins or the shins and feet, however, our patient demonstrates an interesting and unique presentation involving mainly the dorsomedial feet and toes while largely sparing the pretibial region. Unfortunately, few effective therapies are described for elephantiasic PTM. Reported therapies with variable success include intralesional corticosteroids, radioactive iodine, thyroidectomy, intralesional hyaluronidase, Rituximab, Teprotumumb, plasmapheresis, and surgical excision. All of these treatments also take several months to years to see improvement.

For our patient, intralesional triamcinolone was tried without success. Our patient had also received prednisone and Teprotumumab for Graves' ophthalmopathy without improvement in his PTM. There is one case in the literature with a patient that presented with a similar distribution of PTM that was successfully treated with debulking surgery and intralesional triamcinolone. Thus, the decision was made to attempt surgical debridement/excision of a focal area of the large plaques on the left dorsomedial foot after discussion with the patient. The plan is to continue serial debulking procedures until the patient is content. He was also started on Pentoxifylline as it inhibits the proliferation of fibroblasts and production of GAGs. However, given the high recurrence rates noted in elephantiasic forms of PTM, other modalities may be needed in the future. Overall, our case highlights the diagnostic importance of a rare form of PTM and the therapeutic challenges it poses.

REFERENCES

1. Chen CT, Lin JC. Elephantiasic pretibial myxoedema. *Indian J Med Res*. 2013;137(3):568. /pmc/articles/PMC3705669/.
2. Cohen JB, Balzer B, Wapnir I, McDougall IR. Elephantiasic pretibial myxedema. *Thyroid*. 2004;14(3):237-238.
3. Fatourechi V. Pretibial Myxedema. *Am J Clin Dermatology 2005 65*. 2012;6(5):295-309.
4. Ferreira M, Zacaron LH, Valle AF do, Gamonal ACC. Successful therapeutic approach in a patient with elephantiasic pretibial myxedema. *An Bras Dermatol*. 2020;95(4):469.
5. Heyes C, Nolan R, Leahy M, Gebauer K. Treatment-resistant elephantiasic thyroid dermopathy responding to rituximab and plasmapheresis. *Australas J Dermatol*. 2012;53(1):e1-e4.
6. Hoesly PM, Tolaymat LM, Sluzevich JC, Keeling JH. Pretibial myxedema successfully treated with intralesional hyaluronidase. *JAAD case reports*. 2018;4(9):874-876.
7. Lee JH, Park SM, Lew BL, Sim WY. Pretibial Myxedema Presenting as Severe Elephantiasis. *Ann Dermatol*. 2018;30(5):592.
8. Mervis JS, Maeng MM, Kirsner RS, Wester ST. Teprotumumab as a novel treatment for pretibial myxoedema. *Br J Dermatol*. 2022;187(5):795-797.
9. Patel S, Choi D, Christianakis S, Wysong A, Crew A. Treatment of Elephantiasic Pretibial Myxedema With Rituximab Therapy. *Cutis*. 2022;109(2):E16-E18.
10. Yu H, Jiang X, Pan M, Huang R. Elephantiasic pretibial myxedema in a patient with graves disease that resolved after 131I treatment. *Clin Nucl Med*. 2014;39(8):758-759.

Chicago Dermatologic Society **Case #2**

[1]Adnan Ahmed, [1]Jenna Lullo, [2]Jodi Speiser, [1]Sacharitha Bowers
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 53-year-old man presented as a transfer from an outside facility with acute liver failure and a rash on the lower extremity. The patient reported developing blisters on his left lower extremity 5 days prior to admission. Shortly thereafter, he noted them appearing on his right lower extremity as well. Associated with these blisters was exquisite tenderness. He also reported diffuse pruritus. He had been started by his primary care physician on a new medication a few weeks prior but could not recall which medication or its purpose. He endorsed intranasal heroin use a few days prior to the rash appearing as well. He denied any fevers or chills.

PAST MEDICAL HISTORY

No pertinent past medical history

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Patient reported occasional alcohol use and consistent intranasal heroin use.

PHYSICAL EXAMINATION

The patient was overall well-appearing. On the bilateral thighs and knees (left>right), a large retiform plaque with focal areas of vesiculation surrounded by peripheral erythema was present. The abdomen and buttocks had numerous linear excoriations. The third and fourth digits of the left hand were cyanotic.

DERMATOPATHOLOGY

Histologic section from initial punch biopsy showed vaso-occlusive fibrin deposition with vessel necrosis. There was also superficial and deep leukocytoclastic vasculitis. Tissue culture for bacteria and fungi were significant for moderate growth of normal skin flora.

ADDITIONAL STUDIES

- A complete metabolic panel was significant for an elevated creatinine of 7.01 (0.6-1.4 MG/DL), ALT of 1,042 (10-40 U/L), and AST of 280 (15-45 U/L). Patient white blood cell count was normal. ANA was positive at 1:40. Patient's cryoglobulin screen, ANCA screen, aldolase and ENA screen was negative.
- Imaging workup, including CT abdomen and pelvis, MRI brain and echocardiogram, were unremarkable. His lower extremity ultrasound from the outside hospital did show deep vein thromboses on the left.

- Initial urine drug screen was negative. A second, extended panel was positive for xylazine and its metabolite 4-hydroxy-xylazine.

DIAGNOSIS
Primary vasculopathy secondary to xylazine use

TREATMENT AND COURSE
Our patient was started on triamcinolone 0.1% ointment to the inflamed areas, as well as local wound care with petroleum jelly and nonstick dressings. Over the following few days, he improved with local wound care and stabilization of his lab work. He required multidisciplinary care from the intensive care, hepatology and vascular services.

At outpatient follow up, he had not been receiving appropriate wound care and there was concern for secondary infection and necrosis of his third and fourth digits. We prescribed oral antibiotics and instructed the patient to go to the emergency department, but he declined. He was subsequently lost to follow-up.

DISCUSSION
Xylazine, also known by its street name as ‘tranq,’ is an alpha-2 adrenergic receptor agonist commonly used as a veterinary muscle relaxant or sedative. It is a non-opioid medication and works by blocking norepinephrine release which can result in many side effects in humans. It is emerging as a common adulterant in many drugs such as heroin, ketamine and fentanyl. Xylazine is often added to increase the total amount of drug or to further mimic its effects.

As xylazine and other adulterants, such as levamisole, become more commonplace it remains important to recognize their cutaneous and systemic effects. Physicians should be on high alert of its use when faced with naloxone-resistant respiratory depression. Other symptoms include CNS depression, hypotension, hyperglycemia and miosis. Its cutaneous effects are primarily ulcerative in nature and can occur at sites proximal or distant from injection. However, the most common site is the lower extremities. Secondary infections and abscesses are also common.

The mechanism behind xylazine’s effects on the skin is thought to be due to its vasoconstrictive effects on local blood vessels. It is thought that the peripheral alpha-induced constriction with trauma from injection can lead to tissue ischemia and necrosis. The analgesia caused by alpha-2 adrenergic agonism also leads to worsening ulceration. Biopsies will typically show fibrin deposition in the superficial blood vessels; however, this is not always the case. For our patient, we posture that the initial vaso-occlusive insult caused his leukocytoclastic vasculitis. We also believe that cyanosis of his fingertips to be a result of this process.

Diagnosis is made by urine drug screen; typically, an extended panel needs to be ordered. Additional work up is similar to that of vascular occlusion and vasculitis. Care for xylazine-induced skin necrosis and its associated symptoms is mostly supportive. Currently, there is no antidote available. Current recommendations involve using petrolatum ointment-based gauze or xeroform gauze. Given that it is a non-opioid sedative, treating its depressive side effects is particularly challenging. Patients will likely need and benefit from multidisciplinary care from various services such as renal, hepatology, and vascular surgery. Our patient’s case also highlights the important of involving social work early in care to ensure follow up appointments are made, and that home health nursing and transportation are arranged. Additionally, addiction medicine is another specialty that is key to care.

Our case depicts the need to maintain a broad differential diagnosis when approaching a patient with new onset retiform purpura and ulcerations. Xylazine skin findings can easily mimic calciphylaxis, cellulitis, pyoderma gangrenosum, vasculitis or vaso-occlusive processes from other etiologies, and deep infections. Literature on xylazine is limited but growing. With the rise in contaminants in various drugs, dermatologists should remain vigilant about their effects on the skin.

REFERENCES

1. Bishnoi A, Singh V, Khanna U, Vinay K. Skin ulcerations caused by xylazine: A lesser-known entity. *J Am Acad Dermatol*. 2023;89(2):e99-e102. doi:10.1016/j.jaad.2023.04.009
2. Carroll JJ. Xylazine-Associated Wounds and Related Health Concerns Among People Who Use Drugs: Reports From Front-Line Health Workers in 7 US States. *Subst Use Addctn J*. 2024;45(2):222-231. doi:10.1177/29767342231214472
3. Edinoff AN, Sall S, Upshaw WC, et al. Xylazine: A Drug Adulterant of Clinical Concern. *Curr Pain Headache Rep*. 2024;28(5):417-426. doi:10.1007/s11916-024-01211-z
4. Kariisa M, O'Donnell J, Kumar S, Mattson CL, Goldberger BA. Illicitly Manufactured Fentanyl-Involved Overdose Deaths with Detected Xylazine - United States, January 2019-June 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(26):721-727. Published 2023 Jun 30. doi:10.15585/mmwr.mm7226a4
5. Malayala SV, Papudesi BN, Bobb R, Wimbush A. Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Philadelphia, Pennsylvania, USA. *Cureus*. 2022;14(8):e28160. Published 2022 Aug 19. doi:10.7759/cureus.28160
6. Oscherwitz ME, Trinidad J, Chen ST. Necrotic skin ulcerations caused by xylazine in people who inject intravenous drugs. *J Eur Acad Dermatol Venereol*. 2024;38(6):e551-e553. doi:10.1111/jdv.19817
7. Pergolizzi J Jr, LeQuang JAK, Magnusson P, Miller TL, Breve F, Varrassi G. The New Stealth Drug on the Street: A Narrative Review of Xylazine as a Street Drug. *Cureus*. 2023;15(6):e40983. Published 2023 Jun 26. doi:10.7759/cureus.40983
8. Rose L, Kirven R, Tyler K, Chung C, Korman AM. Xylazine-induced acute skin necrosis in two patients who inject fentanyl. *JAAD Case Rep*. 2023;36:113-115. Published 2023 Apr 26. doi:10.1016/j.jdcr.2023.04.010
9. Ruiz-Colón K, Chavez-Arias C, Díaz-Alcalá JE, Martínez MA. Xylazine intoxication in humans and its importance as an emerging adulterant in abused drugs: A comprehensive review of the literature. *Forensic Sci Int*. 2014;240:1-8. doi:10.1016/j.forsciint.2014.03.015
10. Warp PV, Hauschild M, Tookes HE, Ciraldo K, Serota DP, Cruz I. A Confirmed Case of Xylazine-Induced Skin Ulcers in a Person Who Injects Drugs in Miami, Florida, USA. Preprint. *Res Sq*. 2023;rs.3.rs-3194876. Published 2023 Jul 26. doi:10.21203/rs.3.rs-3194876/v1

Chicago Dermatologic Society **Case #3**

[1]Rachit Gupta, [1]Jenna Lullo
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 76-year-old male with past medical history significant for type 2 diabetes mellitus and ongoing stage IV relapsed diffuse large B-cell lymphoma (DLBCL) was admitted for a new, diffuse cutaneous eruption of unclear etiology of one week duration. The eruption started on the abdomen before quickly generalizing, and was described by the patient as exquisitely pruritic.

