CASE REPORT

An uncommon culprit of neutropenic fever: a case of Sweet syndrome following induction therapy for acute myeloid leukemia

Ahmed Alderazi*, Alec B. Rezigh

Department of Medicine, Baylor College of Medicine, Houston, TX, USA.

*Correspondence: Ahmed Alderazi Department of Medicine, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA. Email: ahmed.alderazi@bcm.edu

How to cite this article: Alderazi A, Rezigh AB. An uncommon culprit of neutropenic fever: a case of sweet syndrome following induction therapy for acute myeloid leukemia Arch Clin Cases. 2023;10(4):146-149. doi: 10.22551/2023.41.1004.10262

ABSTRACT

Sweet syndrome (SS) is a rare inflammatory disorder characterized by the rapid onset of a characteristically tender rash, fever, and other systemic symptoms. These manifestations are often mistaken for an infection that is not responding to antimicrobials, especially in immunocompromised hosts. We present the case of a 44-year-old woman who developed SS following induction chemotherapy for newly diagnosed acute myeloid leukemia (AML). She exhibited a painful rash on the anterior chest, which spread centrifugally, along with neutropenic fever unresponsive to broad-spectrum antimicrobials. Biopsy of the rash revealed a dense neutrophilic infiltrate within the dermis, confirming the diagnosis of SS. The patient was subsequently treated with systemic steroids with prompt resolution of fevers and improvement of her rash. This case highlights that SS can manifest with a robust neutrophilic infiltrate, even in the context of neutropenia stemming from chemotherapy. SS serves as a crucial consideration in hematologic malignancies, particularly AML, when patients present with fever and cutaneous eruptions. Prompt recognition followed by systemic steroid therapy often leads to symptom resolution.

KEYWORDS: Sweet syndrome; neutropenic fever; acute myeloid leukemia; chemotherapy

INTRODUCTION

Acute febrile neutrophilic dermatosis, often referred to as Sweet's syndrome (SS), refers to a rare inflammatory disorder characterized by the rapid onset of a characteristically tender rash, often accompanied by systemic symptoms like fever, arthralgia, headache and myalgias.

SS has been divided into 3 distinct categories depending on its associated precipitating factor: idiopathic, drug-induced, or malignancy. A set of diagnostic criteria have been proposed for the diagnosis of SS, with the abrupt onset of a painful rash and consistent histopathologic findings being prerequisites for the diagnosis. Although the exact pathophysiology of this disorder is yet to be fully elucidated, it is believed to encompass multiple different mechanisms which ultimately result in a cytokine cascade that leads to a pro-inflammatory state, promoting neutrophil proliferation, maturation, and extravasation into the skin [1].

In this case report, we describe a case of SS in a 44-year-old woman with newly diagnosed monocytic type AML shortly after induction chemotherapy.

Received: August 2023; **Accepted after review:** October 2023; **Published:** November 2023.

CASE PRESENTATION

A 44-year-old woman with a history of type 2 diabetes mellitus was admitted to the hospital with dysuria, fevers, and abdominal pain. She was found to have a white blood cell count of $91x10^9$ cells/L with a differential notable for 70% blasts, 11% lymphocytes, 7% neutrophils and 7% monocytes. Her hemoglobin was 8.9 g/dL and the platelet count was $45x10^9$ cells/L. Urinalysis revealed pyuria with urine culture subsequently growing extended spectrum beta lactamase (ESBL) *Klebsiella pneumoniae*. Pyelonephritis was diagnosed and she was treated with 7 days of levofloxacin with resolution of her symptoms and fevers.

With her elevated peripheral blasts, leukemia was suspected. Bone marrow biopsy was performed and demonstrated a hypercellular bone marrow with 85% blasts, consistent with a diagnosis of AML with monocytic features. Induction chemotherapy with cytarabine/idarubicin (7+3) was initiated.

On day 6 of induction, the patient developed neutropenic fever reaching 38.7 °C and, a day later, multiple tender erythematous papules and plaques with some scattered pustules on the anterior chest (Figure 1A).

