PROTOCOL BOOK • DECEMBER 11, 2024

CHICAGO DERMATOLOGICAL SOCIETY

Monthly Meeting

Co-hosted by University of Chicago Department of Dermatology

Chicago Dermatological Society

PROTOCOL BOOK
December 11, 2024

Co-hosted by
University of Chicago
Department of Dermatology

Guest Speaker: Dr. Adam Rubin

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INVITED GUEST LECTURER

Dr. Adam Rubin

Adam I. Rubin, MD is the Director of the Section of Dermatopathology, in the Ronald O. Perelman Department of Dermatology at the New York University Grossman School of Medicine, and NYU Langone Health. He also directs the Nail Clinic and sees patients of all ages at NYU Langone Dermatologic Surgery & Cosmetics Associates. Dr. Rubin specializes in nail disorders, nail surgery, and histopathology of the nail unit. He is currently the Editor-in-Chief Elect of the *Journal of Cutaneous Pathology*. Dr. Rubin is the lead editor for the 4th edition of Scher and Daniel's Nails: Diagnosis, Therapy, Surgery. He is an author of the 3rd and 4th editions of the Atlas and Synopsis of Lever's Histopathology of the Skin, and an associate editor of the 11th and 12th editions of Lever's Histopathology of the Skin. Previously he was an associate editor or assistant editor for *Pediatric Dermatology, Dermatologic Surgery*, and *JAMA Dermatology*. Dr. Rubin is a current Member at Large of the Board of Directors of the American Society of Dermatopathology, and was previously a member of the Executive Committee of the International Society for Dermatopathology. He is a board member of the European Nail Society, and directs the annual European Nail Society Nail Histopathology Workshop. Dr. Rubin is the President of the Council for Nail Disorders (CND), and has served as the Secretary-Treasurer and Treasurer of the CND. He was elected as the chair of the Auditing Committee of the International Nail Society. At the American Medical Association (AMA) House of Delegates, Dr. Rubin serves as a delegate from the American Academy of Dermatology. He previously was chair of the Governing Council of the AMA Specialty and Service Society Caucus. Dr. Rubin has served in the AMA as the American Society of Dermatopathology's inaugural advisor to the RUC (AMA/Specialty Society Relative Value Scale Update Committee) advocating for fair payment in dermatopathology. Dr. Rubin has served as the President, Treasurer, and Member at Large of the Executive Committee of the Philadelphia Dermatological Society, as well as an at Large director on the board of the Pennsylvania Academy of Dermatology and Dermatologic Surgery. He served as the Overall Program Chair of the 99th Annual Atlantic Dermatology Conference.

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PROGRAM

Co-hosted by
University of Chicago
Department of Dermatology

December 11, 2024
Gleacher 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: Common Nail Clinic Consults and How to Manage Them** *Adam Rubin, 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: Nail Surgical Procedures for the General Dermatologist** *Adam Rubin, MD*
2:00 p.m.	**Program adjourns**

AT THE FOREFRONT
UChicago Medicine

University of Chicago
Department of Dermatology

Chicago Dermatological Society Meeting
December 11, 2024

Dermatology Residents

Fourth Year
Sarah Semaan, MD
Gaurav Agnihotri, MD
Colton Funkhouser, MD
Liesl Schroedl, MD

Third Year
Kelsey Gradwohl, MD
Victoria Lee, MD, PhD
Mina-Abena Maranga, MD, MSc

Second Year
Alanna Shefler, MD
Sneha Butala, MD
Grace Wei, MD, MPH, MSc

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Resident Case Presentations & Discussion

PRESENTERS

Alanna Shefler MD; Diana Bolotin MD; Mark D. Hoffman MD; Oluwakemi Onajin MD; Christopher R. Shea MD

Patient A

HISTORY OF PRESENT ILLNESS

A 53-year-old white male presented to the University of Chicago Dermatology Section for evaluation of a growth on his right index finger that had been present for at least 10 years. He was initially seen by our department in 2014 for an asymptomatic, discolored, and thickened right index fingernail. He failed initial treatment with ciclopirox 8% topical solution, so his right index nail plate was curetted in 2016 and sent for histologic interpretation that showed "nail plate with serum and parakeratosis", findings that can be seen following trauma. He was treated with terbinafine 250 mg daily for 90 days for onychomycosis of multiple toenails with resolution of toenail findings. However, his right index fingernail continued to remain thickened and dystrophic, so he was additionally treated with fluconazole 50 mg weekly for 28 weeks without improvement. A subsequent fungal culture was negative. Given concern for possible wart, he was then treated with cryotherapy followed by intralesional Candida antigen on two occasions with minimal to no improvement. Due to treatment resistance, a nail matrix/bed biopsy was recommended for definitive diagnosis.

PAST MEDICAL HISTORY

Basal cell carcinoma, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease

FAMILY HISTORY

No pertinent family history.

SOCIAL HISTORY

No pertinent social history.

MEDICATIONS

Atorvastatin, chlorthalidone, insulin glargine, insulin lispro, olmesartan

ALLERGIES

No pertinent allergies.

PHYSICAL EXAMINATION

Dermatologic examination revealed a dystrophic right index fingernail with hyperkeratosis on the radial side of the nail and yellow-brown longitudinal discoloration with increased transverse and longitudinal curvature. The proximal nail fold was erythematous and edematous. The other fingernails and toenails were unaffected.

Intraoperative examination revealed a pink exophytic papule with filiform projections along the nail distal matrix/proximal nail bed, which was shave excised with a 15 blade.

LABORATORY RESULTS
Nail plate fungal culture was negative and bacterial culture demonstrated methicillin-sensitive *Staphylococcus aureus* (MSSA).

IMAGING
No pertinent imaging.

DERMATOPATHOLOGY
Histopathologic analysis of the nail plate demonstrated columns of serous collections and a papillomatous proliferation of the nail epithelium with areas of spongiosis. Histopathologic analysis of the nail bed showed a papillomatous proliferation of the epidermis with interconnecting strands. The dermis had a population of plump spindled cells with round to elongated nuclei. No significant atypia was identified in the nail plate or bed.

DIAGNOSIS
Onychomatricoma

TREATMENT & COURSE
The patient was seen in the Dermatology Procedures unit for nail avulsion and biopsy. The hyperkeratotic nail bed was avulsed and sent for both histopathologic and microbiologic evaluations. Upon avulsion, an exophytic papillomatous papule was noted and shave excised. The base of the excision was treated with cautery. The patient was advised to continue with wound care with mupirocin ointment for 2 weeks.

Given the benign pathologic findings, clinical monitoring for recurrence and symptoms was recommended. Since the patient was treated with mupirocin post-operatively, no further treatment for MSSA was recommended.

At 6-month follow-up, there was significant improvement of the hyperkeratosis of the fingernail with a small residual focus of hyperkeratosis present proximally. There was also mild residual nail dystrophy of the affected side of the nail. The finger was asymptomatic and the patient elected to continue to monitor the area clinically.

Patient B

HISTORY OF PRESENT ILLNESS
A 72-year-old African American female presented to the University of Chicago Dermatology Section with a one-year history of tender, discolored, and disfigured fingernails and toenails. She reported 7/10 fingernails and all toenails were affected. She had not tried any treatments for these changes. She reported no other skin or mucosal changes. Her only new medication during this time was hydralazine, which was discontinued.

PAST MEDICAL HISTORY
End stage renal disease, renal cell carcinoma (RCC) s/p right nephrectomy in 2013 with recurrent metastatic RCC to liver

FAMILY HISTORY
No pertinent family history.

SOCIAL HISTORY
Previously worked as a forklift operator.

MEDICATIONS
Losartan, sevelamer, spironolactone

ALLERGIES
No pertinent allergies.

PHYSICAL EXAMINATION
Examination revealed several fingernails (L5, R1, R2) and all 10 toenails with green-yellow longitudinal discoloration of the entire nail plate for the majority affected, along with associated subungual debris, pachyonychia (thickening of the nail plate), and dystrophy. Pincer nail deformities were noted on several fingernails and toenails. Several fingernails (L4, R4, R5) demonstrated proximal leukonychia. Under the distal edge of the left first toenail plate was a bulbous tumor.

LABORATORY RESULTS
Culture of her fingernail demonstrated *Candida parapsilosis* complex. Her GFR was 6 and platelets and albumin were within normal limits.

IMAGING
No pertinent imaging.

DERMATOPATHOLOGY
Histopathologic analysis of her right first fingernail clipping demonstrated bacteria and debris in addition to multiple discrete round to oval spaces filled with serum. GMS stain failed to highlight fungal elements.

DIAGNOSIS
Onychomatricoma

TREATMENT & COURSE
Avulsion by hand surgery was considered. She was subsequently lost to follow-up and died from non-dermatologic complications.

