Chicago Dermatological Society

PROTOCOL BOOK
May 3, 2023

Co-hosted by Rush University
Medical Center
Department of Dermatology

Guest Speaker: **Steven T. Chen, MD MPH MS-HPEd**
Vice Chief of Education, MGH Dermatology
Co-Director, Comprehensive Cutaneous Lymphoma Program, MGH Cancer Center
Co-Director, Oncodermatology Program, MGH Dermatology
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Chicago Dermatological Society
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Program

Co-hosted by Rush University Medical Center, Department of Dermatology

Wednesday, May 3, 2023
University of Chicago Gleacher Center
Chicago, Illinois

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**

Joerg Albrecht, MD PhD - CDS President

9:00 a.m. - 10:00 a.m. **Morning Lecture**

"More than meets the eye: Transforming cancer care through dermatologic immune related adverse events"

Steven Chen, MD MPH MS-HPEd

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**

"Case based Approach to the Care of Cutaneous Lymphomas: From Steroids to Stem Cells"

Steven Chen, MD MPH MS-HPEd

Program adjourns

RUSH

Rush University Medical Center
Department of Dermatology
May 3, 2023

Dermatology Residents

Third Year
Catherine Emerson, MD
Ryan C. Kelm, MD

Second Year
Julie Bittar, MD
Morgan Decker, MD

First Year
Elise Brunsgaard, MD
Rachel Lefferdink, MD
Emily Medhus, DO

TABLE OF CONTENTS

CHICAGO DERMATOLOGICAL SOCIETY

CASE 1

Presented by Ryan C. Kelm, MD, Penelope Skopis, MD,
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 64-year-old male was transferred from an outside hospital for evaluation of worsening lower extremity ulcerations and digital gangrene. He stated his symptoms began following the Moderna COVID vaccine in 2020 and progressively worsened. Prior to admission, he was evaluated by an outside rheumatologist for fingertip color changes, digital ulcerations, and a leg rash, which was thought to be secondary to Raynaud's phenomenon and leukocytoclastic vasculitis. He was managed with a prednisone taper.

At the time of his initial admission to the outside hospital, he presented with respiratory failure. His hospital course was complicated by worsening CHF, myocardial infarction, acute-on-chronic kidney injury necessitating dialysis, subacute pulmonary embolism, and worsening gangrene to his distal right foot and left-hand 2nd and 3rd digits.

The patient was ultimately transferred due to concern for vasculitis and atypical hemolytic uremic syndrome, for which he was being treated with plasmapheresis (PLEX) and eculizumab. Notably, cryoglobulins were negative, and he was started on a heparin drip at the outside hospital. He denied fever, night sweats, weight loss, easy bleeding, neuropathy, and enlarged lymph nodes.

PAST MEDICAL

Chronic kidney disease, Congestive heart failure, Hypertension, Hyperlipidemia.

SURGICAL HISTORY

Left-hand 4th & 5th digit amputation from a traumatic accident.

FAMILY HISTORY

Mother died of Leukemia/Lymphoma.

SOCIAL HISTORY

Noncontributory

MEDICATIONS

Fluticasone, Prednisone 10 mg, Hydrochlorothiazide, Aspirin, Metoprolol, Heparin drip

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Cold, dusky violaceous discoloration extending from the right mid-foot distally with retiform purpuric patches proximal to necrotic tissue. The left 2nd and 3rd fingers are also distally dusky purple from the palm. Distal to the DIPs, the fingers are black and necrotic. The left thumb has areas of erythema at the pulp, which are tender. Lower extremities with scattered petechiae, healing ulcerations on left lower extremity, and atrophie-blanche-like scarring.

A review of the patient's photos demonstrated retiform purpura with ulceration to the distal lower extremities.

LABORATORY RESULTS

Normal

Hematology
- No eosinophilia

Chemistry
- Hepatic function
- Homocysteine, methylmalonic acid, folate, vitamin B12
- LDH
- Iron studies
- Ferritin
- SPEP – ambiguous, requiring IFE

Coagulation
- HIT antibody and serotonin release assay
- Antiphospholipid antibody panel
- Hypercoagulability panel
- PT
- ADAMTS13

Immunology
- RNA polymerase III antibody
- C3 & C4
- ANA, RF
- Quant immunoglobulins – small decrease in IgM

Microbiology
- Blood cultures
- Urine cultures
- Hepatitis B
- HIV
- Respiratory viral panel

Abnormal

Hematology
- CBC – anemic, thrombocytopenic, and eventually developed leukopenia.
- Haptoglobin – elevated 205

Chemistry
- CMP – BUN 60, Creatinine 2.15,
- BNP – 2220

Coagulation
- PTT and Thrombin time elevated

Immunology
- Immunofixation electrophoresis – Monoclonal IgG kappa 4,000 mg/L; kappa elevated 16.96 (ref range 0.33-1.94); lambda 0.98; kappa/lambda 17.31
- Cryoglobulins via IFE on cryoprecipitate – elevated to 5.0%
- ANCAs: c-ANCA 1:80
- Beta2-microglobulin – elevated 3.10

Urine
- Turbid, increased protein, blood, WBC, RBC, hyaline casts

IMAGING STUDIES

Unremarkable
- Vascular ultrasound studies
- CT C/A/P
- CTA left upper extremity.

SPECIAL STUDIES

Blood flow cytometry immunophenotyping demonstrated 3% of total cellularity composed of kappa-restricted B-cells with CD19, CD5, and CD38 expression while being negative for CD20 and CD23, consistent with CLL.

Peripheral blood smear with pancytopenia, without lymphocytosis, and no circulating blasts or schistocytes

Bone marrow biopsy demonstrated findings consistent with mature B-cell lymphoma with CLL phenotype, representing 30% of marrow cellularity.

Renal biopsy demonstrated membranoproliferative glomerulonephritis with focal intracapillary thrombi and arteriolar thrombosis that stain positive for IgG kappa consistent with crystal cryoglobulinemic glomerulonephritis type 1 (IgG kappa) with focal areas involved with CLL.

DERMATOPATHOLOGY

Inpatient 4 mm punch biopsy of erythematous edge of retiform purpura located on the right dorsal foot demonstrated hyper- and parakeratosis, extravasated red blood cells in the papillary dermis with dermal medium-sized blood vessels occluded by fibrin thrombi, consistent with thrombotic vasculopathy.

DIAGNOSIS

Type 1 cryoglobulinemia secondary to chronic lymphocytic leukemia

CLINICAL COURSE

After the diagnosis of Type 1 cryoglobulinemia secondary to CLL complicated by crystal cryoglobulinemic glomerulonephritis type 1, the patient was started on a prednisone taper and weekly PLEX until starting chemotherapy. Cryoglobulins became undetectable. The patient elected for amputation to his gangrenous right foot and left-hand 2nd and 3rd digits. Chemotherapy with acalabrutinib was initiated 1-month post-amputation. Following discharge, the patient has been readmitted on multiple occasions for anemia and AKI, which has been managed and subsequently discharged. He is now continuing treatment with acalabrutinib.