Associated symptoms included a sore throat, conjunctival injection, productive cough with green-tinged sputum, and possible weight loss of almost ten pounds.

A short course of methylprednisolone attempted by Hematology/Oncology was felt to worsen his eruption. A trial of diphenhydramine was also unsuccessful at ameliorating his symptoms.

The patient denied any recent sick contacts or recent illnesses. He started allopurinol approximately 1 month prior to rash onset and stopped 4 days prior to presentation. He received his first infusion of Pola-BR approximately 2 weeks prior to symptom onset, which was co-administered with lorazepam, acetaminophen, albuterol, dexamethasone, diphenhydramine, famotidine, hydrocortisone sodium succinate (injection), ondansetron, meperidine, and pegfilgrastim.

The patient's DLBCL had relapsed despite multiple therapies, outlined below:

1. 6 cycles of R-CHOP *(rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone)*, complicated by tumor lysis syndrome.
2. 3 cycles of RICE *(rituximab, ifosfamide, carboplatin, and etoposide)*.
3. Chimeric antigen receptor T-cell (CART) therapy *(utilizing axicabtagene ciloleucel)*. Induction therapy prior to receiving CART therapy consisted of fludarabine and cyclophosphamide. After CART treatment, a one-time dose of dexamethasone and tocilizumab was administered due to concern for cytokine release syndrome.
4. 1 cycle of Pola-BR *(polatuzumab vedotin, bendamustine, and rituximab)*. Cycle 2 was held in light of his diffuse cutaneous eruption.

Initial biopsies and clinical presentation were felt to be consistent with a severe morbilliform drug reaction to allopurinol. However, despite discontinuation of the likely culprit and use of clobetasol 0.05% ointment wet wraps, the patient's eruption did not improve.

PAST MEDICAL HISTORY

Blastomyces infection
Chemotherapy-induced pancytopenia
Diffuse large B cell lymphoma
Glaucoma
Hyperlipidemia
Hypertension
Osteoarthritis
Prostate cancer, in remission
Type 2 diabetes mellitus

MEDICATIONS
Acyclovir, Apixaban, Atorvastatin, Dapagliflozin, Insulin detemir, Insulin lispro, Metformin, Prednisone, Multivitamin, Ondansetron, Pantoprazole, Semaglutide, Sulfamethoxazole-trimethoprim, Tamsulosin

ALLERGIES
Allopurinol

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
This patient spoke Spanish only, so a certified Spanish interpreter was used for all communication with the patient and his family.

PHYSICAL EXAMINATION
The patient was erythrodermic, with many areas of overlying scale. There were a few erosions on the superior aspect of the chest. His legs also demonstrated erythematous annular and arcuate crusted and scaly plaques. There was no involvement of the mucosal membranes.

DERMATOPATHOLOGY
Due to limited improvement with therapies, multiple punch biopsies were completed over a several month period. All three biopsies demonstrated marked interface dermatitis with dyskeratotic keratinocytes and prominent dermal eosinophils, concerning for a robust drug reaction vs. a viral reaction. However, these were re-reviewed given decreasing clinical suspicion of a drug reaction, and also demonstrated marked follicular involvement concerning for graft versus host disease.

A punch biopsy obtained for aerobic/anaerobic culture, AFB culture, fungal smear and culture did not demonstrate any abnormalities.

ADDITIONAL STUDIES
- Lab workup was negative for EBV, measles, ANA, syphilis, HIV 1/2, HSV 1/2, Rickettsia panel, cryptococcal antigen, galactomannan antigen, beta-d-glucan, strongyloides, Histoplasma, Blastomyces
- Lab workup was positive for CMV (>200 IU/ml) and elevated B12 (1198).

DIAGNOSIS
Favored graft-versus-host disease, due to autologous CAR T-cell therapy

TREATMENT AND COURSE
The patient was started on systemic corticosteroids to treat presumed graft-versus-host disease (GVHD). His initial dose was approximately 1.2 mg/kg of oral prednisone, which was tapered over a five-week period. He was also continued on clobetasol 0.05% ointment twice daily to the affected areas on the trunk and extremities.

Within 2 weeks of starting systemic corticosteroids, the patient's symptoms and clinical examination markedly improved. His symptoms started to flare again after the prednisone taper was complete, so he was re-initiated on a slow taper of prednisone, with a starting dose of approximately 0.6 mg/kg.

He continues on prednisone 30 mg daily, and he was recently started on methotrexate 12.5 mg weekly with plan for close follow-up.

DISCUSSION

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in adults, with an incidence of 7.2 cases per 100,000 patients in the United States. Despite the aggressive nature of DLBCL, a majority of patients improve with standard therapy utilizing R-CHOP. However, for patients with relapsed DLBCL, second-line treatment options are often ineffective and prognosis is considered to be poor. Chimeric antigen receptor T-cell (CART) therapy has shown promise for patients with relapsed DLBCL, and is increasingly being used as a second-line therapy. One study found that 55% of patients were alive at 4 years after receiving an autologous CART treatment (axicabtagene ciloleucel or *axi-cel*), compared to approximately 46% of patients alive at 4 years who received other standard therapies for relapsed DBLCL.

Though CART therapies are overall relatively well-tolerated, numerous side effects and toxicities have been described including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, hemophagocytic lymphohistiocytosis, cytopenias, infections, and disseminated intravascular coagulation. While these adverse effects are well-characterized, there is a paucity of literature characterizing the prevalence and presentation of graft-versus-host disease (GVHD) after CART therapy.

GVHD has been described in 10-33% of patients receiving CART therapy, usually in two distinct scenarios: previous allogeneic hematopoietic stem cell transplantation (allo-HSCT) prior to autologous or allogeneic CART therapy, or after undergoing allogeneic CART therapy. Our patient did not receive an HSCT, and all FDA-approved CART therapies for hematologic malignancies, including axi-cel, which our patient received, utilize autologous T-cells. In our literature review, there are no reports of autologous CART therapy being complicated by GVHD. Autologous CART is not expected to result in GVHD due to the therapy being derived from the recipient's own T-cells, theoretically eliminating the risk of autoreactivity.

Despite the lack of reports in the literature, our patient's clinical presentation and histopathology obtained from multiple biopsies in the setting of his treatment history for relapsed DLBCL is convincing for GVHD favored to be from an autologous CART therapy (*axi-cel*). The other major diagnosis that was considered was a robust drug reaction from a component of Pola-BR. However, the patient's cutaneous symptoms continue to persist despite having not received Pola-BR for more than three months, which would be highly unusual for a drug reaction. His other medications such as semaglutide, pantoprazole, apixaban, and atorvastatin have been implicated in drug eruptions, however none of these medications were started or adjusted prior to the onset of his symptoms.

Though GVHD has not yet been reported with autologous CART treatment, it has been described with other types of autologous transplants. It is typically more common with allogeneic HSCTs, but a milder form of GVHD has been well-described as a complication of autologous HSCT. Zenz et al. describe a severe GVHD-like syndrome attributed to the use of alemtuzumab in conditioning before autologous stem cell transplantation (auto-SCT) in patients with CLL. Nakamura et al. completed a pilot study demonstrating that autologous GVHD could result in patients who underwent autologous peripheral blood stem cell transplantation with use of either cyclosporine or tacrolimus. Lee et al. describe and review multiple cases of GVHD after patients with multiple myeloma underwent auto-SCT. This was thought to be due to alteration of immune function from the tumor itself, or from conditioning agents used prior to transplantation which can impair the ability of the thymus to remove autoreactive T-cells.

Though there are no reports in the literature and the risk of GVHD due to autologous CART therapy appears to be much lower than after autologous SCT, our patient's clinical presentation and biopsy findings strongly favor a diagnosis of GVHD due to autologous CART treatment. Systemic corticosteroids have been instrumental in controlling his disease activity, but methotrexate was initiated recently with the goal of reducing his dependence on corticosteroids.

This case is intended to highlight a diagnostic dilemma, and review the risks of developing graft-versus-host disease in patients who have undergone CAR T-cell treatment.

REFERENCES

1. Wang SS. Epidemiology and etiology of diffuse large B-cell lymphoma. *Seminars in Hematology*. 2023;60(5):255-266. doi:10.1053/j.seminhematol.2023.11.004
2. Testa U, Leone G, Pelosi E, Castelli G, Hohaus S. CAR-T Cell Therapy in Large B Cell Lymphoma. *Mediterr J Hematol Infect Dis*. 2023;15(1):e2023066. doi:10.4084/MJHID.2023.066
3. Yescarta for Relapsed or Refractory Large B-Cell Lymphoma - NCI. July 10, 2023. Accessed July 30, 2024. https://www.cancer.gov/news-events/cancer-currents-blog/2023/large-b-cell-lymphoma-axi-cel-zuma-7-trial
4. Santomasso BD, Nastoupil LJ, Adkins S, et al. Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. *JCO*. 2021;39(35):3978-3992. doi:10.1200/JCO.21.01992
5. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023;20(6):359-371. doi:10.1038/s41571-023-00754-1
6. Han H, Wang L, Ding Y, et al. Extracorporeal photopheresis as a promising strategy for the treatment of graft-versus-host disease after CAR T-cell therapy. *Blood Advances*. 2024;8(11):2675-2690. doi:10.1182/bloodadvances.2023012463
7. Moradi V, Omidkhoda A, Ahmadbeigi N. The paths and challenges of “off-the-shelf” CAR-T cell therapy: An overview of clinical trials. *Biomedicine & Pharmacotherapy*. 2023;169:115888. doi:10.1016/j.biopha.2023.115888
8. Sanber K, Savani B, Jain T. Graft- *versus* -host disease risk after chimeric antigen receptor T-cell therapy: the diametric opposition of T cells. *Br J Haematol*. 2021;195(5):660-668. doi:10.1111/bjh.17544
9. Kanfar S, Al-Anazi K. Autologous Graft Versus Host Disease: An Updated Review. 2018;1(1).
10. Zenz T, Ritgen M, Dreger P, et al. Autologous graft-versus-host disease–like syndrome after an alemtuzumab-containing conditioning regimen and autologous stem cell transplantation for chronic lymphocytic leukemia. *Blood*. 2006;108(6):2127-2130. doi:10.1182/blood-2006-04-007898
11. Nakamura H, Nakao T, Ujiie H, et al. Induction of autologous graft-versus-host disease after autologous peripheral blood stem cell transplantation. *Journal of Allergy and Clinical Immunology*. 1999;103(5):S457-S461. doi:10.1016/S0091-6749(99)70162-4
12. Lee SE, Yoon JH, Shin SH, Park G, Min CK. Skin Graft-versus-host Disease Following Autologous Stem Cell Transplantation for Multiple Myeloma. *Immune Network*. 2013;13(3):107. doi:10.4110/in.2013.13.3.107
13. Hess AD. Modulation of Graft-versus-Host Disease: Role of Regulatory T Lymphocytes. *Biology of Blood and Marrow Transplantation*. 2006;12(1):13-21. doi:10.1016/j.bbmt.2005.11.002