DISCUSSION
Onychomatricoma is a rare, benign, fibroepithelial tumor of the nail matrix that was first described by Baran and Kint in 1992 [1, 2]. It affects females more than males and has a predilection for fingernails over toenails [3, 4]. Multiple nails may be affected, as was documented in Baran and Kint's original series. It is extremely rare in children with one case report to date [5]. Some authors have suggested that onychomatricomas represent reactive tumors, with trauma to the nail contributing to tumor development [6, 7]. Clinically, an

onychomatricoma presents as longitudinal yellow discoloration (xanthonychia), a thickened plate (pachyonychia) with increased transverse and longitudinal curvature, and multiple holes at the distal margin of the nail plate (described as woodworm or honeycomb) [2, 8, 9]. It can involve either part of or the entire nail, and proximal nail-fold swelling may occur [10, 11]. Situated beneath the proximal nailfold, the tumor consists of fibroepithelial projections that grow longitudinally toward the distal edge, leading to changes of the nailfold [12]. Rarely, an onychomatricoma can result in a pincer nail deformity, as described in one case report [13]. Dermoscopy of onychomatricoma may reveal longitudinal parallel yellow and white lines, splinter hemorrhages, dark dots, thickening of the free edge, and honey-comb or 'woodworm' like spaces at the free margin containing white, yellowish, or black material [12, 14]. Some authors suggest that when classic clinical findings are present along with corresponding nail clipping changes, a nail matrix biopsy may be omitted [12, 15]. Specifically, nail clippings should demonstrate a thickened nail plate with multiple serum-filled cavities and lined by matrix epithelium [2, 9].

Biopsy and excision with histopathologic evaluation, however, is often necessary for definitive diagnosis. Histopathologically, the nail matrix demonstrates deep invaginations filled with a thick V-shaped keratogenous zone and the nail plate portrays multiple channels lined by papillary projections of nail matrix epithelium [3, 10]. The mesenchymal component reveals spindle cells with a collagenous to myxoid stroma, and may occasionally demonstrate slight to severe atypia or a high nuclear-to-cytoplasmic ratio [10]. Immunohistochemically, these spindle cells in the dermis are almost always CD34+ and CD10+ [3, 10, 16]. One recent study demonstrated RB1 loss in the mesenchymal component of an onychomatricoma, whereas the proliferated nail matrix retained RB1 expression – suggesting that an onychomatricoma should be considered a fibrous neoplasm rather than a fibroepithelial neoplasm [10]. Array-based comparative genomic hybridization has shown genomic losses on chromosome 11, 13, and 16 [10, 15].

Onychomatricomas affecting multiple digits is thought to be unusual. A review of the relevant literature discloses one recent letter to the editor, which describes two cases of onychomatricomas affecting three and four fingernails, respectively [8]. One of the cases involved repeated trauma to the nails. Both cases underwent surgical excision with pathologic examination confirming the diagnosis [8].

We present this case series to highlight a rare nail matrix tumor and its associated evaluation and management.

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PRESENTERS
Kelsey Gradwohl MD, Liesl Schroedl MD, Sarah Stein MD, Mark D. Hoffman, MD, Angad Chadha, MD and Christopher R. Shea MD

HISTORY OF PRESENT ILLNESS
A 63-year-old woman presented to clinic with a 4–5-month history of a rash that started on her right lateral thigh and spread to her bilateral upper arms. The skin lesions were tender initially and then became slightly itchy. She had started valsartan 1 month prior to rash onset but had no other medication changes. She stated no history of weight loss, night sweats, fevers, chills, swollen lymph nodes, fatigue, joint or bone pain, oral sores, or recent infection.

PAST MEDICAL HISTORY
Hypertension, hyperlipidemia, depression, stroke, cataracts, and iron deficiency anemia

FAMILY HISTORY
Bladder cancer (mother) and prostate cancer (father)

MEDICATIONS
Valsartan, venlafaxine and bupropion

ALLERGIES
Cephalexin, fenofibrate, iodine, and statins

PHYSICAL EXAMINATION
Patient was well appearing and in no apparent distress. Vital signs were within normal limits. On the left cheek there was an ill-defined erythematous slightly pebbly firm plaque. On the chest there were numerous erythematous to violaceous ill-defined firm thin plaques. On the bilateral upper arms and right lateral thigh there were numerous erythematous to violaceus firm round to oval dermal plaques without epidermal change. Of note on the left upper arm there was a grid-like pattern of punched out atrophic scars which the patient reported was unrelated and long standing, related to a prior vaccination.

LABORATORY RESULTS
Complete blood count with differential, complete metabolic panel, antinuclear antibodies, antineutrophil cytoplasmic antibody, anti-double stranded DNA, anti-histone antibody, rheumatoid factor, cyclic citrullinated peptide antibody, erythrocyte sedimentation rate and c-reactive protein were unremarkable

DERMATOPATHOLOGY
Histopathologic analysis of a punch biopsy specimen from the left upper arm revealed a Grenz zone and an infiltrate of medium to large, atypical lymphocytes with prominent nucleoli and fine chromatin in the dermis and subcutis but sparing the epidermis. The infiltrate dissected collagen bundles and distributed around the adnexa but true adnexotropism was not identified. There was a moderately dense infiltrate of small lymphocytes surrounding the atypical infiltrate.

Immunohistochemical stains revealed that atypical mononuclear cells were positive for CD4, CD56, CD123, and TdT. Atypical cells were negative for CD20, CD3, CD34, AE1/AE3, CD20, NPM1 and MUM1. There was a mixed population of CD3 and CD20 small lymphocytes with a ratio of 3:1.

Next generation sequencing via OncoPlus Universal Cancer Mutation Analysis Panel did not reveal any pathogenic mutations.

Punch biopsy for direct immunofluorescence of perilesional skin from the left upper arm was non-specific.

DIAGNOSIS

Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

TREATMENT & COURSE

Based on the histopathological diagnosis the patient was immediately referred to Hematology Oncology. She underwent a PET-CT scan that demonstrated avid cutaneous nodules that coincided with her clinical lesions and increased uptake of multiple axillary and inguinal lymph nodes. Maxillofacial CT revealed a confluent soft tissue density of the left ethmoid air cells and subsequent biopsy demonstrated BPDCN with an *RB1 c.1215+1 G>A* mutation. Bone marrow biopsy revealed a hypercellular bone marrow (80% cellularity) with 20% involvement of BPDCN; pathogenic mutations were not identified. Karyotype was normal. No leukemic cells were seen on lumbar puncture or peripheral flow cytometry.

Treatment was initiated with intrathecal cytarabine for central nervous system prophylaxis and tagraxofusp (TAG), a CD-123 targeting recombinant protein used to treat BPDCN. Intravenous TAG was dosed once daily for 5 days to complete the first round of therapy. Bilateral total ethmoidectomy, maxillary antrostomy, and left sphenoidotomy was performed by otolaryngology. One month later, after the first round of TAG therapy, the skin lesions appeared to have resolved with post-inflammatory hyperpigmentation remaining. Repeat punch biopsies from the right upper arm and left upper arm showed no residual BPDCN. Repeat bone marrow biopsy revealed a residual BPDCN population accounting for 3-5% of total. Three months later, and one month after a second round of TAG, recurrent violaceous indurated nodules appeared on the bilateral upper arms; a repeat biopsy from the left upper arm demonstrated recurrent features of BPDCN. TAG was stopped and azacitidine and venetoclax was started with plan to repeat bone marrow biopsy and PET scan after count recovery next month.

DISCUSSION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare acute leukemia that characteristically involves the skin and often the bone marrow and blood. There is estimated to be 0.04 cases per 100,000 people in the United States. It constitutes 0.5% of acute leukemias [1]. The median age of onset is 65-67 years, and it has a male predominance (3:1), but also affects women and children. Although the exact etiology is unknown, 10-20% of patients have concomitant or preexisting hematologic malignancies including, but not limited to, myelodysplastic syndrome, chronic myeloid leukemia or acute myeloid leukemia [2].

The malignant cells in BPDCN arise from plasmacytoid dendritic cell, a unique subset of dendritic cells that produce high levels of type 1 interferons, amongst other immunologic mediators, and play an important role in antiviral immunity and wound healing [3]. These cells normally reside in the blood and lymphatic system and are typically absent in healthy skin, though have been observed in some skin conditions, including psoriasis, contact dermatitis and lupus. It is thought that premalignant BPDCN cells migrate from the lymphoid system to the skin where they undergo malignant transformation in response to ultraviolet radiation exposure [4]. From the skin, malignant blasts spread to the rest of the body. The most common sites of dissemination are the bone marrow, lymph nodes and blood. Central nervous system involvement is frequently observed, and liver involvement is also often seen, especially in the setting of bone marrow involvement. Other affected sites may include the spleen, mucous membranes, tonsils, paranasal cavities, lungs and eyes. Our patient had skin, bone marrow, lymph node, and paranasal cavity involvement.

Skin lesions are often the initial manifestation of DPBCN [3]. Lesions typically appear as red, brown, or purple papules, plaques, nodules or tumors. Some have described the lesions as "bruise-like". Lesions present more commonly on the head and upper trunk than lower extremities. In a retrospective review, 73% of patients presented with a single nodule, 14% with diffuse nodules and 12% with bruise-like patches [5]. Morphology (nodular vs. bruise-like) and extent of skin involvement at initial diagnosis did not appear to affect prognosis which is generally poor [5]. Patients may also present with lymphadenopathy, splenomegaly, signs of anemia (fatigue, pallor), leukopenia (infection) and thrombocytopenia (easy bleeding / bruising).