DISCUSSION

Cryoglobulinemia (CG) is characterized by the presence of cryoglobulins in the serum, which are immunoglobulins that reversibly precipitate with cold exposure, typically at temperatures below 37°C. At cold temperatures, their configuration changes becoming water-insoluble, which may increase blood viscosity.[1] Classically, there are three types of cryoglobulinemia. Type I CG comprises single monoclonal immunoglobulins, which are most commonly IgM, occasionally IgG, or, more rarely, IgA.[2] Type II and type III CG are classified as mixed cryoglobulinemia because they comprise two types of immunoglobulins, typically IgG and IgM. Type II CG usually consists of a monoclonal IgM with a polyclonal IgG, whereas type III has polyclonal IgM and IgG. In addition to the common classification, an oligoclonal IgM or mixed monoclonal and polyclonal IgM may be identified with polyclonal IgG, termed type II-III CG, which may indicate intermediate evolution from type III to type II mixed CG.[2] Overall, type I, II, and III represent 10%, 65%, and 25% of CG, respectively.[2]

Of 13,439 patients assessed for CG, 1,675 (12.5%) tested positive.[3] CG was more common in women (female: male 1.55), and the average age of diagnosis was 54.[3]

Overall, the pathogenesis of CG is incompletely understood; however, it is thought to be due to host predisposition and environmental triggers, which lead to aberrant autoantibody production by B-cells and their respective proliferation.[3] The presence of cryoglobulins then may mediate disease via occlusion and/or immune complex formation with resulting inflammatory vasculitis.[2] In addition to temperature, it has been suggested that their pathogenicity may also depend on pH, weak noncovalent interactions, and cryoglobulin concentration.[2]

Type I CG is invariably linked to a B-cell lymphoproliferative disorder, which includes monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom macroglobulinemia, multiple myeloma, and non-Hodgkin lymphomas such as hairy cell leukemia and chronic lymphocytic leukemia.[2] Patients with type I cryoglobulinemia have a ~35 times higher risk of having hematologic malignancy relative to the general population.[4]

The lymphoproliferative disorder may result in high concentrations of monoclonal cryoglobulins, causing hyperviscosity syndrome, which manifests as visual changes, headache, confusion, and chest pain.[5] Skin manifestations of type I CG usually occur at distal, acral sites characterized as purpura, livedo reticularis, ulcers, gangrene, Raynaud's phenomenon, and acrocyanosis. In addition, extracutaneous manifestations may be seen, such as peripheral neuropathy, glomerulonephritis, and arthralgias.[6]

Immunoglobulin subtype and concentration are important factors that may correlate with extracutaneous involvement.[7] Type I CG is most associated with IgM;[3] however, a study from the Mayo Clinic demonstrated IgG as the most common heavy chain detected in a series of 102 patients, with 53%, 39%, and 5% of patients having IgG, IgM, and IgA, respectively.[6] Patients with type I IgG CG are more likely to have higher immunoglobulin concentrations, peripheral neuropathy (42.1% vs 7.7%, p=0.006), and renal involvement (31.6% vs. 3.8%, p=0.011) compared to patients with IgM type I CG.[3,7] In addition, the median cryocrit level is typically higher in patients with renal involvement than in patients without renal involvement.[7] Renal involvement is reported to occur in 4-30.5% of patients with type I CG.[8] It typically manifests as proteinuria, hematuria, and renal insufficiency because of immunoglobulin deposits in glomerular capillaries mediating the proteinaceous thrombus formation.[8,9]

Hepatitis C (HCV) is the most common disease associated with mixed CG, representing 80-90% of cases.[2] In addition, mixed CG may be associated with systemic autoimmune diseases such as Sjogren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, lymphoproliferative diseases, and chronic viral infections such as hepatitis B and HIV; however, bacterial, parasitic, and fungal infections have been implicated as well.[2]

The prevalence of HCV-associated CG is best understood via the ability of HCV to infect B-cells and hepatocytes through the common expression of HCV entry receptor CD81 on the plasma membrane of both cells.[2] This process promotes autoantibody production and stimulates B-cell proliferation. Mixed CG has antibodies with rheumatoid factor activity, which describes the ability of an antibody to bind to another antibody, allowing the formation of immune complexes.[2] The development, accumulation, and circulation of these immune complexes mediate small-vessel endothelial injury causing vasculitis and complement consumption, which is seen in mixed CG.

Some reports suggest that type I CG may cause vasculitis;[10,11] however, it has not been described from a mechanism perspective. The literature does not standardize the term type I cryoglobulinemic vasculitis as some studies suggest using the term "cryoglobulinemic vasculitis" to describe the presence of cryoglobulins in the serum with clinical manifestations without histologic verification of vasculitis.[10,11] In addition, some reports of type I CG with a histologic demonstration of vasculitis do not report the temporal relationship between lesion onset and time-to-biopsy, which is important in determining the etiology of vasculitis as a primary or secondary phenomenon. In addition, type I CG typically has normal complements and a negative rheumatoid factor, indicating no complement activity and immune complex formation.[2]

The diagnosis of CG requires the detection of circulating cryoglobulins, which requires strict laboratory processing. The blood must be transported and processed at 37°C to prevent

premature cryoprecipitation, then stored at 4°C for 7 days to determine if a cryoprecipitate is present, then rewarmed to 37°C.[2] Then, immunofixation of the cryoprecipitate identifies the immunoglobulin components. Given these strict temperature and processing requirements, serologic testing of cryoglobulins is prone to false-negative rates. A large cohort study found that 196 of 2,213 (9%) patients who initially tested negative for cryoglobulins demonstrated a positive result on follow-up testing.[3]

On pathology, type 1 CG demonstrates thrombosis in dermal vessels, like other causes of coagulopathy, which is seen as homogenous eosinophilic material within the vessel lumen.[2] In addition, evidence of vasculitis – neutrophilic karyorrhexis, fibrinoid necrosis of vessel walls, and extravasation of red blood cells – is not seen.[2]

Treatment of type I CG should be directed toward the underlying lymphoproliferative disorder and augmented with plasmapheresis in those with hyperviscosity; however, plasmapheresis monotherapy has not shown benefit .[6] Cold prevention and regular monitoring may be indicated for mild symptoms and/or indolent hematologic disease.[6] Immunosuppressive therapy and plasmapheresis are recommended for severe symptoms with extracutaneous involvement.[7] Therapeutic options include corticosteroids, cyclophosphamide, bortezomib, and rituximab.[2,6]

The prognosis of type I CG is related to the underlying etiology, as lymphoproliferative diseases may portend a worse outcome relative to MGUS.[6,7] In addition, renal and neurologic involvement may suggest a worse prognosis.[6,12] The 1- and 5-year overall survival rate is 97% and 82%, respectively.[6,7] Clinical response rates are high, and symptoms improve with appropriate treatment in 80-86% of patients.[6,7]

In summary, it is important to be aware of the clinical manifestations of type I CG as it may herald an underlying lymphoproliferative disease. In the event of a negative result, with a strong clinical suspicion for type I CG, repeat testing should be done. The immunoglobulin subtype may suggest prognosis, and type I CG does not directly cause vasculitis. Early recognition and treatment are critical to minimize disease progression and the risk of amputation. If recognized and treated promptly, clinical response rates are high.