Chicago Dermatologic Society **Case #4**

[1]Lauren Watchmaker, [2]Alexandra Kiszluk, [3]Dana Griffin, [4]Madhu Dahiya, [3]David Eilers
[1]Division of Dermatology, Loyola University Medical Center
[2]Stritch School of Medicine, Loyola University Medical Center
[3]Edward Hines Jr Veterans' Affairs Hospital Department of Dermatology
[4]Edward Hines Jr Veterans' Affairs Hospital Department of Pathology

HISTORY OF PRESENT ILLNESS

A 72-year-old male presented for evaluation of a tender left ear lobule. Over the past month, the left ear lobule started to enlarge and became painful. He denied any injuries to the ear.

PAST MEDICAL HISTORY

Hyperlipidemia
Hypertension
Lumbar radiculopathy
Parkinson's disease
Post-traumatic stress disorder
Rosacea (papulopustular and rhinophymatous subtypes)

MEDICATIONS

Furosemide, Hydromorphone, Pramipexole, Prazosin, Rosuvastatin

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

No alcohol, smoking, or illicit drug use

PHYSICAL EXAMINATION

Exam was notable for enlargement of the leg ear lobule compared to the right, rhinophymatous changes to the nose, and a few scattered erythematous papules throughout the face.

DERMATOPATHOLOGY

A punch biopsy of the left ear lobule demonstrated a perivascular dermal inflammatory infiltrate with follicular *Demodex* and sebaceous gland hyperplasia.

ADDITIONAL STUDIES

None

DIAGNOSIS

Otophymatous rosacea

TREATMENT AND COURSE

The patient was started on a three-month course of doxycycline 100 mg twice daily. For the symptomatic otophyma, he was also treated with 0.2 ml of 10 mg/ml intralesional triamcinolone. At his six-week follow-up, he reported significant improvement in size and tenderness of the left ear lobule. He has returned to clinic every 1-2 months for 10 mg/ml intralesional triamcinolone injections which continue to provide symptomatic relief.

DISCUSSION

Rosacea is a chronic inflammatory skin disease that often initially presents as transient or persistent erythema of the face with or without pustules and papules. Phymatous changes, characterized by irregular contours and thickened skin, are a result of longstanding inflammation, with rhinophyma (affecting the nose) being the most frequent type. Blepharophyma, metophyma, gnatophyma, and otophyma (affecting the eyelid, cheek, chin, and ear, respectively) are rare findings. In patients with otophyma, unilateral involvement is slightly less common than bilateral (45% vs 55%). Otophyma has also been associated with other inflammatory conditions such as psoriasis and eczema, as well as congenital lymphedema, cellulitis, frostbite, and trauma. Though our patient's otophyma was confined to the ear lobule, this condition can also affect the cymba and cavum concha, leading to obstruction of the external auditory canal.

Reported effective medical therapies for otophymatous rosacea include intralesional corticosteroids, doxycycline, minocycline, and sulfur ointment. In cases where otophyma causes significant distress to the patient, excisional debulking with electrosurgery is a safe and effective option. Conductive hearing loss may result if left untreated. Patients may present to otolaryngology rather than dermatology when hearing loss is present.

Lymphoproliferative neoplasms may clinically mimic phymatous rosacea. In a study of 12 patients with B-cell neoplasms including primary cutaneous follicular center lymphoma, primary cutaneous marginal zone lymphoma, and cutaneous chronic lymphocytic leukemia, there were delays in diagnosis ranging from 4 months to 10 years after an initial diagnosis of phymatous rosacea. Patient ages ranged from 36 to 81 years, highlighting the importance of considering lymphoproliferative disorders as a diagnostic possibility even in younger patients. Much like how gastric lymphoma is associated with *Helicobacter pylori*, it is possible that *Demodex folliculorum* in rosacea may incite chronic antigenic stimulation that results in cutaneous lymphoma.

In sum, otophyma is a rare manifestation of a common condition encountered in dermatology. This case highlights the utility of intralesional triamcinolone for symptomatic relief of painful otophyma. Importantly, dermatologists should have a low threshold to perform biopsies in treatment-refractory or atypical presentations of rosacea because of malignant entities on the differential diagnosis, particularly cutaneous lymphoproliferative neoplasms.

REFERENCES

1. Alcantara-Reifs CM, Salido-Vallejo R, Garnacho-Saucedo G, Velez Garcia-Nieto A. Otophyma: A rare variant of phymatous rosacea. *Am J Otolayngol*. 2016;37(3):251-254. doi: 10.1016/j.amjoto.2016.01.009
2. Barzilai A, Feuerman H, Quaglino P, David M, Feinmesser M, Halpern M, Feldberg E, Tomasini C, Tabibian-Keissar H, Amarilgio N, Hodak E. Cutaneous B-cell neoplasms mimicking granulomatous rosacea or rhinophyma*. Arch Dermatol.* 2012;148(7):824-831. doi: 10.1001/archdermatol.2011.3575
3. Carlson JA, Mazza J, Kircher K, Tran TA. Otophyma: a case report and review of the literature of lymphedema (elephantiasis) of the ear. *Am J Dermatopathol*. 2008;30(1):67-72. doi: 10.1097/DAD.0b013e31815cd937
4. Daniels K, Haddow K. Otophyma: a case report. *J Laryngol Otol*. 2008;122(5):524-526. doi: 10.1017/S0022215107008419
5. Hoffmann M, Braun-Falco M. Rhinophyma-like sebaceous carcinoma. *J Eur Acad Dermatol Venereol.* 2009;23(10):1216-1218. doi: 10.1111/j.1468-3083.2009.03127
6. Khan SL, Podjasek JO, Dimitropoulos VA, Brown CW. Excisional debulking and electrosurgery of otophyma and rhinophyma*. Dermatol Surg*. 2016;42(1):137-139. doi: 10.1097/DSS.0000000000000560

7. Lebas E, Collins P, Somja J, Nikkels AF. A comprehensive update of the atypical, rare and mimicking presentations of mycosis fungoides. *Dermatol Ther (Heidelb).* 2021;11(6):1931-1951. doi: 10.1007/s13555-021-00625-6
8. Mitteldorf C, Kempf W. Cutaneous pseudolymphoma. *Surg Pathol Clin*. 2017;10(2):455-476. doi: 10.1016/j.path.2017.01.002
9. Mohanna MT, Kamarashev J, Hofbauer GFL. Borrelial pseudolymphoma of the nose. *BMJ Case Rep.* 2015;2015:bcr2014205688. doi: 10.1136/bcr-2014-205688
10. van Zuuren EJ, Fedorowicz Z, Tan J, van der Linden MMD, Arents BW, Carter B, Charland L. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. Br J Dermatol. 2019;181(1):65-79. doi: 10.1111/bjd.17590

Chicago Dermatologic Society **Case #5**

[1]Sarah Benton, [1]Jenna Lullo, [2]Jodi Speiser, [1]Sacharitha Bowers
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 61-year-old male with biopsy-proven chronic idiopathic urticaria presented to clinic with hypotension, generalized diffuse urticaria, and diffuse bone pain. He endorsed pruritus and a burning sensation of the skin. He was recently seen by hematology/oncology, who diagnosed him with IgM kappa monoclonal gammopathy. He had also been experiencing recurrent fevers, but he was afebrile in clinic.

PAST MEDICAL HISTORY

Benign prostatic hyperplasia
Helicobacter pylori gastric ulcer
Latent syphilis
Osteoporosis

MEDICATIONS

Ibuprofen

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

No pertinent social history

PHYSICAL EXAMINATION

The patient was ill-appearing and unable to sit upright due to pain. There were generalized, diffuse, small, pink wheals on the arms, back, chest, and abdomen.

DERMATOPATHOLOGY

Histologic sections from a punch biopsy obtained during an admission one month prior to presentation in clinic showed orthokeratosis overlying a relatively unremarkable epidermis. The underlying dermis showed superficial and deep perivascular inflammation consisting of lymphocytes and a superficial interstitial inflammation consisting of neutrophils. There were rare eosinophils.

ADDITIONAL STUDIES

- Vitals revealed a blood pressure of 91/53 mmHg and a temperature of 98.2° F.
- Labs obtained by rheumatology a few days prior to dermatology office visit demonstrated an elevated erythrocyte sedimentation rate (ESR) at 109 (0-25 mm/hour)
- Labs obtained by hematology/oncology the week prior to presentation demonstrated elevated IgM at 1,613 (45-281 mg/dL), decreased complement C4 at 14 (16-38 mg/dL), and elevated free kappa light chain at 2.64 (0.33-1.94 mg/dL). Serum immunofixation demonstrated a significant peak of IgM kappa monoclonal protein observed in the

anodal gamma region and a small peak of IgG kappa monoclonal protein observed in the mid gamma region. Random urine immunofixation showed a small IgM kappa monoclonal protein restriction in the gamma region.
- Bone marrow biopsy obtained a month prior to presentation revealed monoclonal gammopathy of undetermined significance, and small monoclonal kappa B-cell population on flow cytometry.
- IgG, IgA, IgE, anti-dsDNA antibody, free lambda light chain, free kappa/lambda ratio, random urine protein, random urine protein electrophoresis, and complement C3 were unremarkable.