Histopathology will show a dense collection of monomorphic blasts with fine chromatin, irregular nuclei, and subtle nucleoli within the dermis and subcutis but typically sparing the epidermis and adnexa [6]. There is often a Grenz zone. Immunohistochemical analysis will show the atypical cells stain positive for CD4 and CD56 and at least one plasmacytoid dendritic cell marker such as CD123, TCF4, TCL1, CD303 or CD304. Other stains including CD45, CD43, BCL2 and TDT can be variably positive. Atypical cells will be negative for CD3, CD14, CD16, CD20, CD19, CD34, lysozyme and MPO. Karyotype analysis is often performed and can be abnormal in 50-75% of patients [7]. Next generation sequencing reveals mutations in 82% of patients with TET2 and ASKL1 being the most frequently observed [8]. RB1 mutations, as seen in our patient, have been observed with less frequency, but which is hypothesized to lead to loss of tumor suppressor activity in BPDCN [8].

Once a diagnosis of BPDCN is made, lab work up, imaging (commonly PET-CT), bone marrow aspiration, flow cytometry and lumbar puncture are important to evaluate for lymph node, visceral organ and CNS involvement. Treatment for BPDCN typically involves chemotherapeutics and/or CD123 targeting agents as a bridge to allogenic stem cell transplant which offers the highest chance of complete remission. Unfortunately, as patients with BPDCN are often older with multiple comorbidities, many are not candidates for stem cell transplant. All patients receive intermittent intrathecal chemotherapy (i.e. cytarabine) for CNS prophylaxis. Previously, conventional leukemia chemotherapeutic regimens were used to achieve remission, though with limited success [9]. However, in 2018 tagraxofusp (TAG) was approved for use in BPDCN for those age 2 and older. TAG is a recombinant cytotoxic protein composed of truncated diphtheria toxin fused with human recombinant IL-3 that selectively binds to CD123

(IL-3 receptor alpha subunit) which is highly expressed on blastic plasmacytoid dendritic cells. The receptor and bound TAG protein are then brought into the cell via endocytosis and the truncated diphtheria toxin inactivates elongating factor 2, ultimately leading to cell apoptosis [10]. In a study of 47 patients with BPDCN, 72% achieved complete response defined as complete disappearance of BDCN at each initially involved site [11]. A follow up long-term continued access phase prospective trial of 89 patients found that 75% of patients achieved complete response that was sustained for 24.9 months, and the median survival was 15.9 months [11]. In studies of traditional chemotherapeutic agents, complete remission rates ranged from 40-55% and median survival from 8-14 months [9]. Major side-effects of TAG include elevated aminotransferases, low albumin, thrombocytopenia and capillary leak syndrome. Despite treatment, prognosis is poor in BPDCN due to the high rate of relapse and CNS involvement. Relapsed BPDCN is difficult to treat but some can be managed with venetoclax, a BCL2 inhibitor, and a hypomethylating agent such as azacitidine. There are several clinical trials evaluating new targets and combination therapy which provide hopeful future directions in this difficult to treat condition [1].

We present this case to demonstrate a classic presentation of a rare entity and to highlight the importance of dermatology's role in the diagnosis of BPDCN.

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PRESENTERS
Victoria Lee MD, PhD; Oluwakemi Onajin MD; Christopher Shea MD; Angad Chadha MD

HISTORY OF PRESENT ILLNESS

Case 1
A 59-year-old male with a history of hepatocellular carcinoma on tremelimumab (CTLA4 inhibitor) and durvalumab (PD-L1 inhibitor) presented with a pruritic rash that developed two weeks after receiving the initial dose of tremelimumab and durvalumab (C1D17). This initial eruption was responsive to hydrocortisone 2.5% cream and oral hydroxyzine. However, he presented again on C1D30 with new diffuse skin sloughing involving a large body surface area on the trunk and extremities. The affected areas were associated with pain and burning sensation. Medication review revealed that the patient had recently started taking alprazolam to help with insomnia; however, no other new medication exposures were elucidated.

Case 2
A 72-year-old female with high-grade metastatic endometrial serous adenocarcinoma was transferred to the burn intensive care unit for extensive skin sloughing involving 30% of her body surface area. The patient had previously undergone 3 cycles of neoadjuvant chemotherapy with pembrolizumab (PD-1 inhibitor), carboplatin, and paclitaxel roughly 6 months prior to presentation, followed by cytoreductive surgery and 3 cycles of adjuvant chemotherapy with the same three agents. On C6D27, the patient had developed a mildly pruritic rash that had initially responded to topical triamcinolone cream. The mild dermatosis subsequently progressed into a generalized sloughing eruption 2 weeks later (C6D44).

PAST MEDICAL HISTORY
Case 1: treated hepatitis C, hepatocellular carcinoma on tremelimumab and durvalumab, prostate cancer status post radical prostatectomy, chronic thrombocytopenia, hypertension

Case 2: high-grade metastatic endometrial serous adenocarcinoma, newfound small-bowel obstruction, acute-on-chronic dysphagia, hepatitis C, severe malnutrition, hypothyroidism

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
No pertinent social history

MEDICATIONS
Case 1: tremelimumab, durvalumab, hydrocodone-acetaminophen, lactulose, ondansetron, pantoprazole, alprazolam

Case 2: pembrolizumab, carboplatin, paclitaxel, prednisone, unknown NSAID

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION

Case 1: The eruption on initial presentation consisted of scattered erythematous non-blanching macules on the back, upper arms, and chest. Petechiae were present on the abdomen, right shoulder, right axilla, and dorsal feet. Ocular mucosa, oral mucosa, and acral surfaces were uninvolved. Two weeks later, physical exam revealed diffuse sloughing and numerous flaccid bullae on the chest, back, abdomen and upper extremities. Ocular and genital mucosae were again uninvolved. While a few petechiae were noted initially on the hard palate without much involvement of the oral mucosa, the patient did develop complete erosion and hemorrhagic crusting of the vermilion and mucosal lips a few days later; there were no discrete intraoral erosions noted.

Case 2: Physical examination revealed large violaceous tender patches and thin plaques with erythematous rims and widespread denudation on the scalp, face, ears, trunk, and extremities. There was mild hemorrhagic crusting of the lips; ocular and genital mucosae were uninvolved.

LABORATORY RESULTS

Case 1: Complete blood count was notable for relative eosinophilia in the setting of pancytopenia.

DERMATOPATHOLOGY

Case 1: A punch biopsy was performed and demonstrated full-thickness epidermal necrosis with subepidermal bulla formation, and a superficial perivascular dermal infiltrate of lymphocytes and scattered eosinophils. Direct immunofluorescence analysis was negative.

Case 2: A punch biopsy was performed and demonstrated subepidermal blistering with focally necrotic epidermis overlying the subepidermal split. There were focal areas of dyskeratotic cells with notable interface changes in the basement membrane zone, as well as a lymphocytic perivascular infiltrate in the superficial dermis. Direct immunofluorescence analysis was negative.

DIAGNOSIS

Progressive immunotherapy-related mucocutaneous eruption (PIRME)

TREATMENT & COURSE

Case 1

The patient was started on treatment with prednisone 70 mg daily. During admission the patient developed oral stomatitis, which was managed with oral dexamethasone rinse. Tapering of the prednisone dose to 50 mg was attempted 3 weeks after initiation, but 70 mg was reinstated after his eruption worsened on the lower dose. By week 4 of steroid treatment, areas of previous erosion were healed with full re-epithelialization, and he was discharged with the plan for outpatient tapering of steroids. Unfortunately, the patient re-presented to our emergency room several weeks later with disseminated mucormycosis in the setting of systemic steroid use and was transitioned to hospice care.

Case 2
The patient was started on IV methylprednisolone 40mg daily, which was subsequently tapered by 10 mg per week. All lesions had nearly fully re-epithelialized after 3 weeks of systemic steroid treatment. Unfortunately, because the patient demonstrated rapid progression of her malignancy on first-line neoadjuvant therapy, and because was a poor candidate for further chemotherapy or clinical trials, she was ultimately transitioned to hospice care.

DISCUSSION

Immune-related adverse events (irAEs) secondary to immune checkpoint inhibition (ICI) are an important consideration in the morbidity and mortality of patients. ICI related cutaneous irAE can range from pruritus to various dermatitides (eczematous, psoriasiform, lichenoid, granulomatous, etc.) to widespread epidermal detachment mimicking Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN).[1] Progressive immunotherapy-related mucocutaneous eruption (PIRME) is an increasingly recognized entity involving generalized bullous reaction with full-thickness epidermal necrosis that mimics SJS/TEN both clinically and histopathologically, albeit with some important distinctions.[2,11] While PIRME and SJS-TEN may have overlapping features, PIRME is distinguished by having a delayed onset, polymorphic mild antecedent eruption, rare ocular involvement, excellent response to systemic steroids, and more robust dermal lymphocytic infiltrates.

