A Case of Acute Myeloid Leukemia-Associated Necrotizing Sweet Syndrome

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Abstract
Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, is a rare painful skin condition that is characterized by hyperpyrexia, peripheral blood and skin neutrophilia, and edematous skin lesions. Necrotizing SS (NSS) is a severe and locally aggressive condition that histopathologically resembles a necrotizing soft tissue infection. As opposed to necrotizing soft tissue infections, NSS responds to systemic steroids. SS is divided into three subtypes: classical SS, malignancy-associated SS, and drug-induced SS. Within the malignancy-associated SS subtype, both solid tumor and hematologic malignancies have been precursors to developing SS. Here, we present a case of acute myeloid leukemia-associated NSS.

Introduction
Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, is a rare skin condition that affects both adults and children with no gender or racial predominance [1]. An exact incidence of SS has not yet been determined as the condition is primarily described through case reports or case series.

The disease is characterized by four cardinal signs: fever, peripheral neutrophilia found on complete blood count, and painful erythematous lesions with abrupt onset. Generally on
histological examination, SS appears as a diffuse neutrophilic infiltrate with dermal papillary edema that can involve the mid-dermis to the subcutis [2, 3].

SS can be divided into three main subtypes: classical, malignancy-associated, and drug-induced. Within malignancy-associated SS, the association between acute myeloid leukemia (AML) and SS is most well studied. In a recent study of 216 AML patients with biopsied skin eruptions, 5% were diagnosed with SS [4]. Within each subtype, there exists a continuum of clinical variants including bullous SS, cellulitis-like SS, and necrotizing SS (NSS). The case described here is an example of AML-associated NSS.

**Case Report**

A 68-year-old female with a past medical history significant of rheumatoid arthritis and essential thrombocytethemia presented with a 1-month history of malaise and progressive back pain to a community hospital. She denied night sweats, subjective fever, weight loss, and decreased appetite. Laboratory results showed a complete blood count with leukocytosis to 99,100 WBCs/µl (reference: 4,500–11,000). Given this finding, she underwent bone marrow biopsy that demonstrated 30% immature cells, consisting predominantly of promyelocytes, some monoblasts, and myeloblasts. These findings were most compatible with acute leukemia of monocytic differentiation (AML-M5). She was then transferred to our institution to be initiated on chemotherapy with azacytidine and venetoclax and, for several days, tolerated the treatment well.

In the second week of treatment, she developed a 25-cm area of erythema and severe induration with a central focus of two hemorrhagic flaccid bullae on her left posterior thigh (shown in Fig. 1a). In the 24 h following lesion development, the patient developed high fevers and her left thigh became indurated, swelling to double its size (shown in Fig. 1b). She was tachycardic and febrile with a maximum temperature of 101.5°F. Her blood pressure was unremarkable. Blood cultures were drawn, and broad-spectrum antibiotics were started. CT scan revealed cellulitis, fasciitis, and myositis (shown in Fig. 2). Given concern for necrotizing fasciitis (NF), clindamycin and metronidazole were started and the patient was taken to the operating room for debridement. Four sets of blood cultures taken since the onset of symptoms and wound cultures obtained in the operating room showed no growth. Histological examination of the skin and muscle biopsies showed dermal and deep fibromuscular tissue with acute inflammation and extensive hemorrhage and necrosis (shown in Fig. 3). These findings favored a

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Fig. 1. Left posterior thigh skin blistering and edema when symptoms were first noted (a) and 29 h later (b).
diagnosis of NF, but in the setting of negative wound cultures, the findings were deemed compatible with NSS. The patient improved within weeks following the initiation of steroids.

**Conclusion**

Differentiating NSS from NF is critical since the treatment is fundamentally different. NSS is often diagnosed after repeated negative wound cultures and worsening of disease despite surgical debridement and antibiotics, as was seen in the case described here [5, 6]. NSS clinically and histopathologically resembles NF, with features of fat necrosis and myonecrosis, but the lesions occur in the absence of an infectious cause. Pathergy is another prominent feature of NSS, in which intradermal trauma results in a nonspecific inflammatory response. Thus,
surgical debridement, the first-line treatment for NF, can cause new lesion development and exacerbation of NSS [7, 8].

Unlike NF, NSS responds well to steroids [9]. In one case of NSS mistaken for NF, repeated debridement worsened the patient’s inflammatory markers, fevers, and leukocytosis and resulted in a fifth digit amputation [8]. In a study of 48 patients with necrotizing dermatoses, involvement of dermatologist prevented three unnecessary amputations [9].

This case demonstrates the importance of collaboration between consultants to address the difficult clinical scenario of differentiating NSS from NF. Oncology, surgery, and dermatology were all key players in the care of this patient. In cases of diagnostic uncertainty, it is important to have multidisciplinary discussions to determine the best course of management. Given the association between hematologic malignancies and SS, keeping SS on the differential could prevent disease exacerbation from unnecessary debridement and lead to a more rapid initiation of appropriate treatment.

Statement of Ethics

Approval by the University of Maryland Medical School IRB was not required for this study. Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jennifer Strong was involved in the analysis of case data, literature review, drafting and revision of the manuscript, and final approval of the report. Albert Zhou was involved in case report conception, drafting and revision of the manuscript, and final approval of the report. Fahad Alkaabba was involved in case acquisition and analysis, revision of the manuscript, and final approval. Danielle Soldin, Hanan Alharthy, Owais Syed, and Yuchen Liu were involved in case acquisition and report conception, revision of the manuscript, and final approval. Joanne Moon, Kathryn Turney, and Janina Markidan were involved in case acquisition, revision of the manuscript, and final approval. Laura Malone was involved in case acquisition and interpretation, revision of the manuscript, and final approval. Seung Tae Lee and Peter DeRosa were involved in case analysis, revision of the manuscript, and final approval.

Data Availability Statement

All data generated or analyzed by this case report are included within. Further inquiries can be directed to the corresponding author.
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