DIAGNOSIS
Schnitzler syndrome

TREATMENT AND COURSE
The patient was diagnosed with Schnitzler syndrome based on the Lipsker criteria: urticarial skin rash, monoclonal IgM component, arthralgia, bone pain, and elevated ESR and CRP. He was admitted directly to the hospital from clinic for an inflammatory crisis with hypotension and severe pain, with plan to initiate anti-IL-1 medication (anakinra). After negative infectious workup, screening for tuberculosis, and repeat RPR testing, the patient was started on anakinra 100 milligrams subcutaneous daily with dramatic improvement in symptoms within 24 hours. At his two-week outpatient hospital follow-up, the patient continued to have marked improvement of urticaria, arthralgias, and bone pain, despite some residual shoulder and hip pain. He was also evaluated by rheumatology and oncology, who felt there may be an additional underlying diagnosis of fibromyalgia.

DISCUSSION
Schnitzler syndrome is a rare acquired autoimmune condition, with fewer than 300 cases reported in literature. It is associated with IgM monoclonal gammopathy, recurrent fevers, urticaria, arthralgias, myalgias, and bone pain, and most commonly presents in men in their sixth decade. Less commonly, it can be associated with IgG monoclonal gammopathy. Pain is more common in the lower extremity than the upper extremity, and arthralgias typically involve the large joints. Less commonly, patients can develop hepatosplenomegaly, lymphadenopathy, and angioedema.

Schnitzler syndrome is driven by aberrant NLRP3-mediated IL-1β production. NLRP3 is an inflammasome that drives inflammation as part of the innate immune system and is a key mediator of the IL-1 cytokine family.

There are two validated sets of criteria for diagnosis of Schnitzler syndrome: the Lipsker criteria (slightly more sensitive), and the Strasbourg criteria. Lipsker criteria requires that the patient have urticaria, monoclonal IgM component, and two of the following: fever, arthralgia or arthritis, bone pain, palpable lymph nodes, liver or spleen enlargement, elevated ESR, leukocytosis, and/or abnormal findings on bone morphologic investigations. For definite diagnosis with Strasbourg criteria, patients must meet two major criteria and either two or three minor criteria for IgM and IgG monoclonal gammopathy, respectively. Major criteria include chronic urticaria and monoclonal IgM or IgG gammopathy; minor criteria include recurrent fever, objective findings of abnormal bone remodeling with or without bone pain, skin biopsy with dermal neutrophilic infiltrate, and leukocytosis with or without elevated CRP.

Though there are no FDA-approved treatments for Schnitzler syndrome, first line treatment is with the IL-1 receptor antagonist, anakinra, 100 milligrams subcutaneously daily. Other

treatments studied for Schnitzler syndrome include canakinumab, an IL-1b-specific monoclonal antibody; rilonacept, an IL-1 inhibitor; and tocilizumab and sarilumab, IL-6 inhibitors, for refractory cases. Case reports describe successful treatment of Schnitzler syndrome with tofacitinib and colchicine. Treatment with an IL-1 inhibitor decreases inflammation, thereby decreasing risk of AA (secondary) amyloidosis, but does not treat the underlying IgM gammopathy.

Referral to hematology/oncology is important for monitoring for long-term sequelae. Even with treatment, 15-20% of patients will develop a lymphoproliferative disease. The most common complication of Schnitzler syndrome is Waldenström macroglobulinemia. A less common complication of Schnitzler syndrome is AA amyloidosis, caused by increased production of serum amyloid A protein in the liver. Disease prognosis is driven by whether a complication occurs.

REFERENCES

1. Bashir M, Bettendorf B, Hariman R. A Rare but Fascinating Disorder: Case Collection of Patients with Schnitzler Syndrome. *Case Reports in Rheumatology* 2018;2018: 7041576.
2. Bonnekoh H, Erpenbeck L. Neutrophilic dermatoses - Pathomechanistic concepts and therapeutic developments. *Journal der Deutschen Dermatologischen Gesellschaft* 2023;21(4): 374-380.
3. Bonnekoh H, Frischbutter S, Roll S, Maurer M, Krause K. Tocilizumab treatment in patients with Schnitzler syndrome: An open-label study. *The Journal of Allergy and Clinical Immunology: In Practice* 2021;9(6): 2486-2489.e4.
4. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis. *Circulation Research* 2018;122(12): 1722-1740.
5. Gusdorf L, Asli B, Barbarot S, Néel A, Masseau A, Puéchal X, Gottenberg JE, Grateau G, Blanchard-Delaunay C, Rizzi R, Lifermann F, Kyndt X, Aubin F, Bessis D, Boye T, Gayet S, Rongioletti F, Sauleau E, Fermand JP, Lipsker D. Schnitzler syndrome: validation and applicability of diagnostic criteria in real-life patients. *Allergy* 2017;72(2): 177-182.
6. Gusdorf L, Lipsker D. Schnitzler Syndrome: a Review. *Current Rheumatology Reports* 2017;19(8): 46.
7. Gusdorf L, Lipsker D. Schnitzler Syndrome: the paradigm of an acquired adult-onset auto-inflammatory disease. *Italian Journal of Dermatology and Venereology* 2020;155(5): 567-573.
8. Li M, Chen YW, Shen A, Xie YX, Wu Y, Zeng X, Leong PY. Case report: Successful treatment with tofacitinib and colchicine in a patient with Schnitzler syndrome. *International Journal of Rheumatic Diseases* 2023;26(1): 160-163.
9. Matsuda T, Takimoto-Ito R, Lipsker D, Kambe N. Similarities and differences in autoinflammatory diseases with urticarial rash, cryopyrin-associated periodic syndrome and Schnitzler syndrome. *Allergology International* 2023;72(3): 385-393.
10. Takimoto-Ito R, Kambe N, Kogame T, Otsuka A, Nomura T, Izawa K, Tabuchi Y, Yoshifuji H, Takeuchi Y, Kabashima K. Refractory serum immunoglobulin M elevation during anti-interleukin (IL)-1- or IL-6-targeted treatment in four patients with Schnitzler syndrome. *The Journal of Dermatology* 2021;48(11): 1789-1792.
11. Néel A, Henry B, Barbarot S, Masseau A, Perrin F, Bernier C, Kyndt X, Puechal X, Weiller PJ, Decaux O, Ninet J, Hot A, Aouba A, Astudillo L, Berthelot JM, Bonnet F, Brisseau JM, Cador B, Closs-Prophette F, Dejoie T, de Korwin JD, Dhote R, Fior R, Grosbois B, Hachulla E, Hatron PY, Jardel H, Launay D, Lorleac'h A, Pottier P, Moulis G, Serratrice J, Smail A, Hamidou M. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler's syndrome: a French multicenter study. *Autoimmunity Reviews* 2014;13(10): 1035-41.

Chicago Dermatologic Society **Case #6**

[1]Farinoosh Dadrass, [2]Jodi Speiser, [3]Joerg Albrecht, [1]Sacharitha Bowers, [1]Wendy Kim
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology, Loyola University Medical Center
[3]Division of Dermatology, Cook County Health

HISTORY OF PRESENT ILLNESS

A 70-year-old white male with past medical history of a deceased-donor right renal transplant presented to an outside hospital emergency department after receiving a call from his transplant nephrologist noting thrombocytopenia and anemia on bloodwork completed the day prior. He reported a two-week history of a rash, postauricular and submental lymphadenopathy, shortness of breath, fatigue, night sweats, loss of appetite, weight loss, and flank pain starting 48 hours after receiving a COVID-19 booster and RSV vaccine. He was noted to be hypoxic at 89% on room air and a chest x-ray revealed increased interstitial markings concerning for pulmonary edema. He was placed on 2 liters of nasal cannula oxygen and transferred to Loyola University Medical Center for a higher level of care.

Dermatology was consulted for new painful skin lesions in the setting of new thrombocytopenia, worsening anemia, and diffuse lymphadenopathy. The patient reported that his skin lesions had first appeared on his forehead and later spread down his neck and to his chest. He endorsed the continued development of new lesions, some of which were painful. He denied any drainage or prior episodes of these skin lesions.

Of note, the patient self-identified as bisexual and reported anoreceptive intercourse. He denied any known history of gonorrhea, chlamydia, or HIV.

PAST MEDICAL HISTORY

Anemia
Basal cell carcinoma
Deceased-donor right renal transplant
End-stage renal disease (glomerulonephritis vs. minimal change disease)
Gout
Hypertension

MEDICATIONS

Prednisone (5 mg daily), Tacrolimus (4 mg daily)

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

No history of intravenous drug use. Patient identified as bisexual.

PHYSICAL EXAMINATION

The patient was well-appearing with numerous erythematous to violaceous firm papules and thin plaques on the forehead, right cheek, right neck, and upper chest.

DERMATOPATHOLOGY

Histologic sections from a punch biopsy of the right neck were consistent with an atypical vascular dermal proliferation with extravasation of red blood cells. CD31, CD34, D2-40, and HHV8 were positive in the dermal vessels.

ADDITIONAL STUDIES

- A complete blood count demonstrated thrombocytopenia with platelet count at 33 (150 – 400 K/μL) without signs of schistocytes on a blood smear.
- A CD4 count was low at 121 (507 – 1456 CMM).
- HIV quantitative real time PCR was negative. HIV-1 p24 antigen and HIV-1/HIV-2 antibodies were not detected.
- A Karius test demonstrated high levels of Kaposi sarcoma-associated herpesvirus at 9,029 MPM.
- Herpesvirus 8 DNA PCR blood level was elevated at 1,436,589 copies/mL.
- A bone marrow biopsy was obtained with rare cells showing multiple brown dots likely in the nuclei, suggestive of stippled nuclear staining for HHV8. A right inguinal lymph node biopsy demonstrated positive reactivity for CD34 and HHV8.
- Blood cultures, urine cultures, sputum cultures, and bone marrow cultures were unremarkable.

DIAGNOSIS

Iatrogenic (transplant-associated) Kaposi sarcoma (KS)

TREATMENT AND COURSE

The patient's immunosuppression regimen was changed from tacrolimus to sirolimus 1 mg daily, then to sirolimus 2 mg daily per hematology/oncology and transplant nephrology recommendations. His renal failure and thrombocytopenia resolved. His skin lesions were treated with clobetasol ointment twice daily for symptomatic relief.

The patient was admitted to an outside hospital 15 days later for a low-grade fever and fatigue, and was transferred to Loyola University Medical Center for a higher level of care. His labs were significant for pancytopenia and elevated sirolimus levels. Sirolimus dosing was decreased from 2 mg daily to 1 mg daily and then held, which improved symptoms. Sirolimus was restarted at 1 mg daily prior to discharge.