Both patients featured a milder pruritic eruption that preceded the onset of PIRME by two weeks. In both cases, the milder eruption could be treated topically before the patients presented with widespread skin denudation and oral erosions. The pattern of antecedent mild rash progressing over days to weeks to a generalized bullous eruption with mucositis has been well-reported in PIRME.[2] Various clinical patterns of the antecedent rash have been identified, including lichenoid, urticarial, and morbilliform; both of our patients had antecedent morbilliform rashes.[2] This clinical pattern is notably distinct from SJS/TEN, which has a shorter flu-like prodrome and no antecedent mild rash in the weeks preceding the severe eruption. Ocular involvement was not present in either of our two patients and is infrequently reported in PIRME.[2] This stands in contrast to SJS-TEN, in which ocular involvement occurs in most cases.[3] Further, a favorable, rapid clinical response to systemic corticosteroid therapy has been described in PIRME and was seen in both of our cases above; SJS-TEN, on the other hand, does not consistently respond favorably to systemic steroids.[4-6] Previous reports of PIRME have suggested a benign clinical course; while our two cases demonstrated a relatively benign cutaneous course with good skin healing after steroid therapy, both patients died of non-cutaneous complications. Accordingly, PIRME likely carries prognostic and mortality risk independent of the degree of cutaneous involvement. In contrast, overall mortality in SJS/TEN is estimated to be as high as 23%, most of which is attributed to sequelae from and extent of the skin disease.[6]

Histologically, both of our cases were characterized by full-thickness epidermal necrosis along with moderate to robust superficial and deep perivascular lymphocytic inflammation. Previous reports have also noted interface and lichenoid dermatitis in PIRME.[2] This contrasts with the histopathologic findings in SJS-TEN which, in its fully developed state, features full-thickness epidermal necrosis coupled with mild or minimal dermal lymphocytic inflammation; lichenoid dermatitis is not seen in SJS-TEN and while vacuolar interface dermatitis may be present, the infiltrate is typically mild in comparison with the degree of epidermal necrosis. Further

characterization of these immune infiltrates may potentially inform the underlying pathogenesis of PIRME. Preclinical models of irAEs suggest a predominant cytotoxic T cell infiltrate, though cytotoxic T cells are also believed to play a role in traditional SJS/TEN.[7,8]

We present two cases of PIRME and underscore the differences in clinical presentation and histopathology between PIRME and SJS/TEN, with the goal of highlighting an increasingly recognized clinical entity that must be considered by both clinicians and pathologists when faced with an SJS/TEN-like eruption coupled with the histopathologic finding of full-thickness epidermal necrosis. Previous authors have observed the occurrence of PIRME in patients who were started on ICI and an additional medication at the same time, which might suggest a two-hit hypothesis for PIRME wherein the ICI reduces immune tolerance and leads to severe exacerbations of a mild hypersensitivity eruption to the second medication.[2] Additionally, some authors have suggested that ICI re-challenge after resolution of PIRME may be possible, especially if a second causative medication was started at the same time as the ICI.[9,10] While the two patients presented here were started on a second medication along with the ICI (alprazolam, carboplatin, paclitaxel), we could not perform ICI re-challenge without the second medication and therefore we cannot corroborate or refute this two-hit hypothesis. Further investigation of PIRME and testing of the hypothesis will be valuable in characterizing the immune response and the commonly offending drugs. It will also be important to distinguish whether patients who develop PIRME have a pre-existing sensitivity to the culprit medications, or if ICI therapy confers new hypersensitivity to certain agents. Both will be important in informing clinical management for patients presenting with PIRME. Clinicians should consider broadening their histopathological differential diagnosis to include PIRME when evaluating cutaneous disorders that lead to full-thickness epidermal necrosis in patients receiving ICI.

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PRESENTERS
Colton Funkhouser MD, Oluwakemi Onajin MD, Angad Chadha MD

HISTORY OF PRESENT ILLNESS
A 70-year-old woman was admitted to the hospital for workup of failure to thrive. In addition to 25 pounds of weight loss in the past month, she was found to have violaceous papules and bullae on her upper and lower extremities. She developed worsening renal function, with a kidney biopsy demonstrating crescentic glomerulonephritis.

PAST MEDICAL HISTORY
Hypertension, heart failure with preserved ejection fraction, type 2 diabetes, and hyperlipidemia

FAMILY HISTORY
No family history of dermatologic conditions

MEDICATIONS
Hydralazine, hydrochlorothiazide, spironolactone, furosemide, empagliflozin, and metformin

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Bilateral upper and lower extremities with numerous violaceous edematous coalescing papules and bullae, some in a linear distribution

LABORATORY RESULTS

Laboratory Study	Patient Result	Reference Range
White blood cell count	8.5 x 10^3 /µL	3.5 - 11.0 10^3 /µL
Creatinine	3.71 (baseline 0.6) mg/dL	0.50 – 1.40 mg/dL
CRP	193 mg/L	<5 mg/L
ANA	1:640, homogenous	<1:40
pANCA	1:320	<1:10
Myeloperoxidase Ab	>8.0	<1.0
Proteinase Ab	Negative	

Urinalysis with 3+ blood, 2+ protein, urine RBCs >20
Kidney biopsy with crescentic glomerulonephritis
Unremarkable: C3, C4 anti-dsDNA, SSA, SSB, Sm, RNP, SmRNP, cryoglobulins
Negative: serum cryptococcal antigen, serum histoplasma antigen + antibody, serum aspergillus antigen, blastomyces antibody

DERMATOPATHOLOGY
Initial punch biopsy from the left upper arm demonstrated perivascular neutrophilic inflammation with karyorrhectic debris, fibrinoid necrosis of small and medium vessels, erythrocytes extravasation, and microthombi in the lumen of dermal vessels, consistent with a

vasculitic occlusive vasculopathy. Perioidic acid-Schiff (PAS) and Grocott-Gomori methenamine silver (GMS) special stains were negative. Following clinical progression, a repeat biopsy from the right forearm was performed, demonstrating perivascular neutrophilic inflammation with karyorrhectic debris, fibrinoid necrosis of small and medium vessels, erythrocytes extravasation and vacuolated cells resembling *Cryptococcus* in the dermis, overall consistent with small and medium vessel vasculitis with cryptococcoid features. The vacuolated cells were negative for PAS and GMS and diffusely positive for myeloperoxidase (MPO).

DIAGNOSIS

Cryptococcoid vasculitis secondary to hydralazine

TREATMENT & COURSE

Her initial biopsy was consistent with a vasculitic occlusive vasculopathy, and she was treated with pulse methylprednisolone without improvement. Her renal crescentic glomerulonephritis was favored to be related to the vasculitis. She continued to progress despite the high dose steroids, and in addition to worsening renal function, she developed further tense bullae and violaceous papules and plaques on her extremities. Given this clinical progression, a repeat biopsy was performed demonstrating a small and medium vessel vasculitis with cryptococcoid features. During her hospital stay she had received several intravenous boluses of hydralazine for hypertension in addition to taking hydralazine prior to admission. Given the concern for hydralazine-induced vasculitis, the hydralazine was discontinued. Subsequently her cutaneous involvement and renal function significantly improved. After initially receiving pulse methylprednisolone, she was continued on methylprednisolone 32mg daily. She did not develop any new skin lesions and her existing bullae re-epithelialized.

DISCUSSION

Histological findings mimicking *Cryptococcus* have been reported in the setting of neutrophilic dermatoses[1,2], with fewer reports also describing these findings in the setting of cutaneous vasculitis.[3,4] These cases demonstrate capsule-like vacuolated spaces mimicking *Cryptococcus*, which are thought to represent degenerating neutrophils through a non-apoptotic cell death pathway.[3,4] As in our case, previously reported cases of cryptococcoid vasculitis used fungal stains to rule out *Cryptococcus* infection and these cases did not improve with antifungal therapy. [3,4] Additionally, the vacuolated cells were positive for MPO, supporting the cell's neutrophilic origin, and thus antifungal therapy has no significance in the treatment regimen.[1]

Hydralazine-induced vasculitis is a rare, serious adverse effect that has been associated with severe cutaneous and severe pulmonary and renal involvement.[5,6] It is typically associated with positive perinuclear antineutrophil cytoplasmic (p-ANCA) and anti-MPO antibodies. While the full pathogenesis of how hydralazine triggers autoantibodies is not fully elucidated, it is thought that hydralazine accumulates in neutrophilic granules which leads to the binding of MPO and cell death.[4,6] This results in the exposure of previously sequestered cellular antigens to the immune system, causing the formation of autoantibodies such as ANCA and anti-nuclear antibodies (ANA), which may lead to overt systemic autoimmunity.[4,6]

We also report a second case of cryptococcoid vasculitis secondary to hydralazine with striking similarities to a previously published case.[5] Our patient was a 77-year-old female with multiple

chronic comorbidities including hypertension on hydralazine. She developed prominent facial edema and several violaceous bullae on her eyelids, forehead, and cheeks. She also had numerous bullae on her upper and lower extremities, similar to our previously discussed case. Skin biopsy demonstrated small + medium vessel vasculitis with cryptococcoid features. Despite stopping hydralazine and starting high dose intravenous steroids, her vasculitis progressed, and she ultimately passed away. In addition to having cryptoccoid histological features in the setting of hydralazine exposure, our case had similar clinical features to a previously published case. Skaljic et al. highlight the case of a woman in her 70s who developed edematous and umbilicated papules and bullae on the face, arms, and legs.[5] Skin biopsy showed a dense perivascular neutrophilic infiltrate with vasculitis and cryptococcoid inflammatory debris with negative fungal staining. She was also noted to have positive ANA, anti-double-stranded DNA, p-ANCA and anti-MPO antibodies. Hydralazine was discontinued and she was started on high-dose intravenous steroids with improvement in her skin lesions.[5]