Key Points:

- Type I cryoglobulinemia likely heralds an underlying lymphoproliferative disease.
- If clinical suspicion is high with a negative test, consider repeat testing.
- The Immunoglobulin subtype may affect prognosis.
- Type 1 cryoglobulinemia unlikely causes vasculitis and, if seen, is a secondary process.
- Early recognition is important to minimize morbidity and mortality.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 2

Presented by Julie Bittar, MD, Penelope Skopis, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 57-year old female with history of Crohn disease thought to be in remission presented for a 2 year history of a rash on her right thigh was initially evaluated by her PCP and felt consistent with post inflammatory hyperpigmentation from and unknown primary process. She was started on triamcinolone 0.025% cream for her thigh and referred to dermatology. The patient was subsequently lost to follow up until she presented two years later for nonhealing, pruritic rash. The eruption of the lateral thigh was felt to be consistent with atopic dermatitis and the patient was started on clobetasol ointment twice daily, nightly Zyrtec for pruritus, and provided with gentle skincare instructions. Five months later, the patient returned for evaluation of worsening rash and significant lymphadenopathy of the right inguinal node. A 4mm punch biopsy was performed of the right lateral thigh.

PAST MEDICAL & SURGICAL HISTORY

Anemia, insomnia, Crohn disease (diagnosed in 2006, previously on Humira and Azathioprine however not currently on medical treatment) complicated by sigmoid perforation status post exploratory laparotomy with small bowel resection and loop ileostomy creation in 2020, recto-cutaneous fistula status post repair, fibromyalgia, depression, hemorrhoids, hysterectomy, cesarean section.

FAMILY HISTORY

No known family history of cutaneous disease, myeloproliferative syndromes, or autoimmune conditions.

SOCIAL HISTORY

No history of smoking, drinks wine rarely, no recreational drug use.

MEDICATIONS

Clobetasol 0.05% ointment, zolpidem 5mg PO nightly, triamcinolone 0.025% cream

ALLERGIES

Tramadol (hyponatremia)

PHYSICAL EXAMINATION

Involving the right buttock and proximal lateral right thigh there are pink-brown to violaceous firm papules and nodules coalescing into large indurated plaques. Further, involving the right groin there is a 4 cm x 6 cm firm, fixed nodule.

LABORATORY RESULTS

CBC with differential- normal
CMP- normal
LDH- normal (193)

ESR- normal (29)
Lipid panel- normal
A1c- normal (5.4%)

IMAGING STUDIES

Imaging with MRI showed 5.1 x 2.2 x 3.5 cm, enhancing, soft tissue lesion in the right superficial inguinal region as well as two additional mildly enlarged lymph nodes in the right hemipelvis and right inguinal region.

PATHOLOGY

Histopathologic analysis of the 4mm punch biopsy showed an unremarkable epidermis. Throughout the dermis, a granulomatous dermatitis was appreciated with presence of a diffuse infiltrate predominantly of histiocytes with an admixture of neutrophils, plasma cells and lymphocytes. PAS, GMS, and Fite stains were negative for microorganisms. Immunohistochemistry for CD68 highlighted the histiocytes and immunohistochemistry controls show appropriate reactivity.

DIAGNOSIS

Metastatic Crohn Disease

CLINICAL COURSE

After the biopsy results were read as consistent with Metastatic Crohn Disease, referrals were sent for the patient to follow up with gastroenterology for a colonoscopy to evaluate the status of her internal disease as well as with interventional radiology for evaluation of the right inguinal lymph node. Of note, she was not currently treating her Crohn with medical therapy and stated that her GI symptoms were well controlled with a vegetarian diet. Pending malignancy workup, the patient was started on oral metronidazole 250 mg three times daily and clobetasol ointment twice daily to the affected areas.

She underwent ultrasound guided core needle biopsy of the inguinal node which showed preserved lymph node architecture including evenly spaced secondary follicles and open sinuses with bland plasma cells and adjacent medullary cords. No granulomas were seen and flow cytometric studies were negative for lymphoma. The diagnosis of reactive lymphoid tissue was favored. At this time, the patient’s workup is still ongoing.

DISCUSSION

Crohn disease (CD) is a type of chronic inflammatory bowel disease that classically involves the terminal ileum however can affect various parts of the gastrointestinal tract. Extra-intestinal manifestations (EIM) precede the diagnosis of IBD in 25% of cases and typically manifest as inflammatory hepatobiliary, mucocutaneous, ocular and vascular conditions.[1] EIMs of CD in particular are common, with an estimated 40% of CD patients experiencing at least one EIM in their lifetime.[2] Perhaps one of the most common organs of involvement is the skin, which is reported to involve up to 43% of CD patients and is designated the name Cutaneous Crohn disease (CCD).[3]

CCD has been subclassified into three main categories: specific, reactive, and associated lesions.[4] Specific lesions are those that are histologically identical to intestinal CD. These lesions may occur in areas of the skin, contiguous to the GI tract, where there are underlying fistulas or abscesses and are typically associated with active intestinal inflammation. Perianal skin tags may also be present. Specific lesions may also present distant/non-contiguous to the GI tract as pink-violaceous nodules, ulcers, and indurated plaques, termed metastatic CD. A skin biopsy is typically required to confirm the diagnosis. Histological examination can help to identify noncaseating granulomas, which are characteristic of specific CD lesions.

Reactive lesions are those that are triggered by underlying inflammation in the skin, but they are not histologically identical to intestinal CD. Examples of reactive lesions include erythema nodosum, pyoderma gangrenosum, and Sweet's syndrome. Erythema nodosum is the most common cutaneous manifestation of IBD as a whole, affecting between 3-10% of ulcerative colitis patients and between 4-15% of CD patients.[3]

Associated lesions are those that are not directly related to CD but occur more frequently in patients with the condition. For instance, psoriasis is estimated to occur in 1.4% of the general population however has an 8.9% incidence among CD patients.[5] Other examples of associated lesions include bullous pemphigoid, hidradenitis suppurativa, and uveitis.