The patient was seen in follow-up one month after discharge. At that time, his immunosuppressive regimen was left unchanged. Treatment options were extensively discussed, and the patient preferred to trial conservative therapies initially. Cryotherapy was performed on two lesions of KS on the neck and two lesions on the shoulders and back. Off-label timolol 0.5% gel was prescribed for 3-5 additional lesions that were not treated with cryotherapy. The patient was counseled to use timolol 0.5% gel twice daily until follow up. At this follow-up appointment six weeks later, the patient reported that the lesions treated with cryotherapy had either significantly improved or resolved. The lesions treated with timolol 0.5% gel twice daily had not changed significantly. A total of 20 lesions were treated with cryotherapy, and topical timolol was discontinued. Six weeks later, some of the additional lesions treated with cryotherapy had completely disappeared and most had lightened in color. The patient did not report any new lesions and 26 lesions were treated with cryotherapy at this visit. His most recent absolute CD4 cell count has improved to 176 approximately two months after his initial admission. His most recent Herpesvirus 8 DNA PCR blood level had significantly improved to <1000 copies/mL four months after his admission.

DISCUSSION

Kaposi sarcoma (KS) is a rare malignancy associated with infection of B-cells, oral epithelial cells, and “spindle cells” (arising from endothelial cells) by Human Herpesvirus-8 (HHV8). There are four subtypes of KS which include classic, endemic, iatrogenic (i.e.transplant-associated), and AIDS-related. The prevalence of HHV8 in the United States is <5% which is relatively low compared to the >50% prevalence seen in East and Central Africa. Transplant-associated KS is even more rare, with an incidence of 68.6 per 100,000 person-years. The risk of KS is highest 0-2 years post-transplantation, with a decrease in risk following this timeframe. Notably, there is weak evidence to suggest the risk of HHV8 seropositivity may be higher in men who have sex with men.

Our patient developed KS four years after his renal transplant. He was not previously tested for HHV8, making it unclear when he was first infected with HHV8. HIV antigen, antibody, and PCR studies were all negative with a low CD4 count, suggesting his case of KS was iatrogenic secondary to post-transplantation immunosuppression in the context of HHV8 seropositivity. Initially, there was also concern for thrombotic thrombocytopenic purpura secondary to a recent COVID vaccine. Extensive infectious and hematologic workup revealed only a positive qualitative EBV PCR, but a quantitative PCR was undetectable. All other infectious and hematologic workup was negative. Pathology was significant for lymph node and bone marrow involvement of HHV8. The bone marrow biopsy did not show evidence of myelodysplastic syndrome, post-transplant lymphoproliferative disorder, or features of KS. This indicated his systemic symptoms were likely secondary to advanced post-transplantation KS (PT-KS). When the patient was re-admitted 2 weeks later, there was concern for KS-associated immune reconstitution syndrome (KS-IRIS) given the high IL-6 level. Treatment with ganciclovir was considered but deferred due to its nephrotoxicity.

Cases of advanced PT-KS have been known to cause thrombocytopenia and anemia, which improved in our patient after switching to sirolimus. Sirolimus targets KS by demonstrating an anti-tumor mechanism of action through VEGF signaling in addition to the decreased level of immunosuppression it provides. In our patient, this modification in his immunosuppressive regimen contributed to the decrease in his HHV8 serology and the improvement of his cutaneous manifestations.

He noticed significant improvement and resolution of some lesions with cryotherapy, but not with topical timolol. Other treatment options for KS include other topicals (e.g. imiquimod, alitretinoin), surgical excision, intralesional chemotherapy, systemic chemotherapy, or radiotherapy. One case of transplant-associated penile KS was successfully treated with paclitaxel in addition to sirolimus and prednisone. There has also been some evidence for treatment with doxorubicin for pulmonary involvement of KS and pomalidomide in HIV-positive and HIV-negative patients. A different case of PT-KS was treated with imatinib which resulted in grade 4 granulocytopenia, prompting imatinib to be discontinued and treatment transitioned to sirolimus. Antivirals are not currently first-line in treatment of PT-KS, though one case of PT-KS did demonstrate improvement with foscarnet.

We recommend having a high index of suspicion for KS in patients after their transplant with routine dermatology follow-up. Screening of HHV8 before transplant may help stratify which patients should be empirically started on sirolimus as part of their immunosuppressive regimen. Additional studies demonstrating improvement of lesions with sirolimus and cryotherapy may prompt the consideration of inpatient cryotherapy before discharge.

REFERENCES

1. Addula D, Das CJ, Kundra V. Imaging of Kaposi sarcoma. *Abdom Radiol* 2021;46: 5297-5306. Doi: 10.1007/s00261-021-03205-6
2. Anderson M, Ying T, Wyburn K, Ferguson P, Strach M, Grimison P, Chadban S, Gracey D. Transplant-associated penile Kaposi sarcoma managed with single agent paclitaxel chemotherapy: a case report. *BMC Urology* 2021;21(87). doi: 10.1186/s12894-021-00855-y
3. Campistol J, Schena F. Kaposi's sarcoma in renal transplant recipients – the impact of proliferation signal inhibitors. *Nephrology Dialysis Transplantation* 2007;22(Suppl 1): il7-i22. doi: 10.1093/ndt/gfm089
4. Dupin N, Jary A, Boussouar S, Syrykh C, Gandjbakhche A, Bergeret S, Palich R. Current and future tools for diagnosis of Kaposi's sarcoma. *Cancers* 2021;13(5927). doi:10.3390/cance rs13235927
5. El-Agroudy A, El-Baz M, Ismail A, Ali-El-Dein B, Shehab El-Dein A, Ghoneim M. Clinical features and course of Laposi's sarcoma in Egyptian kidney transplant recipients. *American Journal of Transplantation* 2003;3: 1595-1599. doi: 10.1046/j.1600-6135.2003.00276.x
6. Gu L, Lin E, Liu S, Yang N, Kurtansky N, Neumann N, Stoll J, Lezcano C, Pulitzer M, Noor S, Markova A, Rossi A, Dickson M, Deng L. Efficacy of immunotherapy with combination of cryotherapy and topical imiquimod for treatment of Kaposi sarcoma. *Journal of Medical Virology* 2023;95(1): e28396. doi: 10.1002/jmv.28396
7. Ietto G, Gritti M, Pettinato G, Carcano G, Dalla Gasperina D. Tumors after kidney transplantation: a population study. *World Journal of Surgical Oncology* 2023;21(18). doi: 10.1186/s12957-023-02892-3
8. Le J, Gantt S, AST Infectious Diseases Community of Practice. Human herpesvirus 6, 7 and 8 in solid organ transplantation. *American Journal of Transplantation* 2013;13: 128-137. doi: 10.1111/ajt.12106
9. Lebbé C, Legendre C, Francès C. Kaposi sarcoma in transplantation. *Transplantation Reviews* 2008;22: 252-261. doi: 10.1016/j.trre.2008.05.004
10. Luppi M, Barozzi P, Rasini V, Riva G, Re A, Rossi G, Setti G, Sandrini S, Facchetti F, Torelli G. Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. *Transplantation* 2002;74(1): 131-133. doi: 10.1097/00007890-200207150-00023
11. Ramaswami R, Polizzotto M, Lurain K, Wyvill K, Widell A, George J, Goncalves P, Steinberg S, Whitby S, Uldrick T, Yarchoan R. Safety, activity, and long-term outcomes of pomalidomide in the treatment of Kaposi sarcoma among individuals with or without HIV infection. *Clinical Cancer Research* 2022;28(5): 840-850. doi: 10.1158/1078-0432.CCR-21-3364
12. Riva G, Luppi M, Barozzi P, Forghieri F, Potenza L. How I treated HHV8/KSHV-related diseases in posttransplant patients. *Blood* 2012;120(20): 4150-9. doi: 10.1182/blood-2012-04-421412
13. Scheetz S, Pandey D, Pesavento T, Singh P. Pulmonary presentation of Kaposi-sarcoma in a renal transplant recipient. *Cureus* 2020;12(1): e6719. doi: 10.7759/cureus.6719
14. Stallone G, Schena A, Infante B, Di Paolo S, Loverre A, Maggio G, Ranieri E, Gesualdo L, Paolo Schena F, Grandaliano G. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *New England Journal of Medicine* 2005;352(13): 1317-23. doi: 10.1056/NEJMoa042831

Chicago Dermatologic Society **Case #7**

[1]Kathryn Franke, [1]Sacharitha Bowers, [1]Jenna Lullo, [1]Wendy Kim
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 52-year-old male with past medical history significant for pyoderma gangrenosum (PG) presented to the emergency department with 3 days of progressive right upper extremity pain, swelling, and blistering. He was admitted to the surgical ICU for necrotizing fasciitis of the right upper extremity. He was septic, with group A strep bacteremia. He underwent bedside fasciotomy in the emergency department, and he was started on broad-spectrum antibiotics and stress-dose steroids (hydrocortisone 100 mg q8 hours) in the setting of chronic prednisone use. The following day, an excisional debridement of the right upper extremity was completed during which brackish fluid was encountered, which grew group A strep. Stress dose steroids were discontinued on post-operative day (POD) #5, and he was transitioned to his home dose of prednisone 30 mg daily. Plastic surgery and burn surgery were consulted for wound coverage with anticipation of grafting. Dermatology was consulted on POD #13 for peri-operative management of PG.

PAST MEDICAL HISTORY

Hyperlipidemia
Pyoderma gangrenosum

MEDICATIONS

Infliximab (400 mg every 6 weeks), mycophenolate mofetil (1.5 g twice daily), prednisone (30 mg daily)

ALLERGIES

No known drug allergies

FAMILY HISTORY

No history of ulcerative colitis, Crohn's disease, or other autoimmune conditions

SOCIAL HISTORY

Daily alcohol and tobacco use (1-1.5 packs per day). No illicit drug use.

PHYSICAL EXAMINATION

On examination, there was a large post-operative wound on the right upper extremity. Viable muscle was visualized at the base of the wound bed from the right metacarpophalangeal joints to the posterior shoulder. Borders were without significant erythema or duskiness. No pustules or bullae were present along the wound edge. On the right temple and left back, there were large ulcers with violaceous and hyperpigmented rolled borders, thick yellow slough, and scarring.

DERMATOPATHOLOGY

Histologic sections from the initial punch biopsy by an outside provider were consistent with pyoderma gangrenosum.

ADDITIONAL STUDIES

- A basic metabolic panel demonstrated an elevated creatinine 9.39 (0.6-1.4 mg/dL)

DIAGNOSIS
Perioperative management of pyoderma gangrenosum in the setting of necrotizing fasciitis

TREATMENT AND COURSE
On initial evaluation on post-operative day (POD) #13, there was no evidence of pyoderma gangrenosum (PG) at the surgical site. However, the patient was on significantly less immunosuppression during his post-operative course than he was prior to admission. He was septic at that time, with concern from the surgical team regarding wound healing upon grafting. However, given the significant risk of pathergy and evidence of active PG on other locations, we recommended an increase in immunosuppression.

