Painful subcutaneous nodules on the trunk and forearm in a young man

A 26-year-old man with a recently diagnosed mixed germ cell tumor of right testis (T1N1M0S1, AJCC stage IIA) underwent orchiedectomy and received adjuvant chemotherapy with a combination of bleomycin, etoposide, and cisplatin. During admission, a 5-day treatment of granulocyte-colony stimulating factor (G-CSF; Filgrastim, dosage 5 μg/kg/day) was administrated for the prophylaxis of chemotherapy-induced neutropenia. On day 3 of G-CSF therapy, he developed spiking fever with chills and simultaneous skin eruptions on his trunk and right arm. Physical examination showed several firm and painful subcutaneous nodules with overlying brown-to-violaceous discoloration on the left chest and abdomen and a single ill-defined erythematous indurated plaque with tenderness on the right forearm [Figure 1]. There was no history of preceding traumatic events or injection. Vital signs were notable for elevated temperature (39.1°C), tachycardia (heart rate, 112/min), and blood pressure of 108/61 mmHg. Laboratory surveillance revealed white blood cell count of $31.3 \times 10^3/\mu L$ (segment 95.0%) and C-reactive protein (CRP) of 5.29 mg/dL. Diagnostic workup for abrupt onset of fever including chest radiograph, urinalysis, urine, and blood cultures were performed; empiric antibiotic therapy with cefepime was initiated intravenously. A biopsy of one of the subcutaneous nodules on the left chest was carried out for histology evaluation and tissue cultures of bacteria, mycobacteria, and fungi. Microscopically, mild dermal perivascular lymphocytic infiltrates, marked neutrophilic lobular infiltrates with nuclear dust, and septal fibrosis in the subcutaneous fat tissue were noted [Figure 2].

What is Your Diagnosis?

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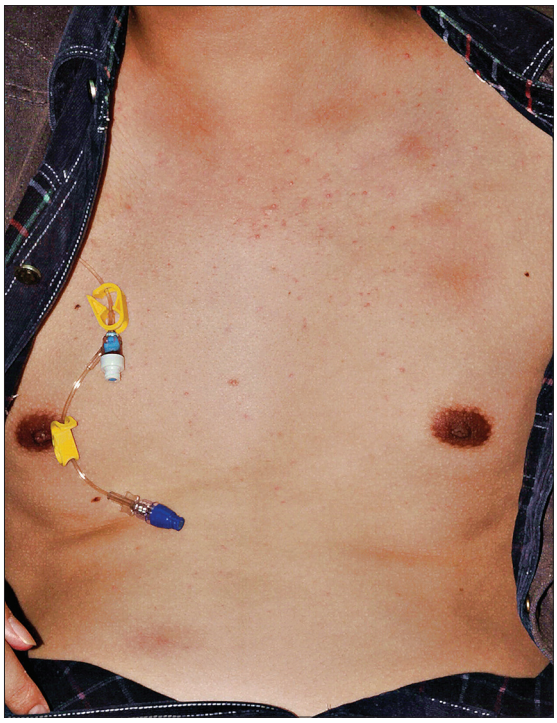

Figure 1a: Firm and painful subcutaneous nodules with overlying purpuric patches on left chest and abdomen