Over the next 2 days, the rash spread centrifugally to the upper abdomen, bilateral upper limbs, neck, scalp, and ears

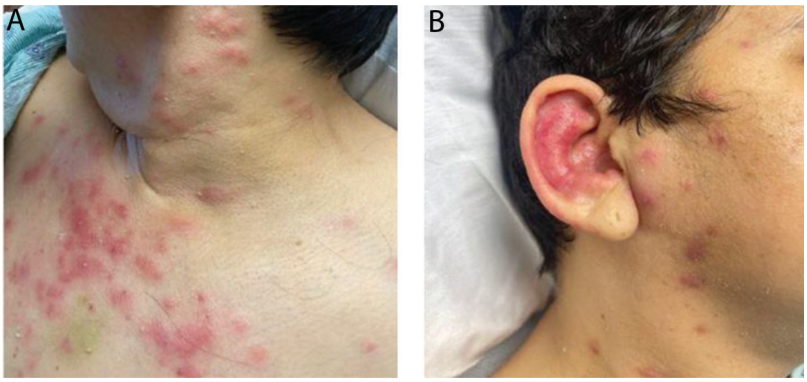

Fig. 1. Tender erythematous papules, pustules and plaques that spread centrifugally from anterior chest (A) to neck and ear (B).

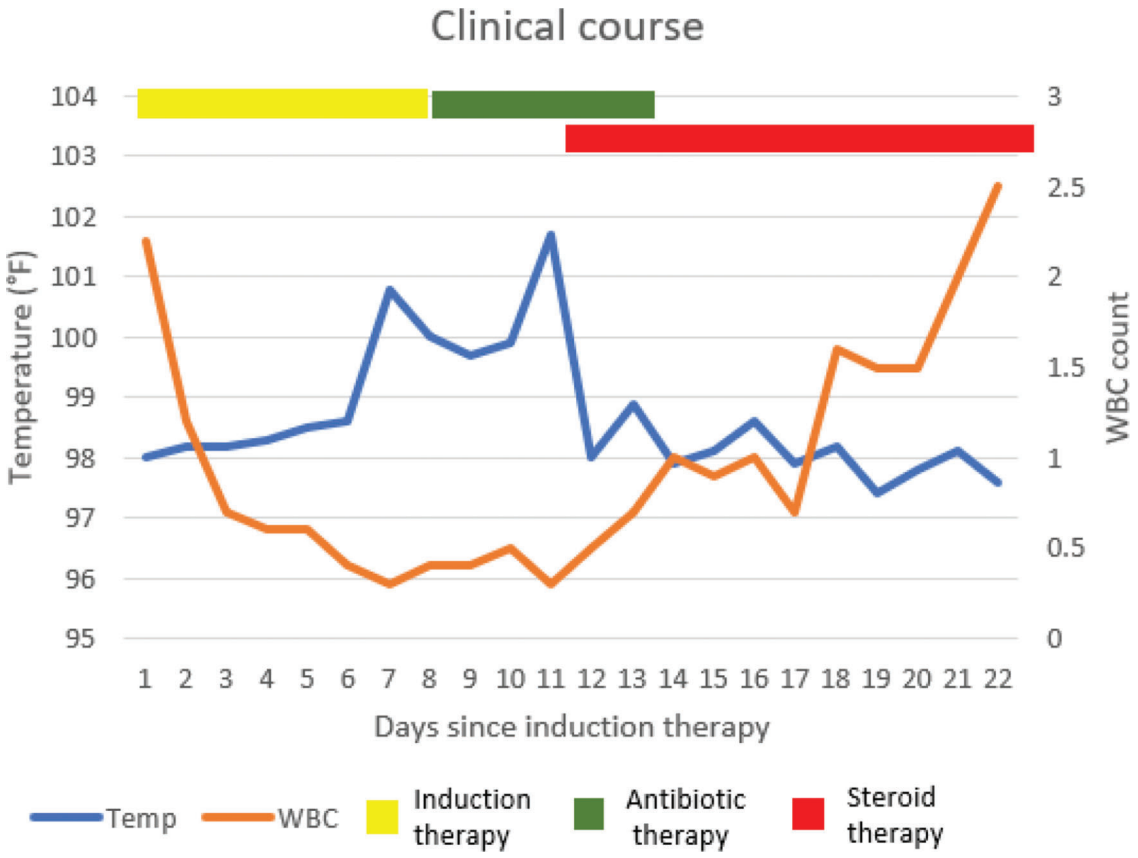

Fig. 2. Line chart demonstrating the clinical course of our patient, with prompt defervescence after initiation of steroid therapy.