Prednisone was increased to 80 mg daily with plans for a slow taper over 5 weeks to his home dose of 30 mg daily. He also received an inpatient infliximab infusion. Mycophenolate mofetil had to be held in the setting of acute renal failure and sepsis. Active PG lesions were treated with timolol 0.5% solution to the center of the ulcers and triamcinolone 0.1% ointment to the rim of the ulcers. The patient's surgical wounds healed appropriately without development of post-operative PG, and following a 4-week hospitalization, he was discharged to inpatient rehabilitation.

Six weeks later, the patient was re-admitted to the hospital for planned repeat debridement of the right upper extremity with split thickness skin grafting. Dermatology was re-consulted on POD #1, and another slow prednisone taper was initiated with a starting dose of 80 mg daily to his home dose of 30 mg daily. Post-operatively, there was no evidence of PG at the surgical wound or graft donor site.

The patient was seen in dermatology clinic three months later with significant improvement in active PG lesions and no evidence of post-operative PG at his surgical sites. Infliximab infusions were continued every 6 weeks.

DISCUSSION
Pyoderma gangrenosum (PG) is a rare inflammatory neutrophilic dermatosis with several distinct phenotypes. The classic ulcerative form is characterized by rapidly forming cutaneous ulcers demonstrating violaceous, undermined borders. The etiology of PG is incompletely understood, though neutrophil dysfunction is thought to play a key role in disease pathogenesis. Various alterations in the innate and adaptive immune system have been reported in lesional skin, and some authors have posited that an adaptive immune response targeted at the pilosebaceous unit is responsible for the disease state.

A hallmark of PG, present in 25-50% of cases, is pathergy, which describes the phenomenon of minor trauma leading to excessive inflammation and development of new PG lesions. For this reason, patients with PG are thought to be poor surgical candidates, as any surgical intervention has the potential to lead to worsening cutaneous disease.

Clinically, post-operative PG presents as worsening erythema around the suture lines or incision that progresses to multiple small areas of ulceration, wound breakdown, and dehiscence. Gunmetal gray borders and pustules can also be seen, and patients often have pain out of proportion to exam. Lesions are typically located at the surgical site and occur ~1 week following surgical intervention, though cases have been reported as early as post-operative day #1 and as late as seven years after surgery. The type of procedure also seems to affect risk of

post-operative PG, with more invasive procedures and breast surgery in particular conveying a higher risk of this complication. Importantly, post-operative PG has a lower association with underlying systemic disease than classic ulcerative PG.

Prompt identification of post-operative PG is essential, as 90% of patients receive antibiotics and 73% undergo debridement prior to diagnosis, which may worsen disease. Once post-operative PG is identified, treatment usually includes oral or IV corticosteroids, which the surgical team may be hesitant to initiate in the post-operative period. Cyclosporine and topical and systemic tacrolimus have also been utilized successfully. Patients usually see rapid improvement within the first day of initiating treatment, though complete healing can take weeks to months. Steroids are tapered cautiously once wounds have stabilized.

In patients with known PG prior to surgery, various medication regimens have been utilized in an attempt to prevent post-operative PG, which can occur in ~15% of patients. Most commonly, oral corticosteroids with or without cyclosporine are utilized, though monotherapy with cyclosporine, azathioprine, or methotrexate has also been reported. Many experts recommend a slow taper of medications over 6 months following surgical intervention. Literature review revealed no differences in efficacy between these regimens, nor between perioperative immunosuppression versus no immunosuppression. However, this finding may reflect confounding by indication given that the choice of peri-operative medication regimen may be correlated with severity of baseline PG. Additionally, it has been posited that subcuticular sutures may reduce risk of post-operative PG, though this has also not been substantiated.

We present this case to highlight challenges in perioperative management of PG patients and emphasize the need for further research to identify optimal strategies to prevent post-operative PG.

REFERENCES

1. Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *American Journal of Clinical Dermatology* 2012;13: 191-211.
2. Almukhtar R, Armenta AM, Martin J, Goodwin BP, Vincent B, Lee B, Dacso. Delayed diagnosis of post-surgical pyoderma gangrenosum: a multicenter case series and review of literature. *International Journal of Surgery Case Reports* 2018;44: 152-156.
3. Di Xia F, Liu K, Lockwood S, Butler D, Tsiaras WG, Joyce C, Mostaghimi A. Risk of developing pyoderma gangrenosum after procedures in patients with a known history of pyoderma gangrenosum—a retrospective analysis. *Journal of the American Academy of Dermatology* 2018;78(2): 310-314.
4. Fletcher J, Alhusayen R, Alavi A. Recent advances in managing and understanding pyoderma gangrenosum [version 1; peer review: 2 approved]. *F1000Research* 2019;8(F1000 Faculty Rev): 2092.
5. George C, Deroide F, Rustin M. Pyoderma gangrenosum–a guide to diagnosis and management. *Clinical Medicine* 2019;19(3): 224-228.
6. Haag CK, Bacik L, Latour E, Morse DC, Fett NM, Ortega-Loayza AG. Perioperative management of pyoderma gangrenosum. *Journal of the American Academy of Dermatology* 2020;83(2): 369-374
7. Kaddoura IL, Amm C. A rationale for adjuvant surgical intervention in pyoderma gangrenosum. *Annals of Plastic Surgery* 2001;46(1): 23-28.
8. Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma gangrenosum: an updated literature review on established and emerging pharmacological treatments. *American Journal of Clinical Dermatology* 2022;23(5): 615-634.

9. Maverakis E, Ma C, Shinkai K, Fiorentino D, Callen JP, Wollina U, Marzano AV, Wallach D, Kim K, Schadt C, Ormerod A. Diagnostic criteria of ulcerative pyoderma gangrenosum: a Delphi consensus of international experts. *JAMA Dermatology* 2018;154(4): 461-466.
10. Tolkachjov SN, Fahy AS, Cerci FB, Wetter DA, Cha SS, Camilleri MJ. Postoperative pyoderma gangrenosum: a clinical review of published cases. *Mayo Clinic Proceedings* 2016;91(9): 1267-1279.
11. Wei EX, Cohen JM, Wong V, Burgin S. Pyoderma gangrenosum. In: Goldsmith LA, ed. VisualDx. Rochester, NY: VisualDx; 2016. URL: https://www.visualdx.com/visualdx/dxDetails.do?moduleId=101&diagnosisId=52242&age=4. Accessed July 14, 2024.
12. Zuo KJ, Fung E, Tredget EE, Lin AN. A systematic review of post-surgical pyoderma gangrenosum: identification of risk factors and proposed management strategy. *Journal of Plastic, Reconstructive, and Aesthetic Surgery* 2015;68(3): 295-303.

Chicago Dermatologic Society **Case #8**

[1]Marisa Luck, [1]Lauren Watchmaker, [1]Robin Wang, [1]Wendy Kim
[1]Division of Dermatology, Loyola University Medical Center

HISTORY OF PRESENT ILLNESS

A 3-week-old female presented to the dermatology clinic for evaluation of a birthmark on the right neck, cheek, and under the chin. The patient was born via normal spontaneous vaginal delivery at 38 weeks 5 days with no birth complications. The mark was present at birth and had not changed in size or color of the birthmark over the past 3 weeks. Her parents noted that the birthmark became slightly redder/darker when the patient cries. The mother also reported a family history of hemangiomas and port wine stains on the maternal side.

PAST MEDICAL HISTORY

Born at term without complication

MEDICATIONS

No medications

ALLERGIES

No known drug allergies

FAMILY HISTORY

Family history of hemangiomas and port wine stains on maternal side

SOCIAL HISTORY

Lives with parents

PHYSICAL EXAMINATION

The baby was overall well-appearing. A faint red patch was present on the right upper medial eyelid and glabella, extending to the right lateral neck. A 5cm x 6cm discontinuous red patch was present on the right mandible and submental chin. On the right anterior ankle, there was a 0.6cm x 0.3cm bright red papule.

DERMATOPATHOLOGY

None

ADDITIONAL STUDIES

- A bedside doppler ultrasound of the right submandibular region and right cheek was performed to evaluate for vascular flow, demonstrating a high-flow vascular lesion in the patient.
- A bedside doppler ultrasound of the port wine stain on the mother's right upper back also demonstrated a high-flow vascular lesion.

DIAGNOSIS

Capillary Malformation-Arteriovenous Malformation

TREATMENT AND COURSE

On follow-up visits, the red patch encompassing the right mandible and submental chin did not grow or thicken and remained stable at 7 weeks, 2 months, and 5 months of age. While there was initial concern for a segmental infantile hemangioma as part of the differential diagnosis, the lack of thickening of the lesion early in life, with stable size, was consistent with a port-wine stain. Due to high flow on bedside doppler and subsequently on formal ultrasound, a diagnosis of CM-AVM was made, and the patient was referred to genetics for evaluation of RASA1 mutation.

DISCUSSION

Capillary malformation-arteriovenous malformation (CM-AVM) is a rare autosomal dominant disorder caused by heterozygous mutations in RASA1, which codes for a protein involved in cellular proliferation and differentiation. The incidence is estimated to be approximately one per 100,000. Clinically, it is characterized by multiple capillary malformations and often includes the presence of AVMs, with fast-flow vascular lesions arising in the skin, muscle, bone spinal cord, and brain. Approximately one third of patients will have fast flow AVMs. Diagnosis is often made by the above suggestive clinical findings and genetic testing for RASA1 mutations.

RASA1 is part of a key pathway involving mTOR pathways that control a variety of cellular functions including cellular growth, differentiation, and apoptosis. Mouse studies have suggested that RASA1 plays a critical role in the survival of endothelial cells during angiogenesis. The majority of RASA1 mutations in CM-AVM lead to premature stop codons and total loss of RASA1 protein. More recently EPHB4 gene mutations have also been implicated in cases of CM-AVM, thought to account for approximately 30% of cases. In the case of RASA1 mutation associated CM-AVM, around 70% of affected individuals have an affected parent, whereas 30% arise from de novo mutations. The wide spectrum of presentations has suggested that there is a somatic “second hit” leading to an inactivating mutation of RASA1 in endothelial cells that are necessary for disease development. A “second hit” inactivating mutation has been reported in case studies with samples taken from affected tissue.

