

When the Skin Speaks for the Bone Marrow: Sweet Syndrome and Pancytopenia as the Initial Manifestation of Occult AML

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ABSTRACT

This case report describes the presentation for a 65-year-old patient with Sweet's syndrome (SS) presenting with systemic symptoms of general weakness, fever, and painful skin lesions on the right arm. He reported a history of weight loss with night sweats, while skin lesions manifested as erythematous plaques and painful papules. The diagnosis was confirmed by skin biopsy, which showed features of significant neutrophilic infiltration on histopathology. Further investigations led to the diagnosis of AML associated with Sweet's syndrome. The study highlights the importance of prompt diagnosis of Sweet's syndrome as a paraneoplastic sign and of using multidisciplinary approach for diagnosis and management of patients with skin lesions and cytopenias.

Keywords: Sweet syndrome; Acute myeloid leukemia (AML); Paraneoplastic

INTRODUCTION

Sweet syndrome is the most frequent febrile neutrophilic dermatosis. It presents with fever, tender erythematous papules, nodules, and plaques that mostly affect the face, neck, and upper limbs, and are distributed in an asymmetrical manner. The involved areas show prominent neutrophilic infiltrates in the upper dermis¹. The exact pathogenesis of Sweet's syndrome remains unclear; however, recent studies have shed light on the role of inflammatory signaling, disease initiation, and its association with malignancies. This includes a better understanding of inflammasome activation,

malignant transformation of dermal infiltrating neutrophils, and genetic factors. The cellular and molecular mechanisms highlight the difficulties in diagnosing Sweet's syndrome due to its similarity with other conditions that share clinical features². Diagnosis is primarily clinical, and histologic examination reveals a neutrophilic infiltrate in the lesions, which is needed to confirm the diagnosis. It is important for clinicians to recognize unusual presentations especially in cases of patients with preexisting diseases like myelodysplastic syndrome, since instead of neutrophils, atypical mononuclear coalescence in the infiltrate may be present³. A large-

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scale study with a significant population showed that Sweet syndrome is a serious dermatological disorder but also stressed the importance of its detection for the early diagnosis of neoplastic disorders. Sweet syndrome can present as an early indicator of recurrent malignancy and may facilitate diagnosis before the related neoplasm becomes apparent⁴. Timely recognition and proper treatment may affect the quality of life of patients. We present a case of Sweet's syndrome in association with AML. The aim of this paper is to emphasize the necessity of early diagnosis of this rare condition and to highlight strategies for the diagnosis and management of such cases.

Case Presentation

A 69-year-old man was admitted with generalized weakness, fatigue, heavy sweating, and painful skin lesions on his right upper limb. He had a history of poor appetite and had lost about 7 kg over the past two months. His weakness and fatigue had gradually worsened in the past month. He had intermittent fevers. Dyspnea had progressed in the past two weeks prior to admission.

The patient had erythematous plaques and painful papules on his forearm and elbow, which had developed in the past two weeks. The presence of lesions along with systemic symptoms suggested the dermatologic condition may have systemic origins. The lesions did not improve after a course of antibiotics.

A thorough review of the patient's history revealed no trauma, livestock exposure, or consumption of local dairy products suggesting zoonotic infection. The patient had no history of tuberculosis, an important differential diagnosis for systemic symptoms with skin lesions.

On physical exam, the patient was not toxic-appearing. The patient's vital signs were stable with fever. The spleen was of normal size and there was no evidence of lymphadenopathy.

Dermatological examination revealed three non-itchy erythematous plaques: two on the right arm and one on the right forearm. Additionally, a non-pruritic erythematous papule was observed on the left forearm, presenting two after the appearance of the plaques. All lesions were tender and edematous

on examination, suggesting an inflammatory process. The plaques on the arm had an annular structure with a central clearing (Figure 1).

The combination of systemic complaints, weight loss, and the specific characteristics of the skin lesions raised a red flag and warranted a multidisciplinary approach. Consultation with an infectious diseases specialist, a dermatologist, and a hematologist was requested to rule out the possibility of malignancies or systemic infections that could explain the patient's clinical presentation.

Initial patient evaluation included CBC, LFTs, RFTs, serum electrolytes, and inflammatory markers (Table 1).