The diagnosis of CCD can be challenging, and a thorough workup including a detailed medical history, physical examination, laboratory testing, skin biopsy, and imaging studies is key. Laboratory testing may clue the clinician into whether there is active underlying intestinal inflammation and may include a complete blood count, erythrocyte sedimentation rate, C-reactive protein, and fecal calprotectin.[6]

Imaging studies such as CT scans and MRI may also be necessary to identify underlying fistulas or abscesses that may be contributing to the skin lesions. Moreover, imaging studies can also can help in the identification of subclinical intestinal involvement and serve as a cancer screening tool in patients with cutaneous CD, given that the estimated risk of colon cancer in CD patients is nearly three times that of the general population.[7] Because of this, regular colonoscopies are also imperative for CD patients. The American College of Gastroenterology recommends that patients with CD involving the colon undergo colonoscopy with biopsies every 1-2 years starting 8-10 years after the onset of disease.[8]

Management of CCD is challenging as no standardized guidelines exist however treatment should be individualized based on the severity of the patient’s disease in the context of their other medical history. For specific lesions due to direct extension of bowel, surgery may be necessary. Meanwhile, for metastatic CD, systemic corticosteroids appear to be the mainstay of treatment. Other treatment options such as topical corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, metronidazole, and TNF alpha inhibitors such as infliximab and adalimumab have been reported with varying levels of success. [9, 10] Close monitoring of the patient’s response to treatment should be adjusted as needed. Overall, management requires a multidisciplinary approach and collaboration between dermatologists, gastroenterologists, and surgeons is important to provide optimal patient care.

Key Points:

- Keep cutaneous Crohn disease in mind for IBD patients
- Know the different types of cutaneous Crohn disease: specific, reactive, associated
- Workup for underlying active intestinal disease
- Treatment depends on the extent of involvement

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 3

Presented by Rachel Lefferdink, MD and Kyle Amber, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 53-year-old woman with a history of dermatomyositis with scleroderma overlap syndrome presented to an outside hospital with two weeks of intermittent fevers, severe fatigue, and left lower extremity erythema and edema. Symptoms initially started one week after the patient received her first infusion of cyclophosphamide for management of her autoimmune disease, for which she was also receiving monthly intravenous immune globulin (IVIG) and prednisone 60 mg daily. She was treated at the outside hospital for presumed sepsis secondary to left lower extremity cellulitis. Despite antibiotic therapy, she continued to have daily fevers ranging 101-102 degrees Fahrenheit, with worsening erythema, pain, and swelling of the left lower extremity. She also developed a new violaceous patch on the left lower extremity and new tender subcutaneous nodules on the right wrist and 4th digit of the left hand. The patient additionally endorsed worsening Raynaud's symptoms, fatigue, and malaise while denying cough, dyspnea, congestion, chest pain, headache, abdominal pain, nausea, vomiting or diarrhea. She was transferred to RUMC for continued management with rheumatology and dermatology.

PAST MEDICAL & SURGICAL HISTORY

The patient had a long-standing history of suspected Sjogren's syndrome treated successfully with hydroxychloroquine until 2015, when she developed worsening joint pains, fatigue, and rash. She was subsequently diagnosed with dermatomyositis, systemic lupus erythematosus and livedo reticularis. For years, her worsening pain was attributed to flares of connective tissue disease, often requiring high doses of prednisone. Symptoms of connective tissue disease continued to progress from 2019-2022, with incomplete response to multiple steroid-sparing agents including rituximab, mycophenolate mofetil, belimumab, azathioprine, methotrexate, IVIg, abatacept, anakinra, and leflunomide. Her symptoms further accelerated during the summer of 2022, and in the fall, failure of tofacitinib prompted a trial of IV pulsed cyclophosphamide and re-initiation of IVIg.

Other past medical history includes diabetes mellitus type 2, fibromyalgia, complex regional pain syndrome, hypothyroidism, supraventricular tachycardia, pericardial effusion, and pulmonary histoplasmosis diagnosed in 2019. Due to intolerance of itraconazole, she was treated with isavuconazole for a 3-month course, at which point urine histoplasma antigen was negative and therapy was discontinued.

FAMILY HISTORY

No pertinent history

SOCIAL HISTORY

No pertinent history

MEDICATIONS
Cyclophosphamide (x 1 dose), IVIg, mycophenolate mofetil, hydroxychloroquine, trimethoprim-sulfamethoxazole prophylaxis, alendronate, bumetanide, metformin, semaglutide, insulin, pregabalin, oxycodone, sildenafil

ALLERGIES
Amoxicillin

PHYSICAL EXAMINATION
Edema of the entire left lower extremity with marked pitting edema from the left mid-thigh to toes; erythema of the left posterior and inner thigh; marked edema with weeping of fluid of the left upper extremity; tender, erythematous nodules on fingers of the right hand, right upper arm and left wrist; pruritic, erythematous and scaly patches of the left lateral leg; violaceous, slightly atrophic plaques on the left anterior knee and right anterior lower leg; sclerodactyly; microstomia.

LABORATORY RESULTS

Normal

CK
aldolase
dsDNA
scl-70
C3/C4
TSH
HIV
CA-125
CEA
CA 19-9
SPEP/UPEP without monoclonal peak
Blood cultures negative
Peripheral smear normal
Cryptococcal antigen

Abnormal

CBC: normocytic anemia
Elevated CRP (158 mg/L)
Elevated ESR (61 mm/hr)
Elevated ferritin (3744 ng/mL) – previous level 9 ng/mL five months prior
Elevated LDH (347 U/L)
Positive urine histoplasma antigen above the limit of quantification
Periodic fever syndromes panel: Variant of Uncertain Significance detected in NLRP12 gene
Cytokine Panel 13: **soluble IL-2R elevated (4597.2 pg/mL)**, IL-10 elevated (15.8 pg/mL), IL-6 elevated (6.2 pg/mL)

IMAGING STUDIES

Left lower extremity Doppler study was negative for deep venous thrombosis; CT imaging of the left lower extremity showed subcutaneous tissue stranding; CT pulmonary angiogram was negative for pulmonary embolism and redemonstrated a stable 0.6 cm subpleural nodule in the lingula.

DERMATOPATHOLOGY

Histopathologic analysis of a punch biopsy of the left thigh revealed an unremarkable epidermis and dermal epidermal junction. Within the superficial dermis there was minimal inflammatory cell infiltrate associated with extravasated red blood cells. The subcutaneous tissue showed no significant pathologic changes. Deeper sections and PAS stains were examined and were unrevealing. The pathology result was consistent with multiple previous skin biopsies.

MICROBIOLOGY

Tissue culture growing dimorphic fungi speciated as histoplasma capsulatum by DNA sequencing.

DIAGNOSIS

Disseminated histoplasmosis

CLINICAL COURSE

After consultation with infectious disease, treatment with IV liposomal amphotericin B was initiated at 3 mg/kg daily. The patient's home mycophenolate mofetil was held to reduce immunosuppression and her prednisone was cautiously tapered by endocrinology. She was discharged home on isavuconazole 372 mg every 8 hours for 6 doses, followed by 372 mg daily for 6-12 months. At one month follow-up, she had improvement in erythema, edema, and induration of the lower extremities, though the tightness in her hands and pain associated with her subcutaneous nodules persisted. She additionally noted worsening of her arthralgias and proximal muscle weakness with tapering immunosuppression.