CM-AVM should be suspected in patients with atypical capillary malformations, which often present as pink-brown multifocal round or oval lesions that are made up of dilated capillaries in the papillary dermis. These are often seen in combination with arteriovenous malformations (AVMs) or arteriovenous fistulas, which can occasionally intracranially. In Parkes Weber syndrome, another genetic syndrome associated with RASA1 mutation, cutaneous capillary malformations with multiple AVFs are accompanied by soft tissue and skeletal hypertrophy of the affected limb. In addition, some patients are noted to have lymphatic malformations with abnormally dilated lymphatic vessels. As part of management following initial diagnosis of CM-AVM, patients should be referred to a clinical geneticist or genetics counselor. Additionally, they should undergo brain and spine imaging and be referred to a neurologist to identify aneurysms or intracranial AVMs. Finally, cardiac complications with overload or heart failure are potential complications for those with significant fast-flow lesions and a cardiology is warranted in these situations.

REFERENCES

1. Al-Olabi L, Polubothu S, Dowsett K, Andrews KA, Stadnik P, Joseph AP, Knox R, Pittman A, Clark G, Baird W, Bulstrode N, Glover M, Gordon K, Hargrave D, Huson SM, Jacques TS, James G, Kondolf H, Kangesu L, Keppler-Noreuil KM, Khan A, Lindhurst MJ, Lipson M, Mansour S, O'Hara J, Mahon C, Mosica A, Moss C, Murthy A, Ong J, Parker VE, Rivière JB, Sapp JC, Sebire NJ, Shah R, Sivakumar B, Thomas A, Virasami A, Waelchli R, Zeng Z, Biesecker LG, Barnacle A, Topf M, Semple RK, Patton EE, Kinsler VA. Mosaic RAS/MAPK variants cause sporadic vascular malformations which respond to targeted therapy. *The Journal of Clinical Investigation*. 2018;128(4):1496-1508.
2. Chen D, Teng JM, North PE, Lapinski PE, King PD. RASA1-dependent cellular export of collagen IV controls blood and lymphatic vascular development. *The Journal of Clinical Investigation* 2019;129(9):3545-3561.
3. Chen D, Van der Ent MA, Lartey NL, King PD. EPHB4-RASA1-Mediated Negative Regulation of Ras-MAPK Signaling in the Vasculature: Implications for the Treatment of EPHB4- and RASA1-Related Vascular Anomalies in Humans. *Pharmaceuticals* 2023; 16(2):165.
4. Choksi F, Weinsheimer S, Nelson J, Pawlikowska L, Fox CK, Zafar A, Mabray MC, Zabramski J, Akers A, Hart BL, Morrison L, McCulloch CE, Kim H. Assessing the association of common genetic variants in EPHB4 and RASA1 with phenotype severity in

familial cerebral cavernous malformation. *Molecular Genetics & Genomic Medicine* 2021;9(10):e1794.
5. de Wijn RS, Oduber CE, Breugem CC, Alders M, Hennekam RC, van der Horst CM. Phenotypic variability in a family with capillary malformations caused by a mutation in the RASA1 gene. *European Journal of Medical Genetics* 2012;55(3):191-195.
6. Edwards LR, Blechman AB, Zlotoff BJ. RASA1 mutation in a family with capillary malformation-arteriovenous malformation syndrome: A discussion of the differential diagnosis. *Pediatric Dermatology* 2018;35(1):e9-e12.
7. Flore LA, Leon E, Maher TA, Milunsky JM. RASA1 analysis guides management in a family with capillary malformation-arteriovenous malformation. *Journal of Pediatric Genetics* 2012;1(2):125-9.
8. Grillner P, Söderman M, Holmin S, Rodesch G. A spectrum of intracranial vascular high-flow arteriovenous shunts in RASA1 mutations. *Child's Nervous System* 2016;32(4):709-15.
9. Haefliger S, Adams S, Nandakumar A, Nguyen L, Wargon O. CM-AVM syndrome - A prospective observational study of unrelated paediatric cases. *Australasian Journal of Dermatology* 2021;62(3):347-353.
10. Lapinski PE, Doosti A, Salato V, North P, Burrows PE, King PD. Somatic second hit mutation of RASA1 in vascular endothelial cells in capillary malformation-arteriovenous malformation. *European Journal of Medical Genetics* 2018;61(1):11-16.
11. Mologousis MA, Ostertag-Hill CA, Haimes H, Fishman SJ, Mulliken JB, Liang MG. Spectrum of lymphatic anomalies in patients with RASA1-related CM-AVM. *Pediatric Dermatology*. 2023;40(6):1028-1034.
12. Moreno-Estébanez A, Losada Domingo JM, Catalli C, González-Pinto González T, Agirre-Beitia G, Campos Rodríguez I, Díaz-Cuervo I, Lasa Elgezua O. A novel mutation of RASA1 in capillary malformation-arteriovenous malformation syndrome in a case with spinal cord involvement. *Clinical Neurology and Neurosurgery* 2020;195:105965.
13. Revencu N, Boon LM, Mendola A, Cordisco MR, Dubois J, Clapuyt P, Hammer F, Amor DJ, Irvine AD, Baselga E, Dompmartin A, Syed S, Martin-Santiago A, Ades L, Collins F, Smith J, Sandaradura S, Barrio VR, Burrows PE, Blei F, Cozzolino M, Brunetti-Pierri N, Vicente A, Abramowicz M, Désir J, Vilain C, Chung WK, Wilson A, Gardiner CA, Dwight Y, Lord DJ, Fishman L, Cytrynbaum C, Chamlin S, Ghali F, Gilaberte Y, Joss S, Boente Mdel C, Léauté-Labrèze C, Delrue MA, Bayliss S, Martorell L, González-Enseñat MA, Mazereeuw-Hautier J, O'Donnell B, Bessis D, Pyeritz RE, Salhi A, Tan OT, Wargon O, Mulliken JB, Vikkula M. RASA1 mutations and associated phenotypes in 68 families with capillary malformation-arteriovenous malformation. Human Mutation 2013;34(12):1632-41.
14. Revencu N, Boon LM, Mulliken JB, Enjolras O, Cordisco MR, Burrows PE, Clapuyt P, Hammer F, Dubois J, Baselga E, Brancati F, Carder R, Quintal JM, Dallapiccola B, Fischer G, Frieden IJ, Garzon M, Harper J, Johnson-Patel J, Labrèze C, Martorell L, Paltiel HJ, Pohl A, Prendiville J, Quere I, Siegel DH, Valente EM, Van Hagen A, Van Hest L, Vaux KK, Vicente A, Weibel L, Chitayat D, Vikkula M. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Human Mutation* 2008;29(7):959-65.

Chicago Dermatologic Society **Case #9**

[1]Megana Rao, [2]David Eilers
[1]Division of Dermatology, Loyola University Medical Center
[2]Section of Dermatology, Edward Hines Jr. Veterans Affairs Hospital

HISTORY OF PRESENT ILLNESS

A 68-year-old male who presented to dermatology clinic for skin cancer surveillance was noted to have lower extremity petechiae, ecchymosis, and a discolored right great toe. For several weeks prior to the visit, the patient experienced intermittent eruptions of petechiae on the right lower extremity from the mid-calf extending to the right foot. The eruptions lasted several days and were associated with intermittent cramping. In the days prior to clinic evaluation, the eruptions worsened, and the great toe developed a blue discoloration overnight.

The patient was evaluated by vascular surgery and non-invasive vascular lab studies were ordered. Approximately 2 weeks later, the patient presented to the emergency department with worsening pain, blue discoloration, and coolness of the right foot and toes.

PAST MEDICAL HISTORY

Basal cell carcinoma (left neck) s/p wide local excision 2019
Bladder cancer s/p cystectomy 1990s
Hypertension
Neuropathy
Type 2 diabetes mellitus

MEDICATIONS

Amlodipine, Hydrochlorothiazide/triamterene, Ketoconazole shampoo, Lisinopril, Meloxicam, Metformin, Methocarbamol, Omeprazole, Zolpidem

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

No present or past tobacco use. Occasional alcohol use

PHYSICAL EXAMINATION

On examination in dermatology clinic, the right lower extremity had non-palpable purpura on the dorsal and plantar foot extending to the calf. Additionally, there was cyanosis and retiform purpuric macules and patches of the great toe and plantar foot. Dorsalis pedis (DP) and posterior tibialis (PT) pulses were 2+.

Two weeks later at admission, there were scattered non-blanching petechiae of the right lower extremity extending from the mid-calf to the dorsal and plantar aspects of the right foot. Blue and white discoloration was present on the right 1st, 2nd, 4th, and 5th digits. On vascular exam, radial/popliteal/DP/PT pulses were 2+ bilaterally. The right lower extremity was cool to the touch from the level of the medial malleolus extending to the toes.

DERMATOPATHOLOGY

Histologic sections from a punch biopsy of the right lower leg showed extravasated erythrocytes in superficial dermis, consistent with purpura. In addition, there were a few microthrombi in small mid-dermal vessels.

ADDITIONAL STUDIES

- Ankle brachial index (ABI) of the right lower extremity was 1.16 (1.0-1.4) and the left lower extremity was 1.22.
- Pulse volume recording (PVR) waveforms of bilateral ankles appeared normal.
- Photoplethysmography (PPG) of the left digits was normal. The left great toe had an absolute pressure of 129mmHg (normal ≥ 50mmHg). PPG of the right digits was normal other than the 1st and 5th digits which were moderately abnormal. The right great toe had an absolute pressure of 24mmHg.
- CT scan of the right lower extremity with contrast revealed a popliteal artery measuring 4.5 x 4.2 cm. A later CT scan also revealed a 3.3 x 3.2 cm popliteal artery aneurysm of the left leg.
- Autoimmune workup was negative and inflammatory makers were negative. Complete blood count and comprehensive metabolic panel were both unremarkable.

DIAGNOSIS

Thromboembolic sequelae of popliteal artery aneurysm

TREATMENT AND COURSE

The patient underwent right popliteal aneurysm resection and placement of an 8mm polytetrafluoroethylene (PTFE) interposition graft with vascular surgery.

He later required partial amputation of the right hallux and amputation of the 2nd-5th digits of the right foot.

DISCUSSION

This case represents an unusual presentation of blue toe syndrome (BTS). BTS is the acute development of a discolored toe, which is often tender to the touch. This diagnosis can only be made after excluding trauma-induced and cold-induced injuries resulting in discolored digits and excluding disorders leading to generalized cyanosis. Some of the more common causes of BTS include embolization (especially cholesterol emboli), thrombosis, hypercoagulable states, and vasculitis. Cutaneous abnormalities are often the earliest manifestation when BTS results from emboli and can occur on the same day as the provoking event, or be delayed as long as several weeks. Depending on the location of the occlusion, peripheral pulses may be well-preserved.