In summary, we present two cases of hydralazine-induced cryptococcoid vasculitis, one of which resolved with the cessation of hydralazine. The improvement with discontinuation of hydralazine further supports hydralazine as a causative medication of drug-induced vasculitis, and should be considered when evaluating ANCA-associated vasculitis refractory to steroids. This case also highlights the potentially confusing *Cryptococcus*-like histopathologic findings, which have rarely been reported in cutaneous vasculitis and may be an indicator for severe systemic disease.[3]

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PRESENTERS
Sarah Semaan MD; Abena Maranga MD; Christopher R. Shea MD; Amy Xu MD

HISTORY OF PRESENT ILLNESS
A 66-year-old man with a history of anemia and intermittent alcohol abuse presented to dermatology clinic with an enlarging, tender scalp mass. He noted persistent purulent and occasionally bloody drainage for months, and sharp pain that interrupted sleep. Prior history was notable for a nearly 30-year history of biopsy-proven dissecting cellulitis of the scalp (DCS) involving the area of concern, treated with multiple modalities including topical steroids, intralesional steroid injections, and oral antibiotics. A recurrence of tenderness, odor, and drainage had prompted him to return to clinic after a prolonged period of stability.
Clinical examination showed a large, sclerotic, alopecic, oblong mass with complete follicular obliteration extending from the occipital scalp to the right frontal scalp, and a focal nodule at the right parietal scalp with cribriform surface and purulent drainage. Numerous enlarged lymph nodes on the right cervical chain were palpable. Given the suspicion for a recurrence of his underlying dissecting cellulitis with overlying superinfection, a tapering course of oral prednisone 40 mg daily combined with doxycycline was begun. A 14-day course of cephalexin was added after bacterial cultures grew Streptococcus agalactiae. Due to persistent activity after 6 weeks, his treatment was changed to adalimumab 40mg subQ every other week.

At 2-week follow-up, the right parietal nodule had rapidly progressed into an exophytic, fungating tumoral mass.

PAST MEDICAL HISTORY
History of longstanding dissecting cellulitis of the scalp, anemia, and intermittent alcohol abuse

FAMILY HISTORY
Colon cancer (Mother), lung cancer (father)

SOCIAL HISTORY
Denies any smoking

MEDICATIONS
None

ALLERGIES
NKDA

PHYSICAL EXAMINATION
Large firm alopecic pink smooth plaque extending from the frontal hairline to the occiput along the right side of the scalp. Within the alopecic plaque there is a 10cm thick plaque with cribriform scarring and deep fissures and hemorrhagic crusting over the R occipital scalp with bogginess and significant drainage on pressure.

DIAGNOSIS
Marjolin cutaneous squamous cell carcinoma arising within dissecting cellulitis of the scalp

TREATMENT AND COURSE

The patient was referred urgently to Oncology. Head and neck computed tomography (CT) scan demonstrated a 14 × 10 × 5 cm tumor of the right parietal-occipital scalp; positron emission tomography–CT scan showed multiple hypermetabolic lymph nodes in the bilateral neck, right axilla, and chest wall. No distinct visceral metastases were noted. He was started on pembrolizumab 200 mg every 3 weeks; carboplatin, paclitaxel, and radiation therapy were subsequently added due to progression of disease. The patient ultimately underwent wide local excision with latissimus dorsi free-flap reconstruction approximately 1 year after initial cSCC diagnosis; all surgical margins and lymph node dissections were negative for residual disease. He continues to follow with Oncology and Otolaryngology for surveillance CT scans every 6 months.

DISCUSSION

Cutaneous SCCs arising within long-standing lesions of follicular occlusive disorders are known to be highly aggressive[1]. Recurrent cycles of tissue destruction and re-epithelialization, persistent hyperproliferative wound healing responses, and extensive scarring resulting in an immunologically privileged site are factors thought to contribute to the aggressiveness of such tumors[2,3]. In a review of 43 cases of HS complicated by cSCC, 36% exhibited lymph node or distant metastasis, and nearly half developed recurrence after surgical excision, with mortality rate approaching 50%[4]. Delays in diagnosis are unfortunately common, likely due to difficulty in distinguishing recrudescence of inflammation from malignant transformation, as well as from high false-negative biopsy rates secondary to the depth and focality of carcinomatous changes[1]. Multiple tissue biopsies from various locations may be required to capture foci of frank cSCC[5,6].

Although cSCC arising within HS is documented in more than 80 case reports, only 1 case of cSCC developing within DCS has been published previously[6,7]. Similar to our case, the patient presented with acute drainage and pain of long-standing DCS of the occipital scalp; notably, the scalp lesions did not appear significantly changed from baseline several months prior. He was started on oral dapsone for presumed DCS flare, but returned 2 months later with interval development of a large, fungating mass. Several biopsies were performed before the diagnosis of cSCC was made, and despite undergoing immediate wide local excision with negative margins, he developed numerous tumoral metastases and expired less than 4 months later.

We present this case to highlight a rare and potentially highly morbid phenomenon occurring as a late complication of DCS. The initial recurrence of our patient's symptoms after a prolonged period of disease quiescence likely represented malignant degeneration into cSCC, with tumor growth accelerating after the addition of adalimumab. As exemplified by our case and that of Curry et al, active inflammatory DCS manifesting as fluctuant, tender, and draining nodules may be difficult to distinguish from malignant transformation. Thus, early and frequent biopsy remains crucial for excluding the development of cSCC within long-standing lesions, and a high index of suspicion is required for patients with sudden recrudescence of inflammatory symptoms after prolonged stable disease.

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PRESENTERS
Gaurav Agnihotri MD; Sarah L. Stein, MD; Arlene Ruiz de Luzuriaga, MD MBA; Adena E. Rosenblatt, MD, PhD

HISTORY OF PRESENT ILLNESS
A 17-year-old male with no significant medical history presented for evaluation of an asymptomatic lesion on his abdomen present for the past five years with minimal change. He was bothered by the cosmesis of the lesion and was interested in having it removed.

REVIEW OF SYSTEMS
Negative for fevers/chills, unintended weight loss, abdominal pain

PAST MEDICAL HISTORY
None

MEDICATIONS
No pertinent medications

ALLERGIES
None

FAMILY HISTORY
No pertinent history

PHYSICAL EXAM
On exam, there was a 1.5 cm x 1 cm well demarcated skin colored oval depressed firm plaque with a slight blue hue on the central abdomen.

DERMATOPATHOLOGY
On histology, the excisional biopsy revealed a poorly demarcated spindle cell proliferation infiltrating the subcutaneous tissue forming a honeycomb pattern. There was mild pleomorphism of the spindle cells with rare atypical mitotic figures along with scattered multinucleated giant cells. The spindle cell proliferation stained diffusely for CD34 and negative for factor XIIIa. Fluorescence in situ hybridization studies showed a positive result for PDGFβ.

DIAGNOSIS
Giant Cell Fibroblastoma

TREATMENT AND COURSE
MRI of the abdomen suggested tumor involvement of subcutaneous fat, above the muscle. The patient was referred for slow Mohs micrographic surgery for complete removal.

DISCUSSION

Giant cell fibroblastoma (GCF) is a soft tissue tumor initially described in 1982 by Drs Enzinger and Shmookler [1]. GCF has been regarded by some as a juvenile form of dermatofibrosarcoma protuberans (DFSP) with clinical and histopathological overlap [2]. GCF has primarily been reported in children less than 10 years of age, with a male predominance [3]. Like DFSP, GCF usually appears as an asymptomatic slowly growing mass in a truncal distribution. While metastasis has been rarely reported in DFSP, there have not been any reports of GCF metastasis, though this is possibly a function of the rare diagnosis of GCF [4].

GCF has been commonly described clinically as an asymptomatic slow growing plaque to nodule, some even becoming protuberant or polypoid [2,3]. One case presented as a superficial ulceration [2]. To our knowledge, no previous cases of GCF have been described as depressed plaques. DFSP generally also begins as an indurated plaque that slowly becomes nodular. Rare atrophic manifestations of DFSP have been described [5].

On histology, both DFSP and GCF show a spindle cell proliferation with parallel or honeycomb patterns of infiltration into the dermis and subcutaneous fat, and rarely into the skeletal muscle [2]. Both can also demonstrate adnexal sparing, myxoid changes, and occasional intralesional melanin pigment [2]. Features considered to be more classic for GCF include multinucleated giant cells and irregular pseudocystic spaces [2]. Notably, these spaces often lack a continuous cell lining and are not always present; they are thought to be due to the progressive dilation of spaces between collagen bundles [4]. Additional histologic features include perivascular onionskin-like lymphocytes and hemorrhage [2].

On immunohistochemistry both GCF and DFSP stain positive for CD34. They also exhibit positive staining for vimentin indicating their shared mesenchymal origins [6]. Furthermore, both tumors have the same chromosomal translocation - t(17;22) - forming a gene fusion product between collagen 1A1 and platelet derived growth factor beta (COL1A1-PDGFβ) [2]. This further supports that GCF and DFSP are closely related entities.

Traditionally, treatment of GCF has been wide local excision but standard margins have not been defined by clinical trials. Like DFSP, GCF demonstrates high local recurrence rates in up to 50% of cases in one series when treated with standard excision [2]. Mohs micrographic surgery is now recommended by the National Comprehensive Cancer Network guidelines for the treatment of DFSP [7]. Since GCF is on a spectrum with DSFP, it may be reasonable to pursue Mohs for GCF treatment as well, with several cases reported in the literature [6,8].

