Sweet syndrome masquerading as a disseminated and pulmonary fungal disease in a child with acute myeloid leukemia: case report and review of the literature

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Title: Sweet syndrome masquerading as a disseminated and pulmonary fungal disease in a child with acute myeloid leukemia: case report and review of the literature

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Abbreviations Key

Abbreviation	Full term/phase
AML	Acute myeloid leukemia

Abbreviation	Full term/phase
PCR	Polymerase chain reaction
CT	Computed tomography
IV	Intravenous
PO	Oral
BAL	Bronchoalveolar lavage
Granulocyte colony stimulating factor	G-CSF

Keywords: acute myeloid leukemia, Sweet syndrome, acute febrile neutrophilic dermatosis, pulmonary nodules

To the Editor:

Sweet syndrome, or acute febrile neutrophilic dermatosis, is characterized by the acute onset of fever and tender, erythematous skin nodules and plaques with skin histology demonstrating neutrophilic infiltration of the dermis. Extracutaneous manifestations such as pulmonary infiltrates are extremely rare. We present a 15-year-old female with a new diagnosis of acute myeloid leukemia (AML) who developed prolonged fever, diffuse painful erythematous maculopapular rash with multiple nodular and ground-glass opacities in the right lower lung on chest computed tomography (CT) with the initial concern of invasive fungal disease. Ultimately, the patient was diagnosed with Sweet syndrome.

A 15-year-old female was diagnosed with AML and began induction chemotherapy (daunorubicin, etoposide, and cytarabine). Shortly thereafter she became febrile and was started on IV Cefepime. On hospital day 6, the patient developed a painful, pruritic erythematous maculopapular rash that was first noticed on her face, neck, torso, and bilateral legs (Figure 1) but quickly spread to her arms and back. Given prolonged fever with neutropenia, disseminated rash, and chest CT findings of multiple hazy nodular and ground-glass opacities in the right lower lung which raised concerns for possible fungal etiology, IV Amphotericin B was started empirically. Extensive work-up for invasive fungal infection including serologic testing for Histoplasma, Aspergillus, and Blastomyces and fungal PCR from both BAL and skin biopsy were all negative. Skin biopsy did not reveal any bacterial or fungal elements, but instead demonstrated neutrophils at various stages of maturation infiltrating the superficial subcutaneous tissues which was highly consistent with acute febrile neutrophilic dermatosis, or Sweet syndrome. Her rash evolved again by forming more targetoid areas with central papule with peripheral clearing (Figure 1) during neutrophil recovery. Her fever resolved on hospital day 16. Repeat chest CT demonstrated complete resolution of pulmonary nodules within 3 weeks from the scan indicating that fungal etiology was less likely. Over the next several weeks, the patient's rash became lighter in color, and within three months, her rash had resolved.

Our case highlights diagnostics and treatment challenges of an unusual and rare case of sweet syndrome that mimics invasive fungal disease. Cutaneous manifestations almost always present first, but extracutaneous manifestations of the syndrome have been reported including pulmonary, ocular, cardiac, and neurologic. Pulmonary manifestations with only 4 cases reported in literature [5,9,10,11](Table 1). Chest radiographs can reveal diffuse pulmonary infiltrates or nodules mimicking pulmonary invasive fungal infection. When BAL is performed, high neutrophil counts without an identified organism are often found like in our case. Lung biopsies can also reveal interstitial inflammation and alveolar infiltration of neutrophils though is not always feasible.[7] Cutaneous manifestation almost always precede pulmonary involvement.[8]

The pathogenesis of Sweet syndrome is not well understood. Mechanisms of neutrophil proliferation are proposed which can be seen in patient who received G-CSF. Notably, our patient did not receive G-CSF during this hospitalization, nevertheless, her rash did become more diffuse and coalesced as her neutrophil recovered. Additionally, there is also concern that a mutation in a specific gene that encodes a receptor tyrosine kinase may cause persistent activation of cell proliferation. This hypothesis of pathogenesis may explain why Sweet syndrome is more common in AML patients. Diagnostic criteria of Sweet syndrome requires two

major criteria and two of four minor criteria[2]. Our patient demonstrated both major criteria as well as two minor criteria of fever and known hematologic malignancy. Treatment is usually with corticosteroids; however, symptoms usually self-resolve over weeks like in our case

Our patient's clinical presentation was more clinically consistent with Sweet syndrome than a fungal etiology because of the rash's rapid, diffuse, and painful onset. Although pulmonary manifestations certainly occur in the setting of disseminated fungal infection in immunocompromised hosts, usually these manifestations are accompanied by respiratory status changes such as dyspnea or hypoxia. Additionally, fungal elements would most likely be visualized on histological evaluation of the skin biopsy, which were not appreciated on our patient's specimen.