An incisional skin biopsy of the plaque on the right forearm was performed. Histopathological examination showed dermal edema and a pronounced neutrophilic infiltrate within the dermis with diffuse distribution. Endothelial cell swelling and RBC extravasation were noted. Mild peri-eccrine lymphocyte infiltration was also present, along with moderate epidermal spongiosis (Figure 2).

The microscopic findings confirmed the diagnosis of Sweet syndrome. Sweet syndrome is a rare, acute febrile neutrophilic dermatosis often associated with systemic illness, particularly malignancies. Because of pancytopenia and elevated ESR in the context of the known association between Sweet syndrome and malignancies, bone marrow aspiration and biopsy was performed. The peripheral blood smear revealed medium-sized myeloid blasts. Flow cytometry showed 22% myeloid blasts with an immunophenotype positive for CD13, CD33, CD64, and CD117, and negative for CD34 and HLA-DR, which is highly suggestive of AML (non m3). Bone marrow aspiration revealed a hypercellular marrow with dysplastic changes and approximately 25% medium-sized myeloid blasts (Figure 3). These findings confirmed the diagnosis of Sweet's syndrome in association with acute myeloid leukemia (AML). Given the patient's age and performance status, treatment with azacitidine and venetoclax was initiated. This resulted in resolution of the skin lesions and hematologic remission of the AML. Unfortunately, the leukemia subsequently relapsed, and the patient died from the disease.

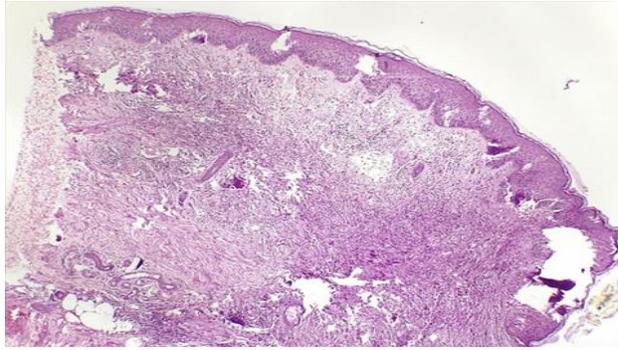
Table 1: Patient's laboratory results

Variable	Value	Unit
WBC	9.8	$\times 10^9/L$
RBC	3.58	$\times 10^9/L$
Hb	10.3	g/dL
MCV	91.1	fL
Platelets	118000	μL
ESR	73	mm/hr
Urea	25	mg/dL
Cr	0.9	mg/dL
Uric acid	2.5	mg/dL
Na	132	mEq/L
K	3.9	mEq/L
Bilirubin total	0.8	mg/dL
Bilirubin direct	0.2	mg/dL
AST	32	U/L
ALT	50	U/L
Alp	275	U/L
CRP	+1	mg/dL
LDH	475	U/L

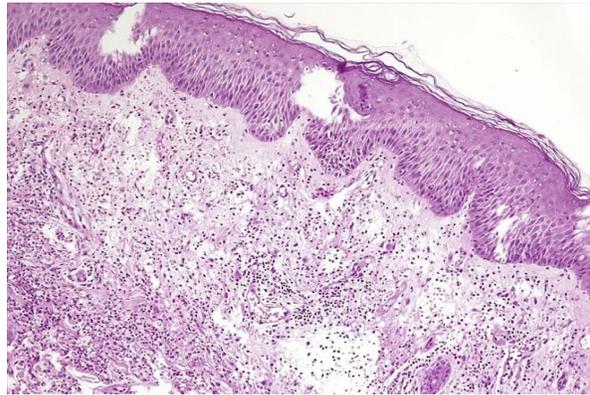
WBC: White blood cells, RBC: Red blood cells, Hb: Hemoglobin, MCV: Mean corpuscular volume, ESR: Erythrocyte sedimentation rate, AST: Aspartate transaminase ALT: Alanine transaminase, ALP: Alkaline phosphatase, CRP: C-reactive protein, LDH: Lactate dehydrogenase



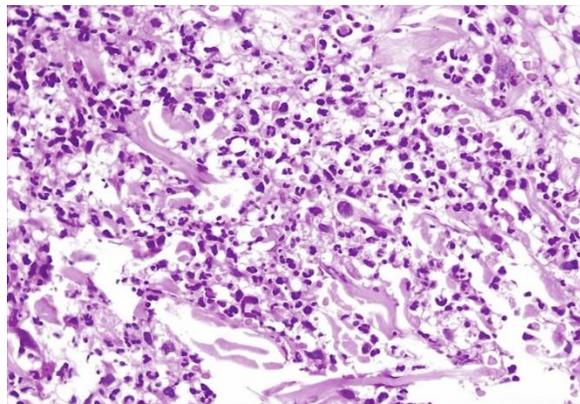
Figure 1. Skin lesions: Erythematous and edematous papules and plaques on upper extremities