(Figure 1B). The patient was started on cefepime for empiric treatment of neutropenic fever. Blood and urine cultures were subsequently negative and no potential source of infection was ultimately identified. Biopsy of the rash from the anterior chest was performed, revealing neutrophilic infiltration of the dermis with upper dermis edema and scattered reactive fibroblasts. Fungal and bacterial stains and cultures were negative. A presumptive diagnosis of SS was made and the patient was started on prednisone with prompt improvement of symptoms, including decreased erythema and tenderness of the rash and resolution of fevers (Figure 2). She was discharged two weeks after rash onset following count recovery to complete a 5-week steroid taper. Follow up 2 weeks into her steroid taper demonstrated near complete resolution of the rash. No recurrence of the condition was reported at an 8-month follow-up visit.

DISCUSSION

Since its first description by Dr. Robert Sweet in 1964, SS has been seen as the prototype of neutrophilic dermatosis, a group of heterogeneous conditions which share the same histologic pattern of dermal neutrophil infiltration without evidence of infection or vasculitis.

The incidence rate of SS in the general population is not well established, as the majority of literature on this rare dermatosis is limited to case studies and case series. One case series in Scotland reported an annual incidence rate of 2.7 per 1 million [2], although the incidence is likely increasing due to the more frequent use of culprit medications like growth factors [3]. Cases of SS are often divided into 3 categories depending on the clinical setting in which they present, with most cases falling into the classic (often also called idiopathic) category. Up to 10-20% of cases are diagnosed in the setting of malignancy (malignancy-associated SS) [4], and the remainder occur in relation to exposure to certain medications (drug-induced SS). SS can occur at any age, but the median age of onset is 30-50 years. Classic SS is associated with a 1:4 female predominance [5,6], though this female predilection is less consistently described in other subtypes of SS [4].

Malignancy-associated SS has been associated with multiple hematologic and solid malignancies, with the majority of cases reported in AML [3]. One retrospective cohort of 2,178 patients with AML found the incidence of SS to be 1% in this population [7]. Interestingly, the presence of SS can be a harbinger of an undiagnosed malignancy or relapse, prompting some authors to advise conducting a malignancy workup when SS is diagnosed [3].

Although the exact pathophysiology of this disorder is yet to be fully elucidated, it is believed that certain triggers (e.g., preceding infection, malignancy, medications) result in different immune responses that culminate in a dysregulated cytokine response that favors neutrophil proliferation, maturation, and dermal localization [1,8]. Clinically, this often manifests as a tender, erythematous rash (papules, plaques, nodules or papules), neutrophilic leukocytosis, fever and other systemic symptoms such as arthralgia. Extracutaneous SS has also been described, with diffuse neutrophilic infiltration of the lungs being the most common extracutaneous manifestation [3]. One of the more specific manifestations of SS (along with other neutrophilic dermatosis) is the phenomenon of pathergy, which refers to the propensity of minor skin trauma to induce localized skin lesions in this disease.

Given the broad differential diagnosis that exists in the context of a rash with systemic symptoms (including infectious, inflammatory, autoimmune and malignancy), a set of criteria was proposed by Su and Liu in 1986 for the diagnosis of SS, which were modified by von den Griesch in 1994 [9]. The criteria require the fulfillment of both major criteria and at least 2 minor criteria in order to diagnose SS (Table 1). Walker et al. suggested a modified set of minor criteria to allow for diagnosis of drug-induced SS (Table 2) [10].

In our patient, the temporal relationship between starting steroids and subsequent clinical and symptomatic improvement was clear, as shown in Figure 2. Notably, our patient was recently started on induction chemotherapy, which likely masked the leukocytosis that is expected with SS. The lack of leukocytosis (and often, neutropenia) has been well described in cases of SS with hematological malignancies owing to the natural progression of malignancies and associated chemotherapy [11].

Systemic corticosteroids are the mainstay of treatment for SS, although alternative first line therapies include potassium iodide and colchicine [5,12]. The recommended dose for systemic corticosteroids is prednisone 0.5-1mg/kg, with a gradual taper over 4 to 6 weeks [12], which our patient received. Characteristically, therapy results in prompt improvement in signs and symptoms (in fact, this response to therapy is part of the minor criteria for the diagnosis SS). However, SS has been known to recur. Higher rates of recurrence have been described in cases of malignancy-associated SS, though the presence of cutaneous SS itself does not appear to result in additional mortality in the setting of malignancy [7,13].

Table 1. Modified criteria for diagnosis of SS [9]. Both major and at least 2 minor criteria are required for diagnosis.