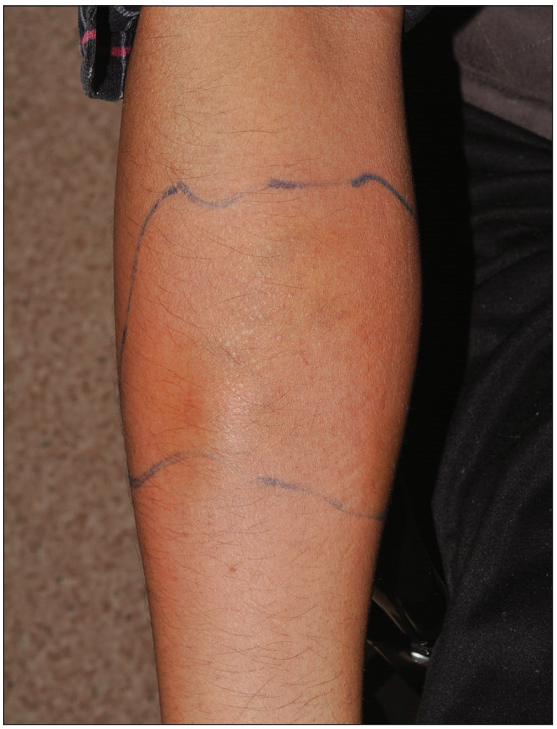

Figure 1b: One erythematous indurated plaque with tenderness on right forearm

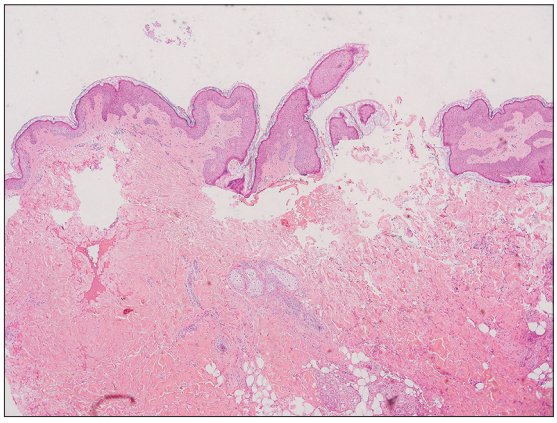

Figure 2a: Biopsy shows mild perivascular lymphocytic infiltrates in the dermis (H and E, ×40)

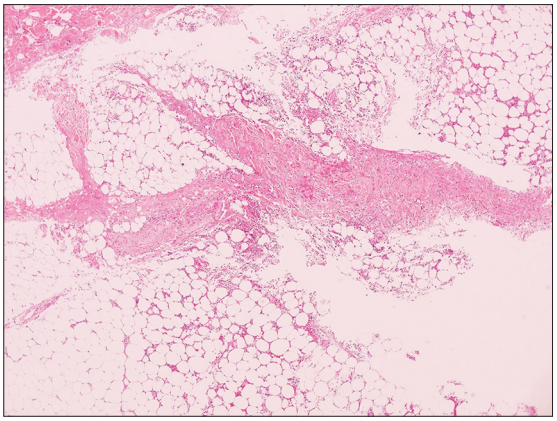

Figure 2b: Subcutaneous septal fibrosis and inflammatory infiltration in fat lobules (H and E, ×40)

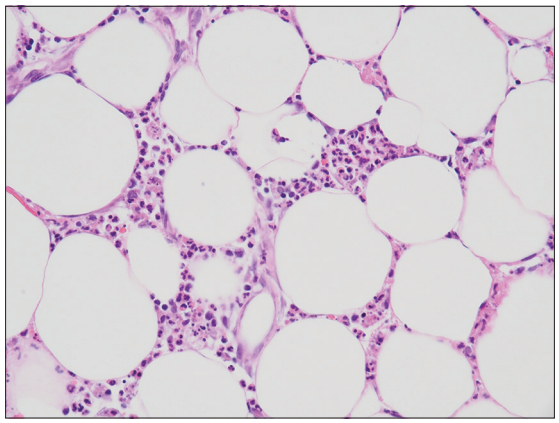

Figure 2c: The predominantly neutrophilic infiltrates and nuclear dust in fat lobules (H and E, ×200)

Answer

Subcutaneous Sweet's syndrome

The histopathologic studies revealed panniculitis with heavy neutrophilic infiltration in the fat lobules with leukocytoclasia and extravasated erythrocytes, but no vasculitis; the dermal neutrophilic infiltrate was minimal. There were no granulomas or foreign body. Special stains including periodic acid–Schiff, Gomori methenamine silver, and acid-fast stain were all negative. Chest radiograph and urinalysis were unremarkable. The blood, urine, and tissue cultures did not yield any growth. The painful subcutaneous lesions gradually subsided 5 days after discontinuing G-CSF. The presentation of the clinical course and histopathologic findings were compatible with the diagnosis of subcutaneous Sweet's syndrome.[1]

Sweet's syndrome has the characteristic features of abrupt onset of pyrexia, neutrophilia, and tender erythematous papules and plaques. Sweet's syndrome is an infrequent reactive skin disease classified into three clinical settings: classical, malignancy-associated, and drug-induced.[2] Malignancy-associated Sweet's syndrome was first described in a patient of testicular carcinoma in 1971, but is now most commonly associated with acute myeloid leukemia.