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PRESENTERS
Liesl Schroedl, MD, Angad Chadha, MD, Oluwakemi Onajin, MD

HISTORY OF PRESENT ILLNESS
A 53-year-old female with history of seizure, migraine, and asthma presented to the University of Chicago Emergency Department for new-onset right lower extremity erythema and pain. She was subsequently admitted for a presumed diagnosis of cellulitis. At that time, she denied recent infection or initiation of new medications preceding the symptoms. She reported no upper respiratory infection symptoms, fever, hemoptysis, hematochezia, or hematuria. Doppler studies at that time were negative for deep vein thrombosis, and she was started on an antibiotic regimen of doxycycline and amoxicillin-clavulanate for one week with resolution of her symptoms.
At hospital follow-up one month later, she had continued to do well without interval resurgence of the erythema or tenderness. Interestingly, though, the erythema and tenderness of her right lower leg reappeared a few days after her clinic visit, this time accompanied by fever. Direct hospital admission was recommended, but the patient elected to trial empiric doxycycline; she completed one week of this, again with resolution of her symptoms.
One month later, however, she experienced yet another flare of erythema of the right lower leg as well as a new development of nodular lesions in the distribution of the erythema. She began a course of doxycycline once again, but this time her symptoms persisted after five days of therapy, prompting her presentation to Dermatology clinic.

PAST MEDICAL HISTORY
Seizures
Migraines
Asthma
Sinusitis
Bipolar disorder

FAMILY HISTORY
No known family history of dermatologic or vascular conditions.

SOCIAL HISTORY
No alcohol, tobacco, or illicit drug use.

MEDICATIONS
Albuterol sulfate inhaler PRN
Aripiprazole 90mg daily
Budesonide-formoterol inhaler once daily
Bupropion 150mg daily
Butalbital-acetaminophen-caffeine 50-325-40mg PRN
Clonazepam 0.5mg PRN
Cyclobenzaprine 5mg QHS PRN
Hydrocodone-acetaminophen 5-325mg
Lamotrigine 250mg daily
Methylphenidate 10mg daily
Pregabalin 75mg daily
Venlafaxine 37.5mg daily
Verapamil 180mg daily

ALLERGIES
Sulfa

PHYSICAL EXAM
The right proximal lower leg displayed four discrete erythematous indurated exquisitely tender firm nodules, and the right distal lower leg exhibited an ill-defined erythematous to violaceous indurated firm plaque. The left lower leg was clear; there were no lesions on the posterior calves or the thighs. The remainder of her cutaneous examination was unremarkable.

LABORATORY DATA
Studies at the time of the patient's third flare revealed:
- Eosinophilia to 16.8% (with 1400 absolute eosinophils)
- Erythrocyte sedimentation rate (ESR) mildly elevated at 36
- C-reactive protein mildly elevated at 17.9
- Complements within normal limits
- Rheumatoid factor and cyclic citrullinated peptide antibody negative
- Urinalysis normal, no hematuria or proteinuria
- Antinuclear antibody positive at a titer of 1:180 with nucleolar pattern
    - Reflex antibody panel was pan-negative
- Anti-neutrophil cytoplasmic antigens negative
- Acute hepatitis panel negative
- Tissue culture from a nodular lesion negative for bacterial, fungal, and mycobacterial growth

IMAGING
Ultrasound Right Lower Extremity
Negative right lower extremity venous Doppler.

X-ray Right Tibia/Fibula
Soft tissue swelling without definite radiographic findings to suggest osteomyelitis.

CT Right Lower Extremity
Soft tissue swelling and overlying skin thickening about the distal tibia-fibula and foot dorsal surface, particularly the anterior half. No subcutaneous gas. No deep fascial enhancement.

CT Pelvis
Mildly prominent lymph node in the right lower quadrant but otherwise no acute pelvic abnormality.

DERMATOPATHOLOGY
A punch biopsy obtained from an indurated nodule on the right lower leg revealed deep dermal granulomatous and neutrophilic inflammation with many eosinophils and focal vasculitis.. Periodic acid-Schiff stain was negative for fungi or basement membrane thickening. The methenamine silver stain was negative for fungi. The Ziehl–Neelsen and Fite special stains were negative for mycobacteria.

DIAGNOSIS
Atypical cellulitis-like presentation of eosinophilic granulomatosis with polyangiitis

TREATMENT AND COURSE
Based on the aforementioned histopathology, the differential diagnosis included eosinophilic granulomatosis with polyangiitis (EGPA) versus nodular vasculitis. Further history was elicited from the patient, including a background of longstanding, difficult-to-treat asthma and sinusitis. With this knowledge at hand, clinical suspicion was raised for EGPA. She was started on oral prednisone 40mg daily for one week with rapid improvement in her right leg erythema and pain. She was referred to Rheumatology for further evaluation; they were in agreement with a provisional diagnosis of EGPA and recommended initiation of methotrexate 20mg weekly along with prednisone taper. After two months of therapy, her right lower leg erythema and nodules had fully cleared, and methotrexate dose was lowered to 15mg weekly. However, she thereafter developed hip and shoulder girdle pains, and there was concern for possible spondyloarthritis. She was subsequently started on etanercept along with continuation of methotrexate 15mg weekly for better control of her joint symptoms, and the skin remained quiescent. An increase in methotrexate dose or trial of meprolizumab were in consideration if the skin were to flare again.

DISCUSSION
EGPA is a systemic vasculitis traditionally characterized by prodromal asthma and sinusitis with later-onset eosinophilic infiltration of one or more organ systems, granuloma formation, and vasculitis. It affects primarily adult patients but can impact children more rarely.[1] Pulmonary involvement is most common, with pulmonary infiltrates occurring in 40-70% of EGPA patients. Cardiac involvement is less frequent but tends to be associated with ANCA negativity and profound eosinophilia and portends a poorer prognosis. Gastrointestinal vasculitis does occur in 20-50% of EGPA patients and similarly heralds poor prognosis. Renal involvement is rare in comparison to granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Neurologic features can be present as well, including mononeuritis multiplex or sensory deficitis.[2] Cutaneous presentations include palpable purpura, petechial macules, dermal or subcutaneous nodules, urticaria, and livedo reticularis. Histology of cutaneous lesions typically demonstrates small- or medium-vessel vasculitis, granulomas, or eosinophilic infiltrate, but often may not exhibit all three features simultaneously.[1]

Several sets of classification criteria for EGPA have been proposed over recent decades; however, there has not been a validated diagnostic algorithm established.[3] In 1990, the American College of Rheumatology suggested that a diagnosis of EGPA should be based on possessing four of six features: eosinophilia >10%, asthma, neuropathy, lung infiltrates, paranasal sinus changes, and histological evidence of extravascular eosinophils.[4] More recently in 2022, a new collection of weighted criteria differentiated between positively scored items (elevated eosinophil count, obstructive airway disease, nasal polyps, extravascular eosinophilic-predominant inflammation, mononeuritis multiplex) and negatively scored items (c-ANCA or anti-PR3 positivity, hematuria). A patient with established small- or medium-vessel vasculitis who achieves a score of 6 or greater by these parameters can be classified as having a diagnosis of EGPA with 85% sensitivity and 99% specificity.[3]

Treatment algorithms for EGPA stratify by the presence of life-threatening features, including renal insufficiency, proteinuria, cardiomyopathy, gastrointestinal tract, nervous system involvement, and diffuse alveolar hemorrhage. In severe cases, the goal is to induce remission

with high-dose pulsed intravenous steroids followed by high-dose oral steroids and either cyclophosphamide or rituximab. After remission is achieved, maintenance therapy is performed with some combination of steroids, rituximab, and disease-modifying antirheumatic drugs (DMARDs).[3] A relatively newly developed anti-interleukin 5 antibody called mepolizumab was validated in a 2017 randomized controlled phase 3 trial to confer a significantly higher number of weeks in remission and higher proportion of patients in remission compared to placebo.[5] Its use has been recommended for maintenance of remission in both mild and severe cases of EGPA but not as a first-line therapy. Cases of EGPA without severe features are typically initially managed with glucocorticoid monotherapy followed by mepolizumab or DMARDs.[3]

Of particular interest are the sundry cutaneous and histopathologic manifestations of EGPA. As mentioned previously, palpable purpura, petechiae, hemorrhagic bullae, livedo reticularis, urticaria, and papulonodular lesions can occur.[6] Other less common skin presentations include pustules, vesicles, erythema multiforme, ulcerations, oral mucosal ulcerations, and atopic dermatitis. In one case series of pediatric patients with EGPA, the most frequently occurring skin manifestation was purpura, impacting over half of patients. Subcutaneous nodules and erythematous rash both affected roughly 28% of the patients in the series.[1] Histologically, the small- and medium-sized muscular arteries in the dermis tend be impacted, with the presence of tissue eosinophils in a perivascular or interstitial distribution. Necrotizing granulomas are variably present; highly characteristic but not always observed is a palisading neutrophilic and granulomatous dermatitis with eosinophilic granules surrounding degenerated bundles of collagen, known as “red granulomas.”[7]

The case presented here is unique in its cellulitis-like presentation. It is unusual that the patient’s initial manifestation was repeated episodes of apparent cellulitis, which ultimately evolved into the more discrete subcutaneous nodules that are relatively classic of EGPA and were refractory to antimicrobial therapies. Thus far it appears that a similar presentation has not been described in the literature. Other features of this patient’s presentation were more typical for EGPA, including her comorbidities of asthma and sinusitis, ANCA negativity (only about 25% of patients with EGPA have a positive p-ANCA or anti-MPO antibody[8]), and positive response to corticosteroids. This particular case emphasizes the importance of recognizing the wide array of cutaneous expressions of EGPA and thus exploring a broad differential diagnosis when evaluating a patient with presumed cellulitis.

