Diagnostic Snapshot

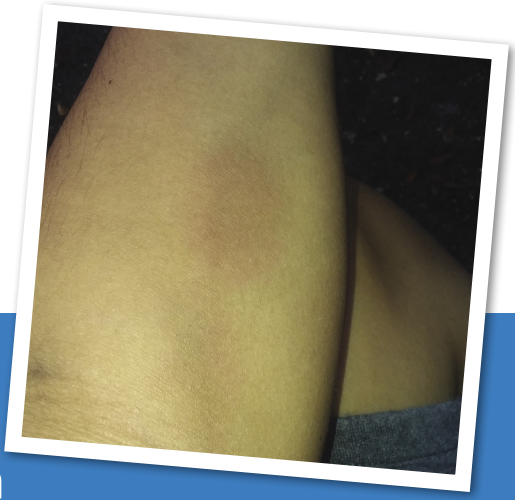

Figure 1.

Painful Nodules and Recurrent Fever in a Patient With Acute Lymphoblastic Leukemia

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Author's disclosures of conflicts of interest are found at the end of this article.
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ONCOLOGIC HISTORY

Mr. S is a 39-year-old Hispanic male with a diagnosis of Philadelphia chromosome–negative acute lymphoblastic leukemia, diagnosed in October 2015 with a hyperdiploid karyotype and mutations in *TP53* and *NRAS*. He was enrolled on a clinical trial with Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin [Adriamycin], dexamethasone) plus ofatumumab (Arzerra), achieving a complete remission following induction. He completed 8 cycles and proceeded to monthly maintenance therapy with POMP (6-mercaptopurine [6-MP; Purinethol], vinristine [Oncovin], methotrexate [MTX], prednisone). The initial dosing was vincristine at 2 mg intravenously on day 1, 6-MP at 50 mg three times daily, MTX at 42.5 mg weekly, and prednisone at 200 mg daily on days 1 to 5. He required dose reductions and delays in therapy due to recurrent myelosuppression and transaminitis, as well as occasional granulocyte colony-stimulating factors (pegfilgrastim or filgrastim; G-CSF) for help with count recovery.

In August 2017, Mr. S was taking 6-MP at 50 mg daily and MTX at 15 mg weekly (vincristine and prednisone doses remained the same). He remained on prophylactic ciprofloxacin, fluconazole, and valacyclovir. Overall, he tolerated maintenance therapy well. He required admission for febrile neutropenia in October 2016 and again in December 2016, but otherwise had no acute complications.

HISTORY OF PRESENT ILLNESS

In September 2017, Mr. S presented to the emergency center with complaints of fever of 38.3°C, malaise, and body aches. Bloodwork showed a white blood cell (WBC) count of 2.7×10^9/L, hemoglobin (Hgb) of 11.6 g/dL, platelet count (PLTC) of 141,000/µL, and absolute neutrophil count (ANC) of 1.97×10^9/L. A nasal wash was positive for rhinovirus. He received levofloxacin and was discharged.

Three days later, Mr. S. reported painful and erythematous nodules on his extremities with associated fever, chills, and malaise. He continued taking levofloxacin despite his symptoms. The nodules resolved after 1 week, resulting in hyperpigmented macules. He continued on POMP with a reduced dose of MTX (15 mg weekly).

Mr. S returned monthly for initiation of each cycle of POMP. In October 2017, he was relatively asymptomatic; however, his ANC was 1.03×10^9/L so MTX was reduced to 12.5 mg weekly. In November 2017, he reported a minimally productive cough for 3 days, but denied fevers, chills, malaise, or rash. He did not receive G-CSF (pegfilgrastim or filgrastim) and continued on POMP maintenance at a further reduced dose of methotrexate (10 mg weekly).

In December 2017, Mr. S returned for follow-up reporting recurrence of painful nodules on his extremities, dark dyspigmentation of his oral mucosa, and recurrent fevers over 38.4°C. He denied

exposure to animals, pesticides, new soaps or detergents, sick contacts, or recent travel out of the country. He endorsed recently installing insulation in a home. Bloodwork showed a WBC count of 1.4×10^9/L, Hgb of 9.9 g/dL, PLTC of 175,000/µL, and ANC of 0.63×10^9/L. He was instructed to hold 6-MP and MTX. Given the possibility of erythema nodosum based on his presentation, he did not receive G-CSF for fear of further exacerbating the symptoms.

On December 5, 2017, Mr. S returned with similar signs and symptoms. Bloodwork showed a WBC of 1.5×10^9/L, Hgb of 9.8 g/dL, PLTC of 162,000/µL, and ANC of 0.75×10^9/L. He continued to hold 6-MP and MTX and was given filgrastim. He was also referred to dermatology for consultation and potential biopsy.