When discolored digits and other cutaneous findings of thromboembolic events are seen unilaterally, one should be concerned of an underlying vascular process, as was the case in our patient. There have been few reports in the literature describing patients with dermatologic manifestations preceding a diagnosis of a lower extremity aneurysm. In one case, a patient exhibited reticulated violaceous macules on the foot as well as blue discoloration of the fourth and fifth toes. This patient was found to have a popliteal artery aneurysm with mural thrombus. In another case, a patient developed acute onset of painful and discolored toes due to an aneurysm of the crural artery. A third case showed acute discoloration of a toe which prompted imaging and diagnosis of a popliteal artery dissection; the dissection was thought to be a result of an aneurysm.

Popliteal artery aneurysms are most commonly asymptomatic; however, patients with a thrombosing aneurysm can experience a variety of symptoms including pain, paresthesias, pallor, or poikilothermia. Additionally, if there is distal embolization of the thrombus, this can result in blue toe syndrome and acral cyanosis. While the incidence of popliteal artery aneurysms has not yet been documented, a few studies have determined that prevalence increases with age, peaking in the sixth or seventh decade. Our patient fell into this age range and had several non-modifiable risk factors including male gender and white race.

This case represents an unusual presentation of popliteal artery aneurysms resulting in blue toe syndrome and other thromboembolic cutaneous findings and highlights the importance of a timely and accurate diagnosis.

REFERENCES

1. Brown PJ, Zirwas MJ, English JC 3rd. The purple digit: an algorithmic approach to diagnosis. *Am J Clin Dermatol*. 2010;11(2):103-116.
2. Deng L, Deng W. The Evolution of Blue Toe Syndrome in a Diabetic Patient. *Am J Med*. 2023;136(1):e1-e2.
3. Hirschmann JV, Raugi GJ. Blue (or purple) toe syndrome. *J Am Acad Dermatol*. 2009;60(1):1-22.
4. Kano Y, Shigehara Y. Blue toe syndrome caused by cholesterol crystal embolisation in a patient with warfarin use. *BMJ Case Rep*. 2023;16(10):e257927. Published 2023 Oct 5.
5. Karmody AM, Powers SR, Monaco VJ, Leather RP. "Blue toe" syndrome. An indication for limb salvage surgery. *Arch Surg*. 1976;111(11):1263-1268.
6. Kügler CF, Poser M, Mosel F, Ruehm S, Rudofsky G. Spontaneous dissection of the popliteal artery in a young man. A rare cause of the blue toe syndrome. *Int Angiol*. 2006;25(1):93-97.
7. Martínez-Morán C, García-Donoso M C, Moreno A, Borbujo Jet al. Blue Toe Sign as the Initial Manifestation of a Popliteal Artery Aneurysm. *Actas Dermo-Sifiliográficas*. 2011;102:551-52
8. Obara H, Matsubara K, Kitagawa Y. Acute Limb Ischemia. *Ann Vasc Dis*. 2018;11(4):443-448.
9. Spronk S, den Hoed PT, Veen HF. Case report: Blue toe syndrome caused by a true crural aneurysm. *J Vasc Nurs*. 2003;21(2):70-71.
10. Tartari F, Di Altobrando A, Merli Y, Patrizi A, Mirelli M, Bianchi T. Blue Toe Syndrome: A Challenging Diagnosis. *Indian J Dermatol*. 2019;64(6):506-507.

Chicago Dermatologic Society **Case #10**

[1]Robin H. Wang, [1]Jenna J. Lullo, [2]Madhu Dahiya, [3]David B. Eilers
[1]Division of Dermatology, Loyola University Medical Center
[2]Department of Pathology & Laboratory Medical Services, Edward Hines, Jr. Veterans Affairs Hospital
[3]Section of Dermatology, Edward Hines, Jr. Veterans Affairs Hospital

HISTORY OF PRESENT ILLNESS

A 30-year-old man presented to dermatology clinic with an eight-month history of non-healing lesions of the perianal region. The lesions were tender and would intermittently drain serosanguinous fluid. The patient denied fevers, chills, or a history of trauma to the area. Past medical history was unremarkable. Prior work up included a colonoscopy two months prior, which showed no evidence of inflammatory bowel disease.

PAST MEDICAL HISTORY

Depression
Post traumatic stress disorder

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

Recreational alcohol use

PHYSICAL EXAMINATION

On the perianal skin, there were two 0.5cm x 0.5cm firm, eroded, erythematous papules located 2.5cm from the anal canal, at 8 o'clock and 11 o'clock relative to the anal canal. There was no evidence of sinus tracts, fissures, or hemorrhoids. Complete cutaneous examination was unremarkable, and no lesions were present in the oral mucosa.

DERMATOPATHOLOGY

Histopathologic analysis of a punch biopsy of the perianal papule at 8 o'clock demonstrated suppurative and lymphohistiocytic granulomatous inflammation with eosinophils and foreign body giant cells. Scattered foci of pale-staining hyaline ring structures were present in the dermis which were focally polarizable. Periodic Acid-Schiff (PAS) stain with diastase highlighted the ring-like structure of the foreign material. Congo red and calcium stains were negative.

ADDITIONAL STUDIES

Aerobic wound culture showed normal skin flora

DIAGNOSIS

Perianal cutaneous pulse granuloma

TREATMENT AND COURSE

The excisional punch biopsy resulted in resolution of the lesion without recurrence to date.

DISCUSSION

Pulse granulomas are unusual foreign body reactions to the implantation of exogenous plant material characterized by the presence of hyaline ring structures admixed with giant cell granulomatous inflammation. Ultrastructural studies have demonstrated that the hyaline ring structures are composed of the cellulose walls of plant material. They can display birefringence with polarization microscopy and are highlighted by PAS staining. Pulse granulomas have been found most frequently in the oral mucosa, and occasionally, in the gastrointestinal tract and respiratory tract. Cutaneous pulse granulomas are exceedingly rare, with less than 10 cases reported in the literature.

Clinically, a cutaneous pulse granuloma may present as a nonspecific erythematous papule or nodule that resembles granulomatous conditions, infectious processes, or malignancies. Excision has been the only trialed modality for treatment, and in all cases reporting an outcome, the pulse granuloma resolved without recurrence.

Previously reported cases of pulse granulomas have been closely associated with underlying chronic inflammatory conditions, chronic fistulas, trauma, or surgical procedures which likely facilitated the implantation of foreign plant material. However, our patient's history was notable for the absence of such contributing factors.

We propose that our patient's perianal pulse granuloma was induced by plant-derived baby wipes. Upon further investigation, the patient reported using baby wipes daily to the perianal area for 1 year. Our patient's baby wipes are composed of lyocell fibers, derived from the regenerated cellulosic fibers of wood pulp. Lyocell fibers have been promoted for baby wipe usage for their 100% biodegradable profile, high absorbance, and gentleness on skin. However, fibers derived from cellulose are highly prone to physical fragmentation and have less tensile strength and elasticity as compared to conventional baby wipes derived from plastics. Thus, it is likely that cellulosic fiber components fragmented off the baby wipe from physical shearing forces during use.

There are several possibilities regarding how the cellulosic fiber components penetrated the perianal skin. One possibility is that cellulosic fiber components entered through subclinical fissures. Another possibility is that our patient initially developed a contact dermatitis to one of the preservative ingredients in the baby wipes such as phenoxyethanol or sodium benzoate, and resultant tissue injury enabled penetration of cellulosic fiber components. Both phenoxyethanol and sodium benzoate are included in the American Contact Dermatitis Society core allergen series. Finally, undisclosed trauma involving plant material to the perianal region remains a possibility. Of note, after discontinuing baby wipe usage, our patient has not experienced new lesions to date.

REFERENCES

1. Taboada Paz L, Suárez Peñaranda JM, García García A. Pulse Granuloma After Tunneled Nasolabial Island Flap: An Unusual Cause for a Cutaneous Nodule on the Face. Am J Dermatopathol. 2023;45(12):862-864. doi:10.1097/DAD.0000000000002542
2. Gil-Pallares P, Vilas-Sueiro A, Monteagudo B, Mosquera-Martínez MT, Fernandez-Flores A. Pulse Granuloma-Like Reaction on the Forearm Following an Accidental Wound. Am J Dermatopathol. 2022;44(4):291-293. doi:10.1097/DAD.0000000000002078

3. Tschen JA, Tschen JA. Pulse granuloma in a rectocutaneous fistula. J Cutan Pathol. 2008;35(3):343-345. doi:10.1111/j.1600-0560.2007.00812.x
4. Rhee DD, Wu ML cheng. Pulse granulomas detected in gallbladder, fallopian tube, and skin. Arch Pathol Lab Med. 2006;130(12):1839-1842. doi:10.5858/2006-130-1839-PGDIGF
5. Rosen Y, Garcia PM, Navale P. Pulse/hyaline ring granuloma revisited: etiologic role of seed-derived storage cells. Virchows Arch. 2022;480(3):499-508. doi:10.1007/s00428-021-03222-2
6. Kirkland Signature Baby Wipes Fragrance Free, 900-count. Costco Wholesale. Accessed July 7, 2024. https://www.costco.com/kirkland-signature-baby-wipes-fragrance-free%2c-900-count.product.100801219.html
7. What is TENCELTM fibers fabric made of? About TENCELTM Lyocell & Modal fiber fabric. TENCELTM. Accessed July 7, 2024. https://www.tencel.com/about
8. Allison T, Ward BD, Harbottle M, Durance I. Do flushed biodegradable wet wipes really degrade? Science of The Total Environment. 2023;894:164912. doi:10.1016/j.scitotenv.2023.164912
9. Schalock PC, Dunnick CA, Nedorost S, et al. American Contact Dermatitis Society Core Allergen Series: 2020 Update. Dermatitis. 2020;31(5):279-282. doi:10.1097/DER.0000000000000621
10. Warshaw EM, Buonomo M, DeKoven JG, et al. Patch Testing to Methyldibromoglutaronitrile/Phenoxyethanol: North American Contact Dermatitis Group Experience, 1994-2018. Dermatitis. 2021;32(4):256-266. doi:10.1097/DER.0000000000000732
11. Kwon S, Zambrano MC, Venditti RA, et al. Microfiber shedding from nonwoven materials including wipes and meltblown nonwovens in air and water environments. Environ Sci Pollut Res Int. 2022;29(40):60584-60599. doi:10.1007/s11356-022-20053-z

Thank You

INDUSTRY PARTNERS

abbvie

Boehringer Ingelheim

Eli Lilly
need logo

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Pfizer

sanofi

REGENERON


CHICAGO DERMATOLOGICAL SOCIETY
CDS
1901