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PRESENTERS
Grace Wei, MD; Colton Funkhouser, MD; Arlene Ruiz De Luzuriaga, MD MPH MBA; Adena Rosenblatt, MD PhD

HISTORY OF PRESENT ILLNESS
A 20-year-old male was referred to the dermatology and infectious disease clinics with a lesion on the right hand that developed two months prior and was associated with tenderness and purulent drainage. He had previously been treated with multiple courses of antibiotics without improvement. He had no fever, chills, or other constitutional symptoms, and had no known trauma to the area. Of note, the patient is studying aquatic science and works at a fish store. He endorsed frequently placing his hands into fish tanks without gloves.

PAST MEDICAL HISTORY
Raynaud's disease, asthma, and seasonal allergies

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
Freshman in college studying aquatic science and works in a fish store. Sexually active with one partner and uses condoms for contraception.

MEDICATIONS
Albuterol inhaler, Flonase nasal spray, and Cetirizine 10mg daily

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Violaceous 2cm thin nodule with focal scale overlying the right 5th metacarpophalangeal joint, no fluctuance or drainage present.

LABORATORY RESULTS
Acid-fast bacilli tissue cultures grew *Mycobacterium marinum*, bacterial and fungal cultures were negative. Complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, and C-reactive protein were within normal limits. Syphilis and HIV testing were non-reactive.

IMAGING
3-view x-ray of the right hand: Minimal soft tissue swelling along the ulnar aspect of the 5th metacarpophalangeal joint. Bones were normal in appearance without evidence of destruction or fracture.

DERMATOPATHOLOGY
Histologic sections from a punch biopsy of the right-hand lesion demonstrated mild hyperkeratosis and acanthosis of the epidermis and granulomatous inflammation with scattered eosinophils in the mid and deep dermis. Gram stain and stains for PAS, methenamine silver, Ziehl–Neelsen, and Fite were negative.

DIAGNOSIS
Cutaneous *Mycobacterium marinum* infection

TREATMENT & COURSE
The patient was started on a course of rifampin 600mg daily and clarithromycin 1g daily with significant improvement. The patient reported complete resolution of symptoms and healing of the lesion with only residual scar.

DISCUSSION

Mycobacterium marinum is a gram-positive, aerobic, acid-fast non-tuberculous bacteria found in both freshwater and saltwater sources [1]. It leads to a tuberculosis-like illness in fish and causes skin and soft issue infections in humans. *M. marinum* skin infections, also known as fish tank granulomas, result from direct contact with contaminated marine animals or water sources such as aquarium tanks, non-chlorinated swimming pools, lakes, and oceans [2]. As a result, those with exposure to aqueous environments, such as aquarium handlers, fisherman, and aquatic athletes, are at particularly high risk. Infections typically occur at sites of minor trauma, which serve as a bacterial entry site, and are not transmissible from person-to-person. The estimated incidence of cutaneous infections with *M. marinum* annually across the United States is roughly 3 cases per 1,000,000 individuals [1].

Mycobacterium marinum skin infections commonly present as a solitary violaceous verrucous nodule or plaque on a distal extremity within three weeks of inoculation. Lesions are usually painful and secondary ulceration, purulent drainage, and crusting can also be seen. Infections that penetrate further into the dermis can spread via lymphatic vessels with new lesions developing along a lymphangitic or sporotrichoid pattern, and can thus mimic sporotrichosis [3]. If *M. marinum* infection is suspected, a skin biopsy with tissue culture should be obtained. As *M. marinum* grows optimally at a lower temperature (30°C) compared to other mycobacteria, the receiving laboratory should also be notified [1]. Positive culture results vary widely across the literature, ranging from 40-80% [2,4]. In culture-negative cases where there remains a high-index of clinical suspicion, additional testing such as polymerase chain reaction (PCR), immunohistochemistry (IHC), and next-generation sequencing (NGS) can also be considered [4,5]. Histologic sections of *M. marinum* infections frequently reveal a nodular granulomatous dermatitis within the dermis, a lymphohistiocytic infiltrate with multinucleated giant cells, and neutrophils, findings which are also common to other granulomatous diseases. Acid fast stains (e.g., Ziehl-Neelsen and Fite) can be helpful to obtain, but false-negatives are common. Gram stain and other special stains such as Periodic acid-Schiff (PAS) and methenamine silver can be obtained to rule out other bacterial or fungal etiologies [4].

Severe *M. marinum* infections involving invasive or disseminated spread can also be seen. These typically occur in delayed or untreated cases and in immunocompromised hosts, including individuals with a history of HIV/AIDS or those on immunosuppressive medications [3]. Increasing reports of cases in patients on biologic therapies, most notably involving anti-tumor necrosis factor agents such as adalimumab and infliximab have also been described [6–8]. Invasive *M. marinum* infection of deeper structures (e.g., tendons, joints, and bones) can result in tenosynovitis, polyarthritis, septic arthritis, and osteomyelitis whereas disseminated *M. marinum* infections involve spread into the bloodstream and internal organs. It is crucial to perform a thorough evaluation to distinguish between infectious versus inflammatory causes of joint pain as initiation of steroid therapy for presumed inflammatory tenosynovitis or arthritis can worsen *M. marinum* infections and increase the risk of further invasion and disseminated spread [9,10].

While there are no standard guidelines for treatment of *M. marinum* infections, management is typically comprised of combination therapy with clarithromycin and rifampin or ethambutol [1,3,11]. Use of tetracyclines, fluoroquinolones, and trimethoprim-sulfamethoxazole have also been described with varying efficacy. Patients should remain on therapy until all cutaneous lesions have healed and continued for an additional one to two months following complete resolution [1]. For immunocompromised patients or more invasive infections, prolonged courses from 6 months to one year are generally required. Surgical interventions such as debridement and excisions can also be considered on a case-by-case basis [2,3,12].

We present this case to highlight the clinical manifestations, diagnostic approaches, and management strategies of a well-known but less commonly seen presentation to the dermatology clinic. Early recognition and initiation of treatment are paramount to decreasing the risk of progression towards invasive and disseminated infection, particularly in immunocompromised patients.

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PRESENTERS
Sneha Butala MD; Oluwakemi Onajin MD; Angad Chadha MD

HISTORY OF PRESENT ILLNESS
A 48-year-old woman with metastatic cholangiocarcinoma, complicated by gastroparesis, ascites and right portal vein thrombosis, was admitted to the hematology-oncology service due to intractable nausea, vomiting, and new-onset hypercalcemia. She was undergoing active treatment with pemigatinib, a fibroblast growth factor receptor (FGFR) inhibitor, which she had started two months ago after completing two cycles of chemotherapy with gemcitabine, cisplatin, and durvalumab.

Dermatology was consulted to evaluate new skin textural changes on her mid-back. These changes began as a small, intensely pruritic nodule two months prior. Since then, the nodule had enlarged and evolved into a distinct indurated plaque that was intermittently tender. She denied trial of topical or oral treatments for these skin changes but reported that her pruritus improved with baths and exposure to hot water.

PAST MEDICAL HISTORY
Metastatic cholangiocarcinoma
Diabetes Mellitus Type II
Gastroparesis
Heart failure with preserved ejection fraction
Hyperlipidemia
Hypertension
Iron deficiency anemia
Vitamin D Deficiency

MEDICATIONS
Chemotherapy:
- Previously completed two cycles of gemcitabine, cisplatin, durvalumab
- Currently on pemigatinib

Creon, Ergocalciferol, Famotidine, Folic Acid, Furosemide, Gabapentin, Insulin, Morphine, Omeprazole, Prochlorperazine prn, Rivaroxaban, Scopolamine, Sennosides-docusate sodium, Sitagliptin, and Spironolactone

ALLERGIES
No known drug allergies

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
Former smoker (23 pack-years)
No alcohol or illicit drug use

PHYSICAL EXAMINATION

Examination of the upper mid-back revealed a large well-demarcated, indurated, infiltrative, plaque with cliff-drop borders. There was mild tenderness to palpation. There was minimal overlying or surrounding erythema.

LABORATORY RESULTS

Laboratory Study	Patient Result	Reference Range
Measured calcium	11.8 mg/dL	8.4 - 10.2 mg/dL
Corrected calcium	12.3 mg/dL	8.4 - 10.2 mg/dL
Albumin	3.4 g/dL	3.5 - 5.0 g/dL
Inorganic phosphate	6.0 mg/dL	2.5 - 4.4 mg/dL
Tumor Marker Parathyroid hormone (PTH)-Related Protein	1.0 pmol/L	< or = 4.2 pmol/L
Parathyroid Hormone	11.0 pg/mL	15 - 75 pg/mL

- Magnesium and lipase levels were within normal limits.
- Complete blood count was consistent with patient's known history of iron deficiency anemia with hemoglobin 11.1 g/dL (11.5 - 15.5 g/dL).
- Tumor markers, carcinoembryonic antigen (CEA) and CA 19-9 within normal limits.

