Key location: left lower leg **CASE 3**

Presented by Evan Stokar MD and Warren Piette MD

History of Present Illness

A 39-year-old Hispanic man with a history of Cushing disease and non-insulin dependent diabetes mellitus presented with hemorrhagic bullae on the left leg of two weeks' duration. The lesions were painful and drained yellow fluid. He denied prior trauma, recent illness, new medications, exposure to shellfish or seawater, or recent travel.

Review of Systems

Positive for 50-pound weight loss over several months
Negative for fever, chills, night sweats, headaches, visual changes, numbness

Past Medical History

Cushing disease, non-insulin dependent diabetes mellitus, hypertension, vitamin D deficiency

Medications

Enalapril, spironolactone, furosemide, potassium, metformin, glipizide, ergocalciferol

Social History

Negative for alcohol or tobacco, positive for remote cocaine use
Works in construction

Physical Exam

General: Well appearing, no acute distress

Skin: Left anterior and medial shin with two large, adjacent purple hemorrhagic bullae with a round and retiform pattern and several satellite lesions along the borders. Minimal yellow discharge.
Left lower extremity with edema and minimal tenderness to palpation
Right lower extremity with trace edema

Laboratory Data

The following labs were remarkable/abnormal:

Glucose	259	[65 – 110 mg/dl]
Hemoglobin A1c	8.2	[4 – 5.7]
Alkaline phosphatase	165	[20 - 120 U/L]
ALT	50	[5 - 35 U/L]

CSF: WBC: 10 [0-5 cells/microL], glucose: 37[40-80 mg/dL], protein150 [15-60 mg/dL], cryptococcus antigen negative, cytology negative, no opening pressure recorded.

Radiology

CT, left lower extremity: no fracture or significant joint effusion. Diffuse subcutaneous edema surrounds the distal tibia and fibula and extends to the ankle. No loculated fluid collection, active osseous destruction or soft tissue emphysema.

CT, chest: 2.8 cm irregular mass in the posterior segment of the left upper lobe.

MRI, brain: 6.2 mm right pituitary microadenoma

Histopathology

Punch biopsy, left lower extremity: epidermal separation, dermal fibrosis and necrosis, and numerous yeast-like organisms consistent with *cryptococcus* species. PAS and mucicarmine stains highlight the organism. There is associated acute on chronic inflammation. There is evidence of vascular congestion secondary to the intense inflammatory process, however, no evidence of leukocytoclastic vasculitis or vasculopathy within the necrotic tissue.

Diagnosis

Disseminated cryptococcosis

Treatment and Course

He was treated with intravenous amphotericin B and flucytosine for presumed disseminated cryptococcosis. Lumbar puncture performed five days after the initiation of treatment did not show evidence of *cryptococcus* in the CSF. Chest CT revealed a 2.8 cm left upper lung mass consistent with Cryptococcus, confirming the diagnosis of disseminated cryptococcosiscus. Brain MRI showed a 6.2 mm microadenoma in the right pituitary, thought to be the etiology of the patient's Cushing disease. Subsequently, an urgent pituitary resection was performed, in an attempt to relieve the patient's immunosuppressed state.

After induction therapy with amphotericin and flucytosine, the patient was transitioned to high-dose intravenous fluconazole, however, his leg ulcer continued to progress. Subsequent debridement resulted in worsening ulceration, despite restoration of the patient's immune status following pituitary resection. Ultimately, above-knee amputation was performed, as the deep tissue in his left leg was deemed unsalvageable.

Despite treatment with high-dose fluconazole, the patient developed new areas of swelling on the left arm and right leg. Biopsy of these lesions confirmed cryptococcus, now with a significant purulent exudate, and CT showed deep fluid collections, while cultures were negative. The patient was retreated with amphotericin and flucytosine, and taken to the operating room for incision and drainage of these deeper fluid pockets. At this point, the development of abscesses in the setting of long-term antifungal therapy was attributed to an immune reconstitution inflammatory syndrome (IRIS), following removal of the pituitary microadenoma and restoration of normal cortisol levels. He was placed on modest dose prednisone to prevent further tissue destruction. He was eventually stabilized, transitioned back to high dose fluconazole, and discharged from the hospital after roughly three months.

Discussion

Cryptococcus is a pathogenic, encapsulated budding yeast that is a common cause of opportunistic infection. *Cryptococcus neoformans* accounts for a significant proportion of the burden, however, the emerging *cryptococcus gattii* has proven to be pathogenic as well. Infection is typically subclinical, except in the setting of immunosuppression, where the organism may cause significant morbidity and mortality. Primary infection involves the lungs, but the organism can disseminate to other organs of the body, including the central nervous system, skin, bones, and prostate.

Clinical diagnosis is often difficult because of the varied appearance of cryptococcal skin lesions. Cutaneous infection classically presents in HIV as umbilicated, molluscoid papules, but can also comprise a wide range of lesions as seen in our case. Clinical recognition is essential for timely initiation of therapy. Incorrect initial diagnosis due to

atypical presentations may lead to inappropriate or significantly delayed treatment, which may negatively impact outcomes.