In cases of patients with cytopenia or severe bone marrow disease, the degree of neutrophilia within the dermis and the maturation of cells seen can be variable, making the diagnosis more challenging than in classic presentations. In cases with more immature myeloid precursors like the current case, it is important to rule out a diagnosis of leukemia cutis. In our case, the immunohistochemical profile of the immature neutrophils did not match that of the patient's known leukemia and the cells did not demonstrate blast markers (CD34), helping to exclude this possibility.

Sweet syndrome can often masquerade as other conditions, such as disseminated fungal infections in immunocompromised pediatric patients, it is vital to consider Sweet syndrome in the differential diagnosis and obtain a skin biopsy in any oncology patient with fever and worsening rash at the time of recovery. By diagnosing Sweet syndrome early, unnecessary antimicrobials and procedures can be avoided and, in the case of leukemia patients, chemotherapy should not be delayed as fungal etiologies are ruled out. This is the first described case of pulmonary involvement of Sweet syndrome in a pediatric patient with AML and increases knowledge of Sweet syndrome as a differential diagnosis in pediatric oncology with fever and worsening rash.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest to disclose.

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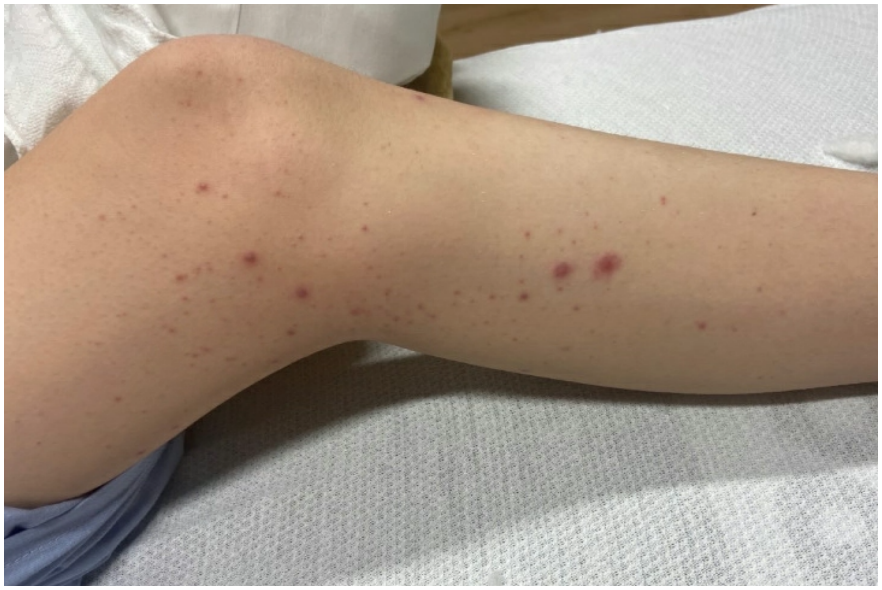