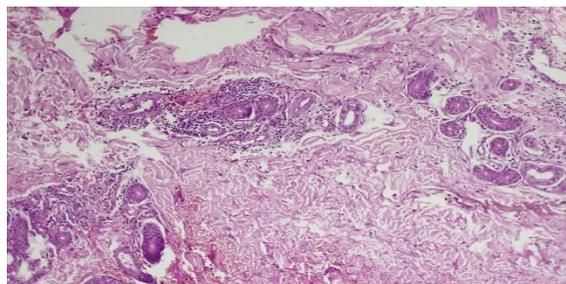
A) Dermal edema with diffuse and intense neutrophilic infiltration



B) Notable dermal edema



C) Intense neutrophilic infiltrations



D) Focal peri-eccrine lymphocytic infiltrations

Figure 2. Skin biopsy

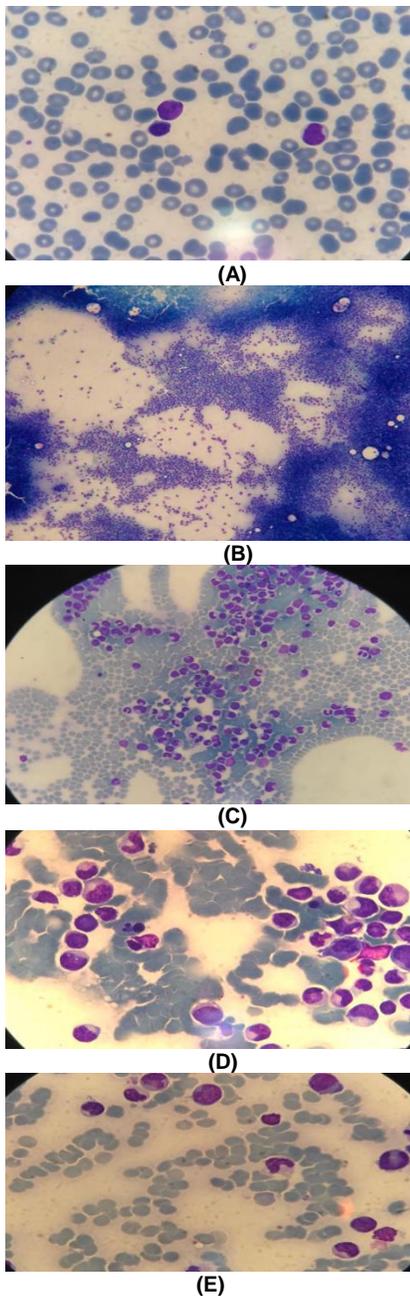


Figure 3: Peripheral blood smear (Image A) demonstrates circulating blasts with high nuclear-to-cytoplasmic ratio, fine chromatin, and scant cytoplasm. Bone marrow aspirate smears (Images B, C, D and E) show markedly hypercellular fields with dense aggregates of myeloblasts displaying fine chromatin, prominent nucleoli, and occasional cytoplasmic granules, consistent with extensive marrow infiltration by acute myeloid leukemia.

DISCUSSION

In 1964, Dr. Robert Douglas Sweet named a condition that had a **small number of** but significant identifications in a series of eight women "acute febrile neutrophilic dermatosis." These patients had four major characteristics: fever; the presence of polymorphonuclear leukocytes neutrophils in the blood; the presence of painfully raised plaques in the limbs, face, and neck; and histological evidence for a significant dermal infiltration by mature neutrophil polymorphs. While he acknowledged that the clinical picture resembled that of erythema multiform, Dr. Sweet considered it to be a separate pathological entity not recorded in the medical literature before this time. The condition would later become widely known as Sweet syndrome⁵.