DISCUSSION

Histoplasma capsulatum is dimorphic fungus endemic to specific regions of the United States, most notably the Ohio and Mississippi river valleys and the southeastern states. It can also be found in other parts of the world including Central and South America, Africa, Asia, and Australia. It thrives in soil containing large quantities of bat or bird droppings. Persons become infected with histoplasma after breathing in the fungal spores, which transform into yeast once inside the body. Most infected individuals develop mild self-limited respiratory symptoms or are asymptomatic. In immunocompromised hosts, however, the infection can be severe and disseminate via hematogenous spread to other parts of the body.[1] Patients with autoimmune connective tissue disease (ACTD) may be susceptible to this dissemination due to disease-related immune abnormalities and organ system dysfunction, as well as the immunosuppressive agents used to treat them.

The most common symptoms of disseminated histoplasmosis (DH) are fever, fatigue, and weight loss. These symptoms, along with other clinical findings such as pleural effusion, pericarditis,

endocarditis, myalgias, arthralgias, lymphadenopathy, hepatosplenomegaly, elevations in liver enzymes, and pancytopenia, are also associated with ACTD.[2] Further, while approximately 10-15% of cases of DH have cutaneous manifestations, most are immunologic reactions such as erythema nodosum or erythema multiforme. Less commonly the fungus itself spreads to infect the skin, causing pustules, papules, plaques, nodules and, rarely, cellulitis. In ACTD, it has been hypothesized that underlying microangiopathy makes the soft tissues more vulnerable to invasion by histoplasma, leading to cutaneous findings that may mimic flares of those diseases.[3]

Several cases have described DH mimicking cutaneous and rheumatologic signs of ACTD. Such cases include four patients with dermatomyositis presenting with panniculitis as the predominant manifestation of DH,[2,4] and another patient with dermatomyositis presenting with myositis, fasciitis, and yeast on biopsy. [3] There have also been reports of patients with rheumatoid arthritis on immunosuppression who have developed panniculitis, focal myositis, and other signs of dermatomyositis that have been determined to be secondary to DH.[5,6] In patients with systemic lupus erythematosus, DH has presented as acute multifocal tenosynovitis and polyarthritis, both of which could be mistaken for symptoms of ACTD.[7,8] To our knowledge, this is the first reported case of DH mimicking acute inflammatory edema in a patient with ACTD.

This overlap in presentation may contribute to delayed diagnosis of DH in patients with ACTD. Such misdiagnoses can lead clinicians to increase immunosuppression, leading to progression of the fungal infection. The large number of possible opportunistic infections in patients undergoing immunosuppression for ACTD further contributes to the diagnostic uncertainty. In the case of our patient, gradual progression of her symptoms prompted escalation of her immunotherapy to cyclophosphamide. While her acute deterioration following cyclophosphamide resembled flare of her autoimmune disease, her history of pulmonary histoplasmosis, as well as inadequate response to heavy immunosuppression, prompted investigation for an infectious etiology.

Previous studies indicate urine histoplasma antigen is positive in approximately 90 percent of patients with DH, although cross reactivity with other disseminated fungal infections, particularly blastomycosis, is common.[9] In patients with cutaneous findings, skin biopsy for tissue culture is an important component of diagnosis. DNA sequencing of the mold growth is highly specific and the preferred confirmatory test.[10] In terms of histopathologic evaluation, special stains with methenamine silver or periodic acid-Schiff are usually required to visualize the tiny 2-4 micron yeast structures, however, absence of such findings does not exclude the diagnosis.[10] Elevated alkaline phosphatase levels, pancytopenia, an increased Westergren sedimentation rate, elevated C-reactive protein levels, high lactate dehydrogenase levels, and increased ferritin expression are non-specific laboratory findings suggestive of a diagnosis of DH in the appropriate patient.[10] In addition, previous reports indicate that soluble IL-2 receptor levels are a useful biomarker for disease activity in patients with DH.[11] Interestingly, both ferritin and soluble IL-2 receptor levels were markedly elevated in our patient and decreased with initiation of anti-fungal therapy.

Treatment is indicated for all patients with DH. Acute disseminated infections are progressive and fatal over a two to 12-week period, while chronic disseminated infections may display recurrent illness over the period of years and are ultimately fatal if untreated.[12,13] Patients with severe disseminated disease are initially treated with a lipid formulation of IV amphotericin B

with subsequent transition to oral itraconazole upon clinical improvement. Limited data exists on the use of isavuconazole for the treatment of DH and there are no clinical trials that have compared the efficacy of different azoles for this condition.[14] This case highlights a unique presentation and treatment of DH in an immunocompromised patient with confounding connective tissue disease.

Key Points:

- Disseminated histoplasmosis can mimic a flare of autoimmune connective tissue disease in patients carrying those diagnoses.
- Opportunistic infections are an important differential diagnosis in patients with autoimmune connective tissue disease, especially in cases of acute progression that may require escalation of immunosuppressive therapy.
- Tissue culture can be an important diagnostic test in these patients.
- Soluble IL-2 receptor levels can serve as a useful biomarker for disease activity in cases of disseminated histoplasmosis.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 4

Presented by Morgan M. Decker, MD, MS, MacKenzie J. Griffith, BS, Penelope K. Skopis, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 48-year-old woman with a history of hypothyroidism, hypertension, and anxiety presented to the hospital with a 3-week history of nausea, vomiting, and generalized fatigue. Two weeks prior to presentation, the patient developed a non-pruritic, non-tender rash on the right cheek that spread to her forehead, left cheek, and nose. The patient denied a history of acne, recent travel, or new hair/makeup products.

The patient was admitted for fever of unknown origin, leukopenia, and axillary lymphadenopathy noted incidentally on CT angiogram of the chest. Interventional radiology was consulted to perform a core needle biopsy of an axillary lymph node, and dermatology was consulted for further evaluation.

PAST MEDICAL & SURGICAL HISTORY

Hypothyroidism in the setting of Grave's disease status post radioiodine ablation, hypertension, morbid obesity, anxiety

MEDICATIONS

Clonazepam, levothyroxine, hydrochlorothiazide, sertraline

REVIEW OF SYSTEMS

Positive for headache, generalized fatigue, decreased appetite, nausea, vomiting

PHYSICAL EXAMINATION

Erythematous-to-violaceous follicularly-centered papules and macules with some overlying crust involving the bilateral preauricular cheeks, forehead at hairline, and nasal dorsum.

LABORATORY RESULTS

CBC with differential notable for neutrophil-predominant leukocytosis (WBC 13.02, Neutrophil # 10.25, neutrophils % 78.7), normocytic anemia (Hgb 11.0, MCV 78.6, RDW 16.3), thrombocytopenia (PC 111)

CMP notable for bicytopenia (WBC 2.43, Hgb 9.0), hyponatremia (134), elevated transaminases (AST 126, ALT 46), elevated D-dimer (1.72) elevated ESR (126), elevated CRP (35.4), positive ANA (>1:1,280) with nucleolar pattern, positive anti-Smith (>8.0), and decreased C3 (133).