CONSULTATIONS AND DIAGNOSTIC STUDIES

At the time of his dermatology consultation, Mr. S's vital signs were temperature 37°C, heart rate of 74 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 113/74, and O_2 saturation of 100% on room air. He reported daily fevers of greater than 38.4°C, malaise, and chills at home. He was awake, alert, and oriented to person, place, and time.

Examination of the upper extremities revealed 1 to 2 well-demarcated, nonblanching, erythematous nonulcerated painful nodules with circumferential desquamation. The lower extremities revealed 3 to 4 large erythematous patches with slight central duskiness and warmth to palpation (Figure 1). A punch biopsy was performed and revealed skin and focal subcutis with purpura (Figure 2). He remained on observation with instructions to return if the rash reappeared.

On December 13, 2017, Mr. S complained of fatigue and body aches. Bloodwork showed a WBC count of 2.1×10^9/L, Hgb of 9.8 g/dL, PLTC of 165,000/µL, and ANC of 0.63×10^9/L. He received pegfilgrastim and continued to hold both 6-MP and MTX.

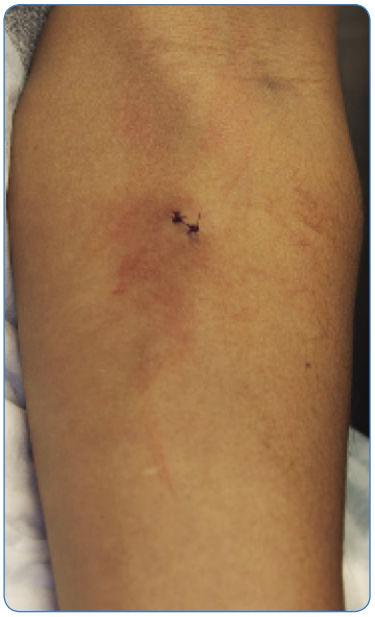

Figure 2. Punch biopsy on left forearm.

On December 27, 2017, bloodwork showed a WBC count of 3.4×10^9/L, Hgb of 9.3 g/dL, PLTC of 129,000/µL, and ANC of 1.63×10^9/L. Mr. S continued to report daily low-grade fevers preceded by an "aura" with profuse sweating, chills, malaise, and "burning skin" at the nodular sites. Further labs showed a C-reactive protein (CRP) elevated at 125 mg/L and an erythrocyte sedimentation rate (ESR) elevated at 53 mm/hr. Mr. S was referred back to dermatology. A repeat deeper biopsy of the left shin revealed skin and subcutis with dermal hemorrhage and septal fibrosis with mild septal and lobular lymphohistiocytic inflammatory infiltrate (Figure 3).

Due to inconclusive evidence, Mr. S. was referred to the infectious diseases department. At the time of initial evaluation, his symptoms were thought to be related to tumor fever. A workup was done including a chest x-ray and blood cultures. The chest x-ray was negative. Blood culture results after 2 days showed no growth.

DIFFERENTIAL DIAGNOSIS

WHICH IS THE CORRECT DIAGNOSIS?

A. Leukemia cutis (extramedullary acute leukemia)
B. Sweet syndrome (acute febrile neutrophilic dermatosis)
C. *Helicobacter cinaedi* bacteremia
D. Pyoderma gangrenosum
E. Lyme disease

SEE BACK FOR ANSWER ▶

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C ***Helicobacter Cinaedi* Bacteremia.** *Helicobacter cinaedi* is a Gram-negative spiral bacterium often isolated from immunocompromised patients. The bacterial was first isolated from rectal swabs obtained from homosexual men with proctitis, proctocolitis, and enteritis (Kawamura et al., 2014). A long incubation period and specialized techniques are essential for detection; it often takes 4 to 10 days for this culture to grow. The main symptom of *H. cinaedi* is fever; however, is it typically accompanied by arthritis and cellulitis at various spots of the body. These spots of cellulitis can be a primary site of infection or a secondary focus through the bacteremia (Kawamura et al., 2014). The typical skin lesion of cellulitis caused by *H. cinaedi* is salmon pink in color and accompanied by swelling. At the same time as the sudden onset of cellulitis, patients often have an elevation of body temperature, WBC count, and CRP.

In Mr. S, the initial skin biopsy was inconclusive; however, the second deeper punch biopsy showed results consistent with septal panniculitis, such as erythema nodosum. Due to the frequent recurrences of disease, prolonged antibiotic treatment is necessary (Uçkay et al., 2006). The reported duration of antibiotherapy ranges from 10 days to 12 weeks depending on the severity.