Subcutaneous Sweet's syndrome is a rare variant of Sweet's syndrome characterized by neutrophilic infiltration exclusively in the subcutaneous fat tissue with minimal dermal involvement. It presents with rapid onset of multiple deep-seated nodules or plaques with erythema and tenderness on the extremities and trunk.[3] In addition, subcutaneous Sweet's syndrome shows other typical clinical findings of Sweet's syndrome such as fever and malaise, and laboratory findings of neutrophilic leukocytosis and elevated CRP levels.[4] G-CSF, a hematopoietic agent known to induce stem-cell proliferation and differentiation of neutrophils, has only been occassionally reported in published cases of drug-induced subcutaneous Sweet's syndrome.[5]

Histopathologically, subcutaneous Sweet's syndrome is a neutrophilic lobular panniculitis with conspicuous leukocytoclasis without vasculitis.[6]

Clinically, the skin lesions of subcutaneous Sweet's syndrome may mimic neutrophilic eccrine hidradenitis or erythema nodosum. Neutrophilic eccrine hidradenitis usually occurs in patients of hematological malignancy undergoing cytotoxic chemotherapy. Spiking fever is predominantly observed in patients with neutrophilic eccrine hidradenitis with neutropenia, which is in contrast to subcutaneous Sweet's syndrome developing during neutrophilia. Erythema nodosum is the most frequent type of panniculitis possibly triggered by infection or medication and mainly exhibits painful nodules on the lower extremities. Neutrophilic eccrine hidradenitis and erythema nodosum can be distinguished from subcutaneous Sweet's syndrome on skin biopsy. Neutrophilic eccrine hidradenitis shows neutrophilic infiltrate within and around eccrine coils in deep dermis, while erythema nodosum is a prototypical septal panniculitis with predominantly lymphohistiocytic infiltrate, although neutrophils may be seen in early lesions. The histological differential diagnosis of neutrophilic lobular panniculitis without vasculitis includes subcutaneous Sweet's syndrome, pancreatic panniculitis, infective panniculitis, alpha-1 antitrypsin deficiency panniculitis, and factitial panniculitis. pancreatic panniculitis typically manifests as erythematous nodules with oily discharge due to enzymatic fat necrosis showing the "ghost-like" adipocytes microscopically. Infective panniculitis usually occurs in the setting of immunosuppression, while basophilic grungy necrosis on histopathology is highly suggestive; the demonstration of microorganisms on special stains and/or cultures is confirmatory. Alpha-1 antitrypsin deficiency panniculitis is an inherited metabolic disorder with histologic characteristics including splaying of neutrophils in reticular dermis and floating fat due to collagenolysis. Extensive hemorrhage and foreign body reaction may be observed in cases of factitial panniculitis associated with self-inflicted or iatrogenic fat injury.[6]

In some patients with drug-induced subcutaneous Sweet's syndrome, the lesions spontaneously resolve after withdrawal of culprit drugs. Administration of systemic corticosteroids may lead to rapid resolution of skin eruptions with favorable response.[5] Dapsone and cyclosporine may be given as the second-line agents, similar to those of Sweet's syndrome in treatment strategy.[7]

It is notable that this patient received another treatment of G-CSF after the next cycle of chemotherapy. Once again, he suffered from a spiking fever with tender subcutaneous nodules at different sites of his body including right forearm, abdomen, and left knee [Figure 3] as a temporally related recurrence 1 day after rechallenge of G-CSF. The skin eruptions dramatically resolved after withdrawal of G-CSF without administration of systemic antibiotics or corticosteroids.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Acknowledgement

The authors thank the patient for granting permission to publish this information.