Major criteria	Minor criteria
Abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules, or bullae	Preceded by a nonspecific respiratory or gastrointestinal tract infection or vaccination or associated with: • Inflammatory diseases such as chronic autoimmune disorders, infections • Hemoproliferative disorders or solid malignant tumors • Pregnancy
Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis	Accompanied by periods of general malaise and fever (>38° C) Laboratory values during onset: ESR >20 mm; C-reactive protein positive; segmented-nuclear neutrophils and stabs >70% in peripheral blood smear; leukocytosis >8000 (three of four of these values necessary) Excellent response to treatment with systemic corticosteroids or potassium iodide

Table 2. Modified criteria for the diagnosis of drug-induced SS [10]. Both major criteria and all minor criteria are required for diagnosis

Major criteria	Minor criteria
Abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules, or bullae	Pyrexia >38 ° C
Predominantly neutrophilic infiltration in the dermis without leukocytoclastic vasculitis	Temporal relationship between drug ingestion and cardinal presentation, OR temporally-related recurrence after oral rechallenge Temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

CONCLUSION

The diagnosis of SS can be challenging given the wide differential diagnosis, especially in the context of hematological malignancies and other immunocompromised states. Therefore, recognition of this rare skin condition, along with its association with hematologic malignancies and some

medications used to treat them, is vital to facilitate prompt biopsy and diagnosis.

Informed consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interest

The authors declare that they have no competing interests.

REFERENCES

1. Heath MS, Ortega-Loayza AG. Insights Into the Pathogenesis of Sweet's Syndrome. *Front Immunol*. 2019;10:414. PMID: 30930894; PMCID: PMC6424218. doi: 10.3389/fimmu.2019.00414.
2. Kemmett D, Hunter JA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. *J Am Acad Dermatol*. 1990;23(3 Pt 1): 503-507. PMID: 2212153. doi: 10.1016/0190-9622(90)70250-L.
3. Raza S, Kirkland RS, Patel AA, et al. Insight into Sweet's syndrome and associated-malignancy: a review of the current literature. *Int J Oncol*. 2013;42(5):1516-1522. PMID: 23546524. doi: 10.3892/ijo.2013.1874.
4. Cohen PR, Kurzrock R. Sweet's syndrome and cancer. *Clin Dermatol*. 1993;11(1):149-157. PMID: 8339190. doi: 10.1016/0738-081X(93)90112-P.
5. Cohen PR. Sweet's syndrome--a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis*. 2007; 2:34. PMID: 17655751; PMCID: PMC1963326. doi: 10.1186/1750-1172-2-34.
6. Villarreal-Villarreal CD, Ocampo-Candiani J, Villarreal-Martínez A. Sweet Syndrome: A Review and Update. *Actas Dermosifiliogr*. 2016;107(5):369-378. English, Spanish. PMID: 26826881. doi: 10.1016/j.ad.2015.12.001.
7. Kazmi SM, Pemmaraju N, Patel KP, et al. Characteristics of Sweet Syndrome in patients with acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):358-363. PMID: 25630528; PMCID: PMC4457594. doi: 10.1016/j.clml.2014.12.009.
8. Joshi TP, Friske SK, Hsiou DA, et al. New Practical Aspects of Sweet Syndrome. *Am J Clin Dermatol*. 2022;23(3):301-318. PMID: 35157247; PMCID: PMC8853033. doi: 10.1007/s40257-022-00673-4.
9. von den Driesch P. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol*. 1994;31(4):535-556; quiz 557-60. PMID: 8089280. doi: 10.1016/S0190-9622(94)70215-2.
10. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol*. 1996;34(5 Pt 2): 918-923. PMID: 8621829. doi: 10.1016/S0190-9622(96)90080-8.
11. Cohen PR, Talpaz M, Kurzrock R. Malignancy-associated Sweet's syndrome: review of the world literature. *J Clin Oncol*. 1988;6(12): 1887-1897. PMID: 3058878. doi: 10.1200/JCO.1988.6.12.1887.
12. Cohen PR, Kurzrock R. Sweet's syndrome: a review of current treatment options. *Am J Clin Dermatol*. 2002;3(2):117-31. PMID: 11893223. doi: 10.2165/00128071-200203020-00005.
13. Zheng S, Li S, Tang S, et al. Insights Into the Characteristics of Sweet Syndrome in Patients With and Without Hematologic Malignancy. *Front Med (Lausanne)*. 2020;7:20. PMID: 32133363; PMCID: PMC7039821. doi: 10.3389/fmed.2020.00020.