Skin manifestations of SS mainly present as erythematous plaques and bumps of different sizes primarily located on the extremities as well as the face and neck. In contrast, further involvement of the trunk, back, and mucosal surfaces is rare⁶. Histopathological examination shows a prominent neutrophil infiltration in the dermal layer⁷. This is an unusual condition that manifests as the sudden appearance of very painful, reddish plaques or nodules that may be accompanied by fever, arthralgia, and systemic symptoms like headache. This condition is primarily diagnosed based on clinical findings; however, histological evaluation of the lesions shows a prominent neutrophilic infiltrate, which is important for confirming the diagnosis⁸. This case embodies the clinical picture of Sweet syndrome. It has a typical febrile pattern and histological findings show a marked neutrophilic infiltrate consistent with the acute onset of painful erythematous plaques or nodules.

Sweet's syndrome is seen in three major clinical settings: classical (or idiopathic), malignancy-associated, and drug-induced. Malignancy-associated Sweet's syndrome (MASS) may present as a paraneoplastic syndrome in patients with established malignancies or those with occult hematologic neoplasms or solid tumors and is most commonly linked to acute myelogenous leukemia. In addition, Sweet's syndrome can be a dermatologic marker for an occult malignancy or evidence of cancer recurrence^{9,10}.

In the setting of malignancy-associated Sweet's syndrome, the overall hypothesis regarding its pathogenesis centers on dysregulation and overproduction of inflammatory cytokines. Interleukin-1 (IL-1), interleukin-3 (IL-3), interleukin-6 (IL-6), interleukin-8 (IL-8), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are key cytokines involved in this pathogenic process¹⁰. Around 10 to 15 percent of documented instances of Sweet's syndrome have been reported in individuals diagnosed with cancer⁷. A high percentage, approximately 85%, of malignancy-related Sweet's syndrome has been linked to underlying hematologic neoplasms, and the most frequent among them has been acute myeloid leukemia. Myeloproliferative neoplasms, diffuse large B-cell lymphoma, Hodgkin's lymphoma, myelodysplastic syndrome, and myelofibrosis have also been reported. Among solid tumors, carcinomas originating from the genitourinary tract, breast, and gastrointestinal tract are most commonly implicated, with adenocarcinoma accounting for 57% of these cases. Recent observations suggest that the incidence of Sweet's syndrome is on the rise, attributed to increased awareness among healthcare professionals¹⁰⁻¹⁴. Sweet syndrome may occur before, at the same time or after a malignancy is diagnosed. In cancer, it usually occurs in older adults and is associated with cytopenias⁸. In one study among the hematologic malignancies associated with Sweet syndrome, AML and myelodysplastic syndromes (MDS) each occurred in 11% of patients, while multiple myeloma (MM) was present in 3%. The frequency of AML in this patient population was 4%^{12, 15}. The pathogenic mechanisms of Sweet syndrome (SS) in acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) are not yet known. Recent studies have shown the presence of genetic mutations in clonal neutrophilic infiltrates in SS lesions, and these are consistent with the primary hematological diseases. Most patients developed Sweet syndrome after their hematologic malignancy was diagnosed. This temporal relationship suggests that cytopenias, such as thrombocytopenia and anemia, may not only indicate undiagnosed AML/MDS but could also be a

consequence of that malignancy's treatment. Additionally, the erythrocyte sedimentation rate (ESR), was observed to be elevated in patients with hematologic malignancies and Sweet syndrome. Casarin Costa et al. found an association of malignancy with high ESR levels in patients with sweet syndrome¹⁶⁻¹⁹.

Changes in blood parameters occurred alongside symptom onset, and both rapidly resolved together. This strong association suggested a possible malignancy, prompting further tests to confirm or rule out the diagnosis.

Sweet syndrome secondary to acute myeloid leukemia (AML) often deteriorates rapidly and typically involves subcutaneous tissue. This presentation is often steroid-resistant, necessitating both a prompt diagnostic workup for an underlying malignancy and the early initiation of chemotherapy. While genetic abnormalities may be implicated in the unusual presentation of the disease, more research is needed to establish this²⁰.

This report underscores the overriding significance of clinicians suspecting Sweet syndrome as a potential paraneoplastic syndrome in patients presenting with cytopenias. Prompt identification and treatment of SS not only may decrease patient discomfort but can also result in earlier diagnosis of underlying malignancies. Future research into the genetic and immunologic aspects of Sweet syndrome in blood cancers will help clarify its pathophysiology and enhance patient care.

This case illustrates the complex interplay between dermatologic manifestations and systemic disease, highlighting the critical role of a multidisciplinary approach in diagnosing and managing patients with atypical cutaneous presentations.

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