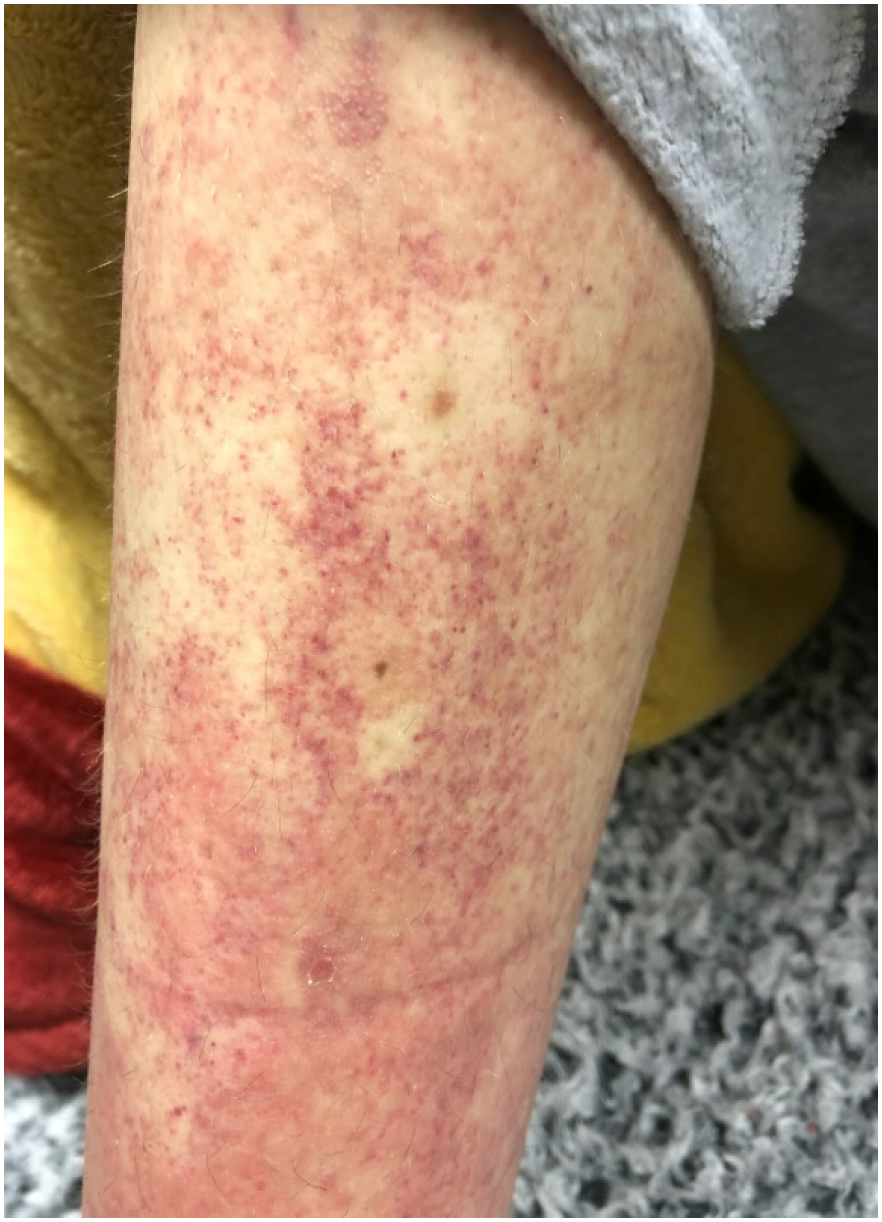

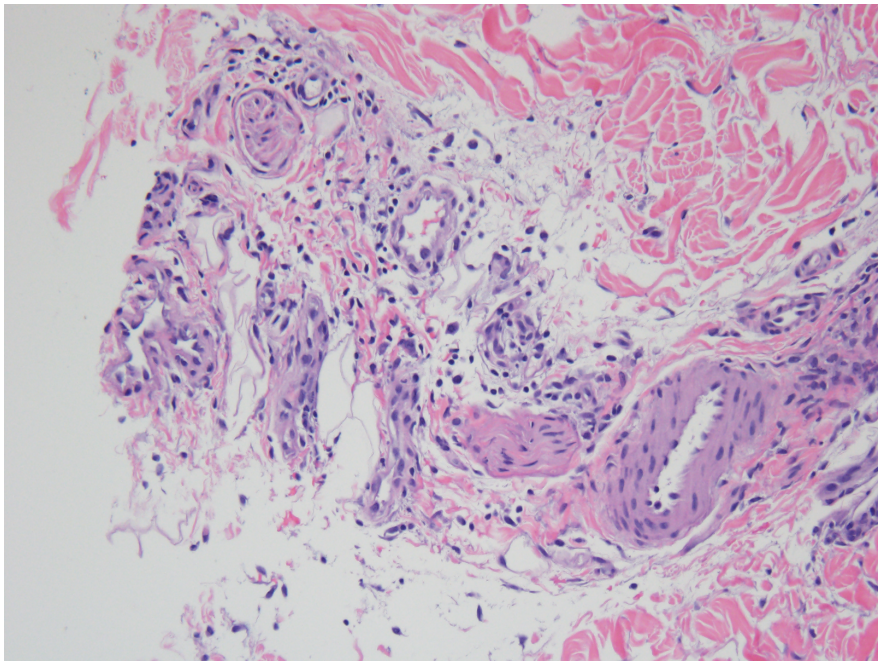

Figure 1:

Rash on right lower extremity, hospital day 6. B) Rash on left lower extremity, hospital day 18. C) High power view of the superficial subcutaneous tissue with a mix of neutrophils at various stages of maturation

Article Reference	**Patient age at time of diagnosis**	**Sex**	**Past medical history**
Collins et al.	27-month-old	Male	None
Tzelepis et al.	17-year-old	Male	Stage IV Hodgkin's lymphoma,
O'Reagan	17-year-old	Male	Common variable immunodeficiency,
Araki et al.	31-day-old	Female	None
Our case	15-year-old	Female	New diagnosis of acute myeloid leukemia within one

Table 1: Cases of pulmonary involvement in Sweet's Syndrome in pediatric patients

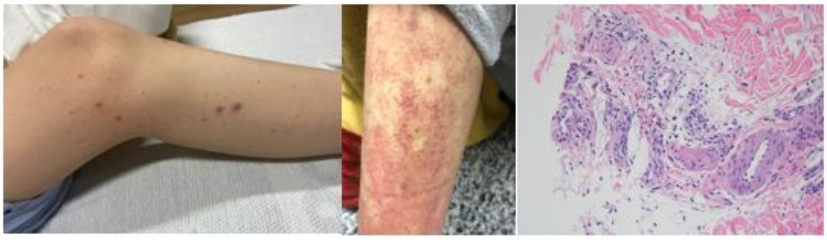

Figure 1:

A) Rash on right lower extremity, hospital day 6. B) Rash on left lower extremity, hospital day 18. C) High power view of the superficial subcutaneous tissue with a mix of neutrophils at various stages of maturation

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