EXPLANATION OF INCORRECT ANSWERS

A **Leukemia Cutis (Extramedullary Acute Leukemia).** Leukemia cutis is an extramedullary manifestation of leukemia resulting from the entry of neoplastic leukocytes into the skin (Huang, Liu, Ruth, Potenziani, & Hsu, 2017). Patients often present with single or multiple red-brown, violaceous, or hemorrhagic papules, vesicles, nodules, bullae, or plaques. Cutis occurs in 10% to 15% of patients with acute myeloid leukemia (often monocytic or myelomonocytic origin) and is very rare in acute lymphoblastic leukemia (only 1%–3% of patients). Pathology of these lesions would show infiltration of atypical cells into the dermis and subcutis positive for particular cluster of differentiation markers, based on the immunophenotype of the leukemia.

B **Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis).** Sweet syndrome is an inflammatory disorder presenting with abrupt cutaneous manifestations of painful, edematous,

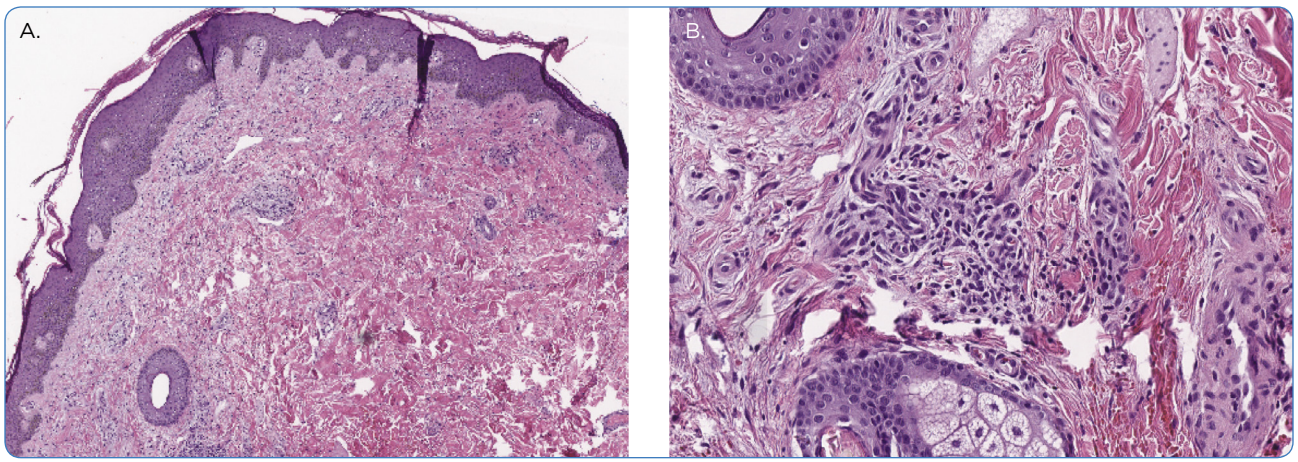

Figure 3. Punch biopsy of left shin. (A) At 2x magnification. (B) At 10x magnification.

and erythematous papules, plaques, and nodules on the skin (Merola, 2018) associated with fever, malaise, and joint and muscle pain. The diagnosis is divided into three categories based on the etiology: classical Sweet syndrome, malignancy-associated Sweet syndrome, and drug-induced Sweet syndrome. The diagnosis is made based on major criteria (abrupt onset of tender erythematous papules and nodules and dense neutrophilic infiltrate in the dermis without leukocytoclastic vasculitis) and minor criteria (fever > 38°C, at least 2 of 4 abnormal laboratory values (WBC count > 8.0×10^9/L, neutrophils > 70%, ESR > 20 mm/hr, and positive CRP; Kazmi et al., 2015). Biopsies of the lesions demonstrate a dense neutrophilic infiltrate in the dermis without vasculitis (Merola, 2018).

Classical (idiopathic) Sweet syndrome is not associated with a malignancy. Malignancy-associated Sweet syndrome is often associated with acute myelogenous leukemia. Drug-induced Sweet syndrome is often associated with G-CSF.