IMAGING STUDIES

CT angiogram of chest – Extensive bilateral axillary and subpectoral lymphadenopathy
Core needle biopsy, right axillary lymph node – Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease)

DERMATOPATHOLOGY

Punch biopsy, left forehead – lymphohistiocytic inflammation centered on a follicle with prominent karyorrhexis and rarity of neutrophils. GMS and Fite stains were negative for microorganisms.

DIAGNOSIS

Kikuchi-Fujimoto disease

CLINICAL COURSE

The patient exhibited improvement with the initiation of prednisone 40 mg daily and hydroxychloroquine 400 mg daily. The patient reported no new skin lesions at 2-week outpatient follow-up, but endorsed persistence of existing acneiform eruption. The patient was prescribed topical tacrolimus 0.1% ointment to the affected areas on face twice daily which led to resolution with postinflammatory hyperpigmented macules over the subsequent four weeks.

DISCUSSION

First described in 1972 in Japan, Kikuchi-Fuijimoto disease (KFD), also known as necrotizing histiocytic lymphadenitis, is a benign, self-limiting condition characterized by fever and lymphadenopathy with nausea, vomiting, weight loss, myalgias, and skin lesions reported in a subset of affected patients.[1,2] The underlying cause is unknown, but it has been hypothesized to represent an exuberant CD8+ T cell-mediated immune response to an infectious agent in genetically susceptible individuals.[3] Epstein-Barr virus, human immunodeficiency virus, human herpes virus 6, human herpes virus 8, and human T lymphotropic virus have been suggested as possible inciting triggers.[1,4] KFD typically affects young adults less than 40 years of age and has been associated with various autoimmune diseases including Grave's disease, Sjogren's syndrome, rheumatoid arthritis, Still's disease, and most importantly SLE.[1] While the relationship between KFD and SLE is not completely understood, SLE may be present before, after, or simultaneously with the diagnosis of KFD.

Definitive diagnosis requires lymph node biopsy, and histopathology can be important in distinguishing KFD from other more serious lymphadenopathies, such as infectious lymphadenopathies (toxoplasmosis, mononucleosis, tuberculosis), lymphoma, and metastatic disease.[1] Microscopic features of lymph node biopsy in KFD include paracortical necrosis and a histiocytic infiltrate.[5] KFD often resolves spontaneously within months of diagnosis, however, in severe cases nonsteroidal anti-inflammatory agents, oral corticosteroids, hydroxychloroquine, methotrexate, and IVIg have been used.[5]

Cutaneous findings have been reported in 40% of cases. Skin findings in KFD are typically nonspecific, manifesting as erythematous macules or patches, papules or plaques, or a maculopapular eruption.[5] Additional reported cutaneous findings include subcutaneous nodules and erythema multiforme.[6] One case of KFD presenting with an acneiform rash has been previously reported.[7] Histopathology of skin biopsies in KFD may exhibit distinctive findings that include dermal lymphohistiocytic infiltrate, necrotic epidermal keratinocytes, non-neutrophilic karyorrhexis, basal vacuolar change, and papillary dermal edema. Immunohistochemistry staining for CD68 is occasionally used to evaluate for histocytes.[5]

In conclusion, KFD should be considered when a patient presents with fevers, lymphadenopathy, and an acneiform rash for which another cause cannot be identified. A lymph node biopsy is essential to establish the diagnosis of KFD, and ANA screening with intermittent clinical evaluation for the development of autoimmune disease, particularly SLE, is recommended.

Key Points:

- KFD should be considered in patients with fever, lymphadenopathy, and an acneiform eruption for which another cause cannot be identified
- Lymph node biopsy is essential to establish diagnosis of KFD
- ANA screening and intermittent clinical evaluation for the development of autoimmune disease, particularly SLE, is recommended

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 5

Presented by Emily Medhus, DO, Penelope Skopis, MD, Pamela Madu, MD.
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 29-year-old female presented for evaluation of a patch of alopecia on the occipital scalp. She first noticed the hair loss 6 weeks prior to presentation, during a prolonged hospital admission for complications related to an intentional overdose. The patch of alopecia had not changed in size or shape. It was mildly pruritic. She denied other areas of hair loss or thinning. Eyebrows were intact and body hair was normal.

PAST MEDICAL & SURGICAL HISTORY

Bipolar depression

FAMILY HISTORY

Noncontributory

SOCIAL HISTORY

Denied tobacco, alcohol, or drug use.

MEDICATIONS

Lithium, melatonin, acetaminophen, polyethylene glycol

ALLERGIES

NKDA

PHYSICAL EXAMINATION

3.8 x 2.9 cm slightly square-shaped, alopecic patch on the occipital scalp with heterogenous pink and brown discoloration centrally, comedone-like black dots scattered throughout, and several broken hairs of similar length.
Eyebrows were intact and body hair density was normal.

LABORATORY RESULTS

Treponemal antibody non-reactive
HIV 1/2 antibodies and antigen non-reactive
CBC notable for normocytic anemia (hgb 11.0, MCV 89.9) and thrombocytosis (plt 567)

DERMATOPATHOLOGY

A punch biopsy was taken from the involved occipital scalp for histopathologic analysis. The sample was then sectioned horizontally at multiple levels. Findings included a normal number of hair follicles, 100% of which were in the catagen/telogen phase, prominent perifollicular fibrosis, scattered foci of pigmentation and apoptotic bodies within the majority of follicles, and numerous lipid laden macrophages and lymphocytes within the subcutaneous tissue where there was also fat necrosis.

DIAGNOSIS
Pressure-induced alopecia

CLINICAL COURSE
The patient was started on topical minoxidil 5% foam applied to the affected area twice daily. She was counseled on limited potential for regrowth based on presence of scarring. We recommended a 3 month follow up, but the patient has not yet scheduled the appointment.

DISCUSSION
Pressure-induced alopecia (PA) is an important cause of alopecia to keep in mind for patients with a history of prolonged hospitalization, long surgeries, or immobilization. Prolonged pressure on the scalp results in ischemia of the underlying tissue and damage to the follicular unit.[1] The resulting alopecia can be scarring or nonscarring depending on the length of tissue hypoxia.[2]

Clinically, PA can mimic other causes of hair loss including alopecia areata and trichotillomania. While a history of recent surgery or immobilization is important, this information may not be readily provided by the patient. Instead, there are clinical clues and specific histopathologic findings that can be helpful in establishing the diagnosis.

The presence of a focal alopecic patch distributed over an area of bony prominence, specifically the occipital or vertex scalp, is a primary feature of PA. There may be broken hairs of similar length within the patches of alopecia, which has been attributed to insult affecting all follicles simultaneously.[3] While broken hairs are commonly seen in trichotillomania, they will not be of the same length.[3]

On trichoscopy, the presence of comedone-like black dots has been shown to be specific to PA.[4] While trichoscopy can be helpful in identifying this feature, the black dots are often large enough to be seen by the naked eye, as is the case with our patient. This clinical feature is likely explained histologically by the scattered foci of pigmentation and apoptotic bodies with the hair follicles.