IMAGING

Computed Tomography (CT) Abdomen/Pelvis

Slight interval progression of multiple hepatic masses compatible with the patient's history of cholangiocarcinoma. Small volume ascites decreased compared to prior.

DERMATOPATHOLOGY

Histopathologic analysis of a punch biopsy specimen from the left mid-back revealed dense sclerotic collagen with eccrine trapping and calcium deposits within the dermis. There was also a very sparse dermal infiltrate of histiocytes and fibroblasts.

DIAGNOSIS

Fibroblast Growth Factor Receptor (FGFR) inhibitor therapy induced tumoral calcinosis cutis

TREATMENT & COURSE

The patient was discharged after improvement of her hypercalcemia with intravenous (IV) fluids and better control of her nausea and vomiting with anti-emetics. After discussion with the patient's primary oncologist, it was decided the patient would require continued treatment with pemgatinib for her cholangiocarcinoma. She was initiated on treatment with IV sodium thiosulfate infusions of 25 grams two to three times per week. Nephrology service was also engaged to continue correction of her calcium and phosphate homeostasis imbalances with oral sevelamer carbonate 800mg three times daily and low phosphorus diet.

Within 2.5 weeks of starting STS infusions and correction of calcium and phosphate values, the patient showed significant improvement in her mid-back plaque with decreased size and firmness. The area became asymptomatic, free of pain and itching, and no new lesions developed. She experienced occasional nausea and vomiting that were not correlated with her

STS infusions and more likely related to her underlying gastroparesis. She was able to continue her pemgatinib treatment successfully.

DISCUSSION

Hyperphosphatemic tumoral calcinosis cutis is an uncommon complication associated with FGFR inhibitor therapy.[1,2,3] FGFR inhibitors disrupt the normal signaling pathways that regulate phosphate metabolism. Specifically, these drugs can inhibit the FGF23 pathway, increasing renal phosphorous reabsorption and the production of 1, 25-dihydroxy vitamin D, which is the biologically active form.[4] This in turn leads to hyperphosphatemia and hypercalcemia and promotes the deposition of calcium phosphate in tissue. This biochemical cascade is a critical factor in the development of calcinosis cutis.

Effective management involves addressing both the underlying hyperphosphatemia and the associated calcific deposits.[1] The use of sevelamer, an oral phosphate binder, in conjunction with a low-phosphorus diet, has been shown to significantly improve serum phosphorus levels, and in one case also result in complete regression of calcinosis cutis due to FGFR inhibitor.[5] Discontinuation of the FGFR inhibitor has also been shown to help clear the calcifications.[6,7] However, in cases where discontinuation is not feasible, as was the case with our patient, alternative treatments are necessary. In these instances, IV sodium thiosulfate (STS) has been shown to be a useful adjunctive treatment.[8] STS works by chelating calcium, promoting the dissolution of calcium deposits and subsequently reducing the size and number of calcinosis cutis lesions. Currently, the recommended dosing for IV STS for the treatment of calcinosis cutis is not well-established due to limited data. However, extrapolating from data on the use of IV STS in other cutaneous calcifying conditions, doses between 12.5-25g at a frequency of two to five times per week is likely reasonable and has shown efficacy in one case report.[8]

There are several notable side effects of IV sodium thiosulfate infusions. Gastrointestinal symptoms including nausea and vomiting are the most common.[9,10] These symptoms can be minimized by slowing the rate of infusion and co-administering anti-emetic agents. Patients can also develop an anion gap metabolic acidosis, warranting close monitoring.[9,11] Our patient briefly experienced a mild metabolic acidosis, which self-resolved within one week and did not recur with further STS treatment. Headache and hypotension have also been reported.[9]

Our case underscores the importance of heightened awareness regarding the potential adverse effects associated with FGFR inhibitors, particularly as the use of this medication class is anticipated to increase in the future. Collaborative effort between dermatologists, oncologists, and nephrologists is crucial for advancing our understanding and management of FGFR inhibitor-induced calcinosis cutis.

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PRESENTERS
Abena Maranga, MD, MSc; Arlene Ruiz de Luzuriaga, MD, MPH, MBA; Angad Chadha, MD

HISTORY OF PRESENT ILLNESS
A 56-year-old male presented to the University of Chicago Emergency Department with three weeks of worsening generalized rash, fatigue, sore throat, fevers, and chills. Aside from a course of metronidazole, a dose of ceftriaxone, and a methylprednisolone dose pack from different providers at outside institutions, he denied any other new medications in the past six months. His rash continued to worsen despite these therapies.

Recent medical history is notable for a hospital admission three months prior to this presentation where he presented with a similarly diffuse rash, flu-like symptoms, and myalgias, and was found to have an elevated creatine kinase. He was diagnosed with rhabdomyolysis. At the time, the patient had been taking diclofenac and atorvastatin, and both medications were discontinued after this admission. He was treated with intravenous fluids with resolution of these symptoms.

PAST MEDICAL HISTORY
Hypertriglyceridemia
Hypogonadism
Barrett's esophagus with dysplasia
Gout
Adjustment disorder with anxiety

PAST SURGICAL HISTORY
None.

FAMILY HISTORY
No pertinent family history.

SOCIAL HISTORY
Endorses recreational marijuana and alcohol use. No recent travel. Works as high school band teacher.

MEDICATIONS
Clonazepam 0.5mg daily
Cyclobenzaprine 10mg daily
Testosterone cypionate 200mg
Tramadol 50mg every 6 hours as needed
Trazodone 50mg daily

ALLERGIES
None

PHYSICAL EXAM

Diffuse facial erythema without edema, widespread erythematous coalescing papules and small plaques, some more violaceous in appearance and others with annular to serpiginous erythematous borders with blanching centers involving trunk and extremities.

LABORATORY RESULTS

CBC

- WBC 13.8, differential with significant eosinophilia (52% eosinophils, abs eos 7.1k/uL)

CMP

- Cr 1.03, BUN 14, AST/ALT 38/22

Inflammatory markers

- ESR 39, CRP 31

Creatine kinase 96

Respiratory viral panel negative

IMAGING

CT Neck Soft Tissue w/ Contrast

Mild generalized cervical lymphadenopathy.

CT Chest w/ Contrast

Widespread lymphadenopathy in the mediastinum, bilateral hilum, bilateral axilla, and infraclavicular region

CT Upper Abdomen and Pelvis w/ Contrast

Numerous small nodes throughout the mesentery and retroperitoneum. Splenomegaly.

DERMATOPATHOLOGY

H&E

Mild intercellular edema in the epidermis, with superficial perivascular lymphohistiocytic infiltrate and scattered eosinophils in the dermis. There are focal areas with red blood cell extravasation, but frank features of vasculitis are not observed.

Direct immunofluorescence

Tissue was negative for IgG, IgA, IgM, C3 deposition. There was non-specific interstitial deposition of fibrinogen.

ANCILLARY WORK-UP

The patient was evaluated by several other teams. Hematology and oncology was consulted for concern for a myeloproliferative neoplasm with eosinophilia, particularly a lymphocytic variant of hypereosinophilic syndrome. Bone marrow biopsy showed no morphologic evidence of malignancy. Fluorescence in situ hybridization (FISH) karyotyping, RNA fusion assay, DNA sequencing were all negative, and T-cell rearrangement studies were equivocal. A peripheral lymphocyte subset panel showed no notable abnormalities. Peripheral flows returned no abnormal lymphoid population or loss of pan T-cell antigens.

Rheumatology was consulted for an autoimmune etiology of symptoms. The patient's ANA was positive (1:320), but ANCA, RF, SSA, SSB, Jo-1 antibodies were negative.

Infectious disease was consulted for concern for a parasitic/helminthic infection. Stool ova and parasites prior to his presentation was positive for *Endolimax nana,* which is a nonpathogenic colonizing gastrointestinal amoeba. It is not known to cause disease in humans; however, he had completed a course of metronidazole prescribed by an outside provider for this finding prior to his presentation to us. Other invasive fungal, parasitic/helminthic antibodies were negative.

TREATMENT & COURSE

The patient was started on prednisone 60mg daily on the day of admission and went five days without improvement in rash but improvement in eosinophil count. He was increased to prednisone 80mg daily, and the rash slowly improved and the patient was discharged. Post-discharge labs showed normal eosinophil count and follow-up imaging showed resolved lymphadenopathy and persisting splenomegaly.

The patient remained rash free for three months, at which point he noticed the development of new clustered erythematous papules on the knee, ill-defined erythematous patches on the back, and diffuse facial redness. He reported use of diclofenac gel to the knee a day or two prior to the onset of rash, and resolution after discontinuation of use. A repeat open application test was performed, and erythematous patches and thin plaques developed at the site of application on the left arm but also the left flank at the site of apposition. Diffuse facial redness was again observed. After further questioning, the patient then reported that he put on diclofenac gel prior to applying a facial cream and did not adequately wash his hands between application. He was restarted on prednisone 80mg daily with rapid resolution of rash. He has remained rash free to date.

DIAGNOSIS

Unknown

NOTES

Thank You

INDUSTRY PARTNERS

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