D **Pyoderma Gangrenosum.** Pyoderma gangrenosum is a rare autoimmune inflammatory and ulcerative neutrophilic dermatosis of the skin. It often presents as an inflammatory papule or pustule on the lower extremities that progresses and expands rapidly to a painful ulcer with a violaceous border and purulent base (Schadt, 2018). The pain is often greater than expected based on the appearance. Greater than 50% of patients have an associated systemic disease (i.e., inflammatory bowel disease, hematologic disorder, or arthritis), suggesting that dysregulation of the immune system may be a major contributor. Pathogenesis is poorly understood but may be associated with neutrophil dysfunction, genetic factors, and elevation in interleukin and tumor necrosis factor-α (Partridge et al., 2008). Diagnosis is based on clinical findings and histology as well as exclusion of other inflammatory or ulcerative disorders of the skin. Fever may or may not be present.

Bullous (atypical) pyoderma gangrenosum is a variant often seen in patients with hematologic disease and involves the arms and face. Patients typically present with rapidily developing blue-gray, inflammatory bullae, which develop into superficial ulcers (Schadt, 2018). Pustular pyoderma gangrenosum (associated with inflammatory bowel disease) and vegetative pyoderma gangrenosum (superficial granulomatous pyoderma) are two additional variants.

E **Lyme Disease.** Lyme disease is a tick-borne illness caused by *Borrelia burgdorferi* characterized by the characteristic erythema migrans skin lesion. The typical lesion, consisting of erythema with a central clearing, appears in 80% of patients within 7 to 14 days following a tick bite, and is often found in or near the axilla, inguinal region, popliteal fossa, or belt line (Hu, 2018). Multiple erythema migrans lesions are a sign of spirochetemia.

During the first week of infection, patients often display nonspecific signs and symptoms of a viral infection. Upper respiratory and gastrointestinal signs are uncommon and suggest an alternate diagnosis. The ESR is often greater than 2 times the upper limit of normal.

Diagnosis is made by recognition of the characteristic erythema migrans lesion and serologic testing to identify antibodies to *Borrelia burgdorferi* in patients with extracutaneous manifestations (Sanchez, Vannier, Wormser, & Hu, 2016). Serologic testing is often an adjunct to clinical diagnosis and should not halt treatment.

MANAGEMENT

After 5 days, 5 hours, and 7 minutes of incubation, Mr. S's blood culture was positive for *H. cinaedi*. *H. cinaedi* strains tend to be resistant to macrolides and show the lowest minimum inhibitory concentration values for carbapenems, aminoglycosides, and tetracyclines (Kawamura et al., 2014). Fevers and additional symptoms caused by *H. cinaedi*, including his erythema nodosum/cellulitis, resolved after 2 to 3 days of drug therapy with trimethoprim and sulfamethoxazole (Bactrim) double strength (DS) at 800/160 mg 2 tablets twice daily. Mr. S was instructed to complete 6 weeks of this therapy. Since completion, he has denied any recurrence of symptoms (Figure 4).

A high incidence of recurrence (40%) of *H. cinaedi* cellulitis has been documented in previous case reports of immunocompromised patients; however, it was not found to be due to antibiotic resistance (Kitamura et al., 2007). It is possible that this bacterium is a latent pathogen in some tissues, but it is often considered a causative agent of nosocomial infection. Many reports have also described

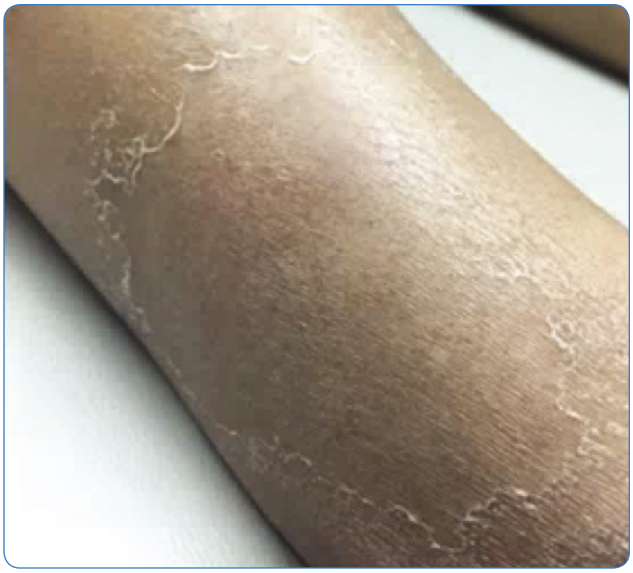

Figure 4. Healing on right lower extremity nodule.

the bacteremia caused by *H. cinaedi* as due to the organism's strong ability for vascular invasion (Kawamura et al., 2014).

Since *H. cinaedi* has been found to be involved in the progression of atherosclerosis due to the chronic inflammatory response it produces (Kawamura et al., 2014), Mr. S must also be monitored closely with a regular lipid profile and monitoring of potential arrhythmias.

Disclosure

The author has no conflicts of interest to disclose.

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