Fewer than twenty reports of necrotizing fasciitis attributed to cryptococcus have been described, all of which occurred in immunosuppressed patients. The lower extremities are the most commonly affected site. As opposed to classic bacterial causes of necrotizing fasciitis, cryptococcal necrotizing fasciitis may present in a bilateral manner. Despite aggressive antifungal therapy, many of the reported cases resulted in significant morbidity and mortality, presumably due to delayed diagnosis. Debridement and skin grafting are used as adjunct therapy in the majority of cases. In two of the cases, there was evidence of bacterial coinfection, likely contributing to the degree of necrosis. Much of the virulence of cryptococcus is related to its ability to survive within the host. It is unclear why cryptococcus is able to present with necrotizing fasciitis, as no virulent toxins have been identified. This case emphasizes the importance of considering fungal sources of soft-tissue infection in immunosuppressed individuals, even when the clinical appearance favors an alternative diagnosis.

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Key location: trunk **CASE 7**

Presented by Anand Haryani MD and Warren Piette MD

History of Present Illness

A 37-year-old otherwise healthy man presented with a pruritic eruption for three months and fever for two days. He was admitted for an infectious workup given prominent leukocytosis. The eruption started on his legs, then spread to the upper body and upper extremities. He additionally reported "body pain" without weakness, hand and foot swelling, and a ten-pound weight loss over the past few months. His clinical symptoms and skin lesions were not responsive to topical hydrocortisone. He denied recent travel, hiking, camping, or sick contacts. All vaccinations were up to date.

Review of Systems

Positive for ten-pound weight loss over three months
Negative for chills, night sweats, cough, shortness of breath

Past Medical History

None

Medications

None

Social History

No illicit drug or tobacco use. Drinks six beers daily

Physical Exam

General:	No acute distress
Eyes:	Conjunctival injection bilaterally
Skin:	Chest and back with diffuse dull red papules coalescing into larger thin plaques with adjacent broad areas of tan hyperpigmentation. Peripheral erythema blanched under diascopy. Dermatographism present on the back

Laboratory Data

The following labs were remarkable/abnormal:

WBC	25 (91.2% neutrophils)	[4.4 - 10.6 k/uL]
Hemoglobin	11.3	[12.9 - 16.9 g/dL]
Platelets	428	[161 - 369 k/uL]
ESR	97	[0 - 20 mm/hr]
CRP	17.75	[0 - 0.5 mg/dL]
Ferritin	13,768	[25 - 330 ng/mL]
Cultures (blood, urine)	Negative	
Rheumatoid Factor	Negative	
ANA	Negative	
Hepatitis Panel	Negative	
Lyme Ab	Negative	
CMV Ab	IgG +, IgM –	
EBV Ab	IgG +, IgM –	

Imaging
Chest, abdomen, pelvis computed tomography: no acute findings
Hand radiography: no bony changes
Transthoraic echocardiogram: normal ejection fraction, no vegetations

Diagnosis
Adult-onset Still disease

Treatment and Course
Once infectious etiologies were excluded, the patient was started on prednisone 40 mg daily. Skin lesions, arthralgia, and leukocytosis improved prior to discharge. Additionally, ferritin level decreased to 1,006 ng/mL three weeks following prednisone initiation.

Discussion
First described in 1971 by Bywaters, adult-onset Still disease (AOSD) is an uncommon systemic inflammatory disorder of unknown etiology. It characterizes a syndrome of seronegative polyarthritis, salmon-colored macular and evanescent eruption, fever, and elevated erythrocyte sedimentation rate (ESR). Its prevalence is estimated to be less than 1 case per 100,000 people, and it affects predominantly young adults. Females are more often affected in Eastern countries than in Western countries. The pathogenesis of AOSD remains unknown, but points toward genetically predisposed hosts developing autoinflammatory disorders, triggered by macrophage cell activation and TH1 cytokines.

In most patients, high fever of unknown origin (FUO) is the presenting sign of AOSD. Classically, patients present with one to two daily fever spikes above 39°C occurring in the afternoon or evening and receding within hours. The frequency of symptoms and signs in descending order has been reported as fever (93%), arthralgia (90%), rash (70%), sore throat (64%), lymphadenopathy/splenomegaly (53%), hepatomegaly (39%), and pericarditis (13%). The course of the disease is most commonly polycyclic intermittent episodes with remission in between, however monocylic and chronic articular variants have been described. The standard criteria set for diagnosis of AOSD is the Yamaguchi criteria. The major criteria are high fever for >1 week, arthralgias for >2 weeks, leukocytosis (>10,000/mm^3 with >80% polymorphonuclear leukocytes, PMNs), and the typical evanescent skin eruption. Minor criteria include sore throat, lymphadenopathy or splenomegaly, liver dysfunction, and the absence of rheumatoid factor (RF) and antinuclear antibodies (ANA). An alternative criterion by Fautrel includes glycosylated ferritin as a specific criterion and does not require exclusion criteria.