One very characteristic histological finding of PA is the presence of all hair follicles in catagen/telogen phase.[5] This finding is not seen in other types of alopecia and is a distinguishing feature. Features of scarring, including perifollicular fibrosis, apoptotic bodies within the hair follicles, and fat necrosis, are nonspecific but useful for guiding patient expectations. The presence of scarring indicates permanent hair loss, and this should be appropriately communicated to the patient.

If scarring is not present, prognosis is good and spontaneous hair regrowth is typically seen within 12 weeks.[6] Supportive therapies such as topical minoxidil 5% solution or foam can also be used. Ultimately, the potential for hair regrowth is dependent on the extent of damage done. Of course, the primary goal should be to prevent PA from occurring in the first place, which can be achieved through pressure offloading measures and frequent patient repositioning.

Key Points:

- Pressure-induced alopecia is an uncommon cause of hair loss and can be either scarring or nonscarring.
- PA can mimic other types of alopecia including alopecia areata and trichotillomania.
- Comedone-like black dots on trichoscopy is a specific finding for PA.
- Conversion of all hair follicles to catagen/telogen phase is a highly characteristic histopathologic finding.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 6

Presented by Katie Emerson, MD, Rachel Sadowsky, BA, and David C. Reid, MD
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HISTORY OF PRESENT ILLNESS

A 65-year-old man presented with three weeks of enlarging left infraorbital erythema, swelling, and ulceration. Three months prior, the patient had traveled to Yucatán, Mexico, where he went cave diving in the jungle. He recalled an initial small papule that developed in the affected area during his trip. Further travel history revealed visits to Costa Rica and the Dominican Republic within the last seven years. He was initially treated with antibiotics without clinical improvement. He then underwent a skin biopsy at an outside institution, which revealed ulcerated epidermis with marked dermal chronic histiocytes and amastigotes on Giemsa stain, consistent with cutaneous leishmaniasis (CL). He received six doses of amphotericin B over nine days, but the course was complicated by nephrotoxicity, with a creatinine elevation to 1.71 mg/dL. Amphotericin B was discontinued, and renal function normalized. He then completed one month of oral fluconazole without improvement in the lesion. The patient presented to our dermatology clinic with worsening pain and an enlarging ulceration, now two months after the onset of the lesion. He denied any fevers, abdominal pain, nausea, vomiting, nasal pain, or discharge.

PAST MEDICAL & SURGICAL HISTORY

Hypertension
Substance abuse disorder
Cirrhosis from chronic hepatitis C

FAMILY HISTORY

Not pertinent

SOCIAL HISTORY

Non-smoker

MEDICATIONS

Furosemide
Buprenorphine-naloxone

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Left infraorbital region: 4.0 × 2.0 cm shallow ulceration with raised, erythematous borders and a 2.0 × 2.0 cm nodular area at the superior edge.

DERMATOPATHOLOGY

3mm punch biopsy: granulomatous inflammation and abundant lymphoplasmacytic infiltrate without visualization of amastigotes.
PCR assay using mini exon DNA: identification of species as *Leishmania mexicana*.

DIAGNOSIS

Complex cutaneous leishmaniasis from *L. mexicana*

CLINCIAL COURSE

Given the proximity of the ulceration to the lacrimal duct system and sinonasal cavity, the patient was referred to otolaryngology for diagnostic endoscopy, which did not reveal any evidence of mucosal disease. After consultation with the Centers for Disease Control and Prevention, the patient was started on oral miltefosine 50 mg three times daily for 28 days. He reported nausea and emesis within several hours of taking miltefosine, which was managed with pre-dose odansetron. After four weeks of miltefosine therapy, the lesion decreased in size and there was re-epithelialization of the distal ulcer edge and eschar formation over the remainder of the ulcer.

DISCUSSION

Leishmaniasis is a parasitic disease caused by over 20 known *Leishmania* species worldwide and is transmitted by the bite of female sandflies.[1] Three main clinical syndromes manifest as cutaneous, mucocutaneous, or visceral disease. Cutaneous leishmaniasis (CL) is the most frequently reported clinical syndrome with an estimated one million annual cases worldwide.[2] Geographical distribution is used to classify *Leishmania* species as Old or New World CL, and definitive speciation is made by polymerase-chain-reaction (PCR) assay.[3] Old World species are endemic to the Middle East, the Mediterranean Basin, northeast Africa, and southeast Asia, while New World species are found in Central and South America.[1,3] While CL can spontaneously heal over a period of 2 to 15 months, systemic treatment may be necessary for complex lesions, cosmetic concerns, or patients with a high risk of disease progression.[4,5] Complex CL is broadly defined by either infection of an immunocompromised host, infection by a species known for mucocutaneous involvement, large or numerous lesions, lesions involving areas unsuitable for local treatment, or continued lesions after failure of local treatment.[1,3,4] Efforts to identify appropriate therapeutic regimens for complex CL have been complicated by significant toxicities and limited by variability in treatment efficacy among species.[4]
As few autochthonous cases of leishmaniasis have been reported in North America, the Pan American Health Organization recommends obtaining a detailed travel history when investigating cases.[2] Given the patient's remote history of travel to Costa Rica, where *L. panamensis* threatens mucocutaneous involvement, he underwent a negative nasal endoscopy. He also had recent travel to Mexico, where *L. braziliensis* and *L. mexicana* are the most common causes of CL in the country, and *L. infantum* contributes to cases of visceral leishmaniasis.[2] The patient's travel history made PCR analysis critical in confirming *L. mexicana* as the causative species, which is associated with cutaneous, diffuse cutaneous, and disseminated cutaneous leishmaniasis.[1]

Our patient exhibited the typical clinical manifestation of CL - initial small papular lesions followed by enlargement and ulceration over the course of several months.[6] Because many CL

infections resolve clinically without treatment, decision on whom to treat are based on several factors, and the Infectious Diseases Society of America has published guidelines for treatment of CL with local or systemic therapy.[7] This case of complex CL warranted systemic treatment due to the facial lesion location, concern for progression and scarring, and previous treatment failure.

There is a relative paucity of *L. mexicana* cases worldwide and no consensus on an ideal treatment regimen. Antimonials such as sodium stibogluconate were traditionally used to treat leishmaniasis, but these are not currently approved for use in the United States.[7] While amphotericin B is frequently used, nephrotoxicity, which developed in our patient, is a well-documented adverse effect. Oral "azoles" have shown good cure rates for several Old and New World *Leishmania* species, including *L. mexicana,* yet treatment failure remains common, and oral fluconazole yielded no clinical improvement in our patient.[4]

Miltefosine is an oral agent that is thought to disrupt membrane lipids and mitochondrial function in leishmanial species.[8] The drug was approved by the United States Food and Drug Administration in 2014 for treatment of New World CL caused by *L. panamensis, L. braziliensis,* and *L. guayanensis*.[6] Minimal data exists in the literature regarding the use of miltefosine for *L. mexicana*. One case series studying the use of miltefosine in 26 CL patients included one patient with local facial infection with *L. mexicana*, whose clinical outcome met criteria for cure after 25 days of treatment with a cumulative dose of 3750 mg.[8] Larger randomized controlled trials have not yet investigated the use of miltefosine in cases of *L. mexicana* CL.