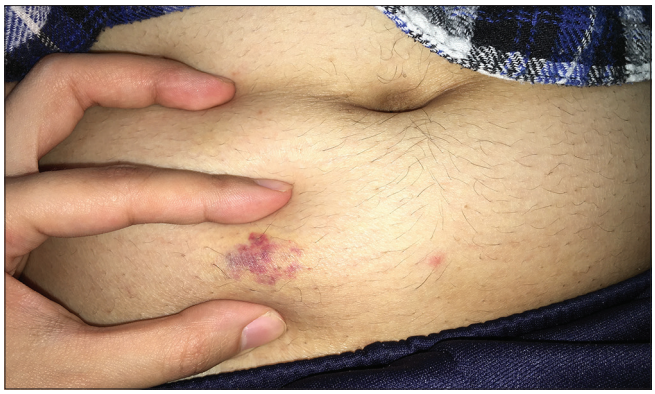

Figure 3a: One tender subcutaneous nodule with overlying purpura developed on the abdomen after rechallenging with granulocyte-colony stimulating factor

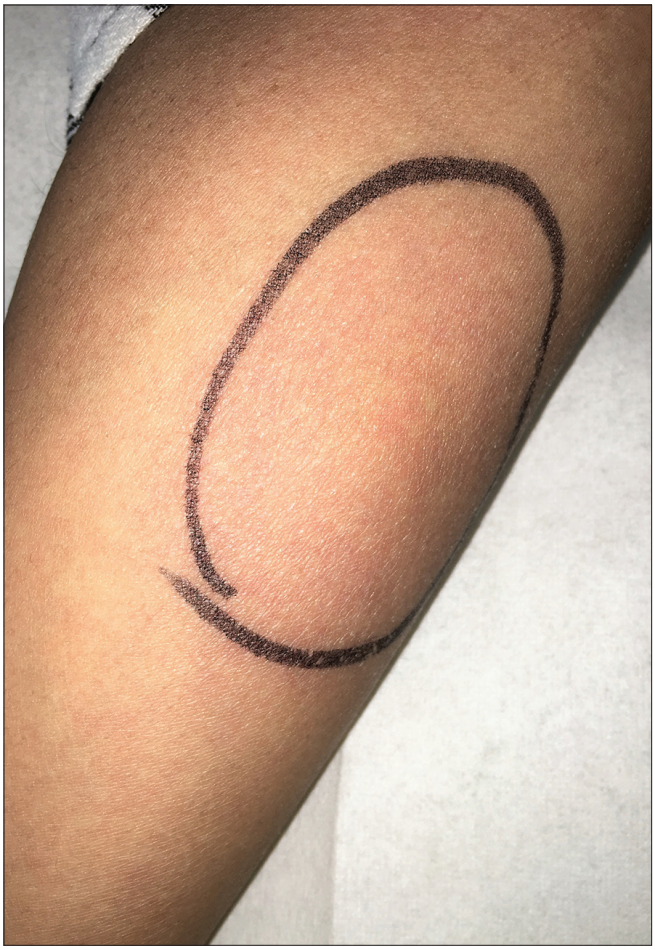

Figure 3b: One tender subcutaneous nodule on right forearm

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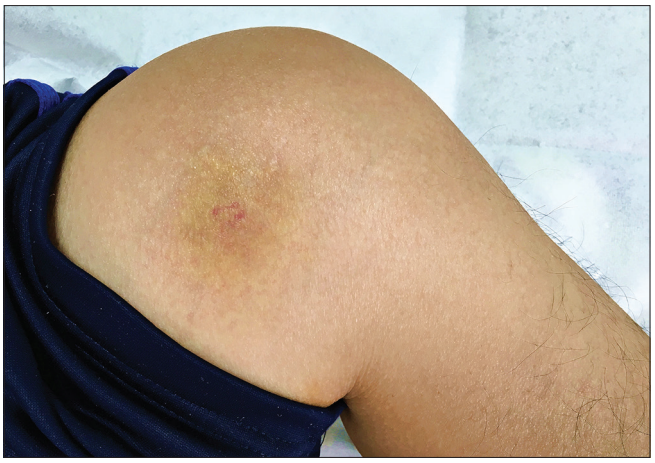

Figure 3c: A similar lesion on left knee

Conflicts of interest

There are no conflicts of interest.

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