In the classic cutaneous presentation of AOSD, the skin is involved in 60-70% of cases and its involvement is seen more often during the febrile period. It most characteristically occurs on the chest, abdomen, and extensor surfaces of the arms, consisting of discrete pink to red macules or slightly edematous papules ranging from 5 to 10 mm in size. The lesions tend to be relatively fixed in shape and site during their daily eruption and seldom itch. In the largest review of AOSD, leukocytosis occurred in 85% of patients and was composed of ≥ 80% PMNs in the majority of patients. Increased C-reactive protein, elevated ESR (≥ 20mm/h), elevated hepatic enzymes, and thrombocytosis (>400x10^9/L), were also noted. ANA, RF, and cyclic citrullinated peptide antibodies were rarely positive. Elevated serum ferritin was observed in 56% of patients, with elevations of more than 3 times normal in 60% of patients. A substantially elevated serum ferritin, with a lowered concentration of glycosylated ferritin, is strongly suggestive of AOSD. In healthy individuals, 50-80% of serum ferritin is glycosylated, but this drops to 20-50% in patients with inflammatory diseases. The histopathology of the classical eruption of AOSD is characterized by a mild inflammatory cell infiltration (lymphocytic, lymphohistiocytic, mixed or predominantly

neutrophilic) in the upper dermis, basal vacuolization, keratinocyte necrosis, presence of karyorrhexis, and dermal mucin deposition.

The most often reported atypical cutaneous presentation is persistent, pruritic papules and plaques, present in 75% of patients, and pruritus 87% of the time. Atypical cutaneous features are often present in addition to the typical evanescent rash, but are the only manifestation in 30-43% of cases. These lesions may develop fine scale and are most commonly located on the trunk, extremities, head, or neck. Photoaccentuation has been noted in several patients. In some cases, plaques are linear, suggesting koebnerization. Other descriptions included prurigo pigmentosa–like, urticarial papules, lichenoid papules, dermatographism-like, dermatomyositis-like, and lichen amyloidosis–like eruptions. More than one morphology or distribution pattern is often observed. The color of the atypical eruption is reported as either erythematous or brown, and less commonly violaceous.

In a current summary of atypical cutaneous presentations of AOSD, a majority of patients had abnormalities on laboratory evaluation. One of the major criteria for classification of AOSD is leukocytosis, which was present in 27 of 28 cases (96%). Transaminitis was present in 19 of 22 patients (86%). Ferritin >2000 µg/L (10 times the upper limit of normal) was found in 22 of 27 cases (81%), but otherwise ranged from 1,266-73,000 µg/L. The histopathology of lesions in the persistent pruritic papule and plaque variant includes dyskeratosis and a sparse superficial dermal infiltrate, often with neutrophils but without vasculitis. Occasionally, dermal mucin deposition, subcorneal or intracorneal pustules, acanthosis, or spongiosis were noted.

Two serious complications associated with AOSD are reactive hemophagocytic syndrome and thrombotic thrombocytopenic purpura. Both are rare and the reason for these associations is unknown. A newly recognized complication of AOSD is its association with malignancy. Recent reports suggest the chronic, persistent presentation may be more suggestive of malignancy. Malignancy may precede, appear concurrently, or present months or years after symptoms and signs of AOSD. Median time between diagnosis of AOSD and detection of malignancy is reported as nine months. Adult onset Still disease-like symptoms were most strongly linked to lymphoma, both B- and T-cell lymphomas. In some cases of what is eventually diagnosed as lymphoma, no clinical lymphadenopathy was present. To a lesser degree, leukemias and myelodysplastic syndrome have also been linked to AOSD-like presentations, some not presenting until six years after the initial diagnosis of AOSD, despite a normocellular marrow biopsy specimen at the time of initial presentation.

The second strongest association for AOSD-like symptomatology is with breast cancer. In most cases, the breast cancer diagnosis is made during the workup of a breast nodule accompanying other AOSD-like symptoms that are refractory to corticosteroids or other nonsteroidal anti-inflammatory medications. Other solid tumors including lung, esophagus, and liver angiosarcoma have been reported. Myeloproliferative, myelodysplastic, papillary thyroid, laryngeal squamous cell, melanoma, ovarian, and kidney malignancies are other more rarely reported associated cancers. In some patients, AOSD resolves after successful therapy of the underlying tumor. Of note, myocarditis is a rare, but potentially life-threatening complication that responds positively to corticosteroids or other immunomodulatory drugs.

Acute AOSD is often treated with nonsteroidal anti-inflammatory agents and corticosteroids. Steroid-sparing medications are often required and include intramuscular gold, D-penicillamine, sulfasalazine, hydroxychloroquine, methotrexate, thalidomide, azathioprine, cyclosporine, cyclophosphamide, or intravenous immunoglobulin. Resistant or chronic cases may require biologic agents, such anti-tumor necrosis factor agents, anakinra (anti-interleukin-1), or rituximab.

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