This case offers an example of the successful use of miltefosine in a patient with proven *Leishmania mexicana* for whom initial therapies were inefficacious and with cosmetically sensitive facial subunit involvement requiring more aggressive therapy. Further research of the therapeutic effect of miltefosine and other antileishmanial therapies against *L. mexicana* and other New World *Leishmania* species is warranted.

Key Points:

- Consider leishmaniasis in the setting of travel to an endemic area
- Travel history and PCR analysis critical
- May self-resolve; however, complex cases necessitate systemic therapy
- Miltefosine: promising therapy for *L. mexicana* cutaneous leishmaniasis
- Further research warranted

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 7

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HISTORY OF PRESENT ILLNESS

74-year-old male with history of type II diabetes mellitus presenting for a 5-year history of progressive pruritic skin lesions. The lesions first developed on his chest, then spread to involve his face, ears, neck, back, abdomen, upper extremities, and proximal lower extremities. He denied any systemic symptoms including fevers, chills, weight loss, fatigue, bone pain, shortness of breath, chest pain, difficulty breathing, abdominal pain, or neurologic symptoms.

PAST MEDICAL & SURGICAL HISTORY

Type II diabetes mellitus

FAMILY HISTORY

No history of lymphoproliferative disorders.

SOCIAL HISTORY

No tobacco or drug use.

MEDICATIONS

Aspirin, empagliflozin, enalapril, glyburide, sildenafil, tamsulosin, insulin glargine

ALLERGIES

None

PHYSICAL EXAMINATION

Diffuse pink-to-orange papules, nodules, and small plaques involving face, neck, ears, chest, upper abdomen, upper back, upper extremities, and right proximal lower extremity.

LABORATORY RESULTS

CBC with differential and CMP within normal limits. Elevated LDH and hyperlipidemia. HBV and HCV negative.

IMAGING AND DIAGNOSTIC STUDIES

PET-CT consistent with primary cutaneous disease.

Bone marrow biopsy with normocellular marrow for age with trilineage hematopoiesis and no morphological evidence of involvement by a lymphoproliferative disorder/dendritic cell neoplasm.

DERMATOPATHOLOGY

A 4mm punch biopsy showed an epithelioid histiocytic proliferation in the dermis extending into the subcutis with a background of small lymphocytic infiltrate. The cells had grooved nuclei with abundant cytoplasm and occasional mitotic figures were noted.

Immunohistochemistry showed the proliferation was positive for CD1a, CD56 and variably positive for CD4 but negative for CD163, CD68, S100, Langerin, Cyclin D1, MPO, CD21 and CD23. No mutation was detected in BRAF Codon 600.

DIAGNOSIS

Indeterminate cell histiocytosis

CLINICAL COURSE

The patient was started on cobimetinib, a MEK inhibitor, starting at 60 mg daily for three weeks on and one week off. At the one-month follow-up, the patient's skin was significantly less red and indurated, and he noticed improvement in pruritus. At the two-month follow-up, there was continued improvement in cutaneous symptoms with flattening of lesions on his chest and back. However, he developed significant edema of the face and ears, and was endorsing systemic symptoms secondary to cobimetinib including decreased appetite and weakness. Therefore, his dose was decreased to 40mg daily for three weeks with a one-week break and an additional week off was given before restarting to help improve overall symptoms. Edema resolved with dose reduction and he noted improvement in systemic symptoms.

DISCUSSION

Indeterminate cell histiocytosis is a rarely reported histiocytic disorder that more commonly affects adults but can also be seen in children. It is often misdiagnosed initially, and classification of the disorder has remained a discussion. The disorder shares features of Langerhans cell histiocytosis, but lacks the pathognomonic Birkbeck granules. Most cases of indeterminate cell histiocytosis are limited to cutaneous involvement. Typical presentation includes generalized skin colored to erythematous papules and nodules involving the head, neck, upper extremities, and trunk [1]. However, rarely extracutaneous involvement has been reported including lymph node, spleen, pancreas, bone, and multi-organ systems [1,2]. Additionally, some cases have been associated with an underlying hematopoietic malignancy [3]. In the most recent systemic review of indeterminate cell histiocytosis, 26% of reported cases were found to have an associated hematologic malignancy with chronic myelomonocytic leukemia being the most common followed by lymphoma and lymphoblastic leukemia [1]. There is currently no standard of treatment. Reported treatments include localized surgical excision, topical steroids, UVB, radiation, and systemic therapies including chemotherapeutic, immunosuppressive, and targeted inhibitor medications [1]. Previous case reports have described successful treatment with methotrexate [4,5], UVB phototherapy [6], and topical 0.5% delgocitinib ointment [7]. For more extensive disease, where greater than 50% of body surface area is involved, efficacy has been reported with etoposide, vinblastine, 2-chlorodeozyadenosine, and cyclophosphamide [8]. A recent systemic review calculated a 5-year overall survival of 62% based on reported cases [1]. Reduced survival was significantly associated with a concomitant diagnosis of acute hematologic malignancy [1]. In patients without an underlying malignancy, 5-year overall survival improved to 90% with a worse prognosis observed in patients with multi-organ system involvement. Children with indeterminate cell histiocytosis had the best overall outcome with the majority achieving complete or partial remission [1].

Cobimetinib is a MEK inhibitor that was approved in October 2022 to treat BRAF negative Langerhans cell histiocytosis. It had previously been approved to treat melanoma. The approval

followed data from a phase II trial of cobimetinib in adults with various histiocytic disorders [9]. Since histiocytic disorders are marked by mutations in the mitogen-activated protein kinase (MAPK) pathway, it was hypothesized that they would be responsive to MEK inhibition. In the small trial of 18 patients, they demonstrated an 89% response rate with 94% remaining progression-free at one year. It showed efficacy in patients regardless of primary mutation. Despite the high response rate, over 50% of patients had their dose reduced during the trial due to an adverse event including reduced ejection fraction, rash, fatigue, diarrhea, and thrombocytopenia [9]. Cobimetinib has not been specifically studied in indeterminant cell histiocytosis. However, given the high response rate, recent FDA approval for BRAF negative Langerhans cell histiocytosis, and lack of standard treatment for indeterminate cell histiocytosis, the decision was made to initiate treatment with cobimetinib for our patient.

Key Points:

- Indeterminant cell histiocytosis is a rare histiocytic disorder with a variable phenotype and clinical course that is often misdiagnosed initially.
- There is no standard of treatment for indeterminant cell histiocytosis and multiple different treatments have been used with varying success.
- Cobimetinib was approved in October 2022 for BRAF negative Langerhans cell histiocytosis and offers a potential new therapeutic option for histiocytic disorders.

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