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Case Report

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Sweet's Syndrome as a Prodromal Manifestation of Acute Myeloid Leukemia

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ABSTRACT

Sweet's syndrome is a rare dermatological condition characterized by a constellation of clinical features, including fever, neutrophilic leukocytosis, painful skin plaques, and dermal neutrophil infiltration. Various etiologies have been documented, encompassing both underlying diseases and pharmacological agents. We present a case involving a 35-year-old female patient who exhibited fever and progressive cutaneous lesions manifesting as a painful erythematous rash on the limbs and trunk. Initially misdiagnosed as seronegative lupus erythematosus, her condition did not improve. A skin biopsy revealed significant neutrophilic infiltration, and she subsequently developed leukocytosis, leading to a diagnosis of acute leukemia upon bone marrow examination. The patient was treated with chemotherapy, resulting in a relative improvement of her skin lesions.

Keywords: Sweet's syndrome; Acute myeloid leukemia; Neutrophil aggregation in the dermis; Case report

INTRODUCTION

Paraneoplastic manifestations can occur in association with various malignancies, either preceding, coinciding with, or following the diagnosis of the underlying condition. Sweet's syndrome is recognized as one such paraneoplastic manifestation, particularly in hematological malignancies. However, it can also arise in the context of inflammatory conditions or as a reaction to certain medications. In cases where Sweet's syndrome is not attributable to drug use or identifiable underlying diseases, it is imperative to consider it as a paraneoplastic manifestation of an underlying malignancy. The case presented herein is an atypical instance of Sweet's syndrome, emerging as a prodromal manifestation of acute myeloid leukemia.

Case presentation

The patient, a 35-year-old woman with no significant past medical history or drug use, presented to the Dermatology clinic with a two-week history of fever, malaise, and rapidly evolving skin lesions. She reported marked tenderness in the affected areas, prompting her hospital visit. Upon examination, multiple well-defined erythematous papules, ranging from 0.5 to 3 cm, were observed on the upper arms, neck, and face. Some papules had coalesced into larger, distinctly raised plaque-like lesions with a purplish hue. Several lesions progressed to form bullae filled with clear fluid, particularly notable on the forearms, surrounded by erythematous halos. The lesions were notably painful upon palpation, contributing to the patient's discomfort. Initial treatment included topical steroids and emollients; however, due to a lack of

improvement and progression of the lesions, laboratory tests were conducted. The laboratory findings indicated a white blood cell count of 4.6×10^9/L with 56% neutrophils, hemoglobin of 10.5 g/dL, platelets of 87×10^9/L, erythrocyte sedimentation rate of 23 mm/hour, CRP of 8 mg/L, creatinine of 0.57 mg/dL, and normal liver function tests. Rheumatological tests revealed positivity for HLA B5, HLA B51, and HLA B52, while other tests returned negative results. Tests related to interleukins were not conducted. Given these findings, the patient was treated with oral corticosteroids and tacrolimus; however, instead of improvement, progression of the skin lesions was observed. Examination revealed additional lesions on her legs, upper arms, and face, predominantly in the form of annular pink plaques, some with crusted centers and visible vesicles, as depicted in Figure 1A.

Investigations

During the monitoring period of the patient's skin lesions, continuous laboratory evaluations were performed, focusing on complete blood counts (CBC), differential counts, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels, which are critical for assessing the patient's hematological status and inflammatory response. The only significant finding during the initial monitoring was mild thrombocytopenia, attributed to the side effects of prescribed medications. Other laboratory parameters remained stable throughout this phase. However, after two months, the extent of the skin lesions on the patient's trunk significantly progressed, accompanied by notable changes in the CBC: the white blood cell count rose to 103×10^9/L with atypical cells present, hemoglobin decreased to 9.4 g/dL, and platelets dropped to 37×10^9/L. These substantial alterations necessitated further investigation, prompting a bone marrow aspiration and biopsy, which revealed a high number of blast cells consistent with myeloid blast cells of acute myeloid leukemia M4 on flow cytometry. Chromosomal analysis indicated a 46XX karyotype and NPM1, CEBPA and, FLT3 wild type in genetic mutation. Additionally, neutrophil aggregation was noted in the dermis upon skin biopsy. This study was conducted in accordance with ethical guidelines, and the protocol was approved by the Institutional Review Board, with the approval code IR.AJUMS.REC.1403.551.

Treatment

The patient underwent chemotherapy utilizing a 7+3 regimen. Ten days following the administration of the 3+7 regimen, the patient entered the nadir phase and developed pancytopenia. During this period, he experienced fever and neutropenia, which was effectively managed. After the initiation of broad-spectrum antibiotics, the patient's fever subsided, and by day 23, her white blood cell count exceeded 1500. Within a few days, the CBC showed signs of recovery. Concurrently, the skin lesions began to improve, as illustrated in Figure 1C. Following the resolution of the nadir phase, a subsequent bone marrow examination was conducted, revealing that the patient achieved complete remission, with notable improvement in the skin lesions.

Outcome and follow-up

The patient is a candidate for allogeneic bone marrow transplantation. At the time of this article's submission, the patient remains in complete remission and is receiving high-dose cytarabine (HIDAC) chemotherapy, while also being placed on the waiting list for the bone marrow transplantation department.

DISCUSSION

Sweet syndrome is a rare, non-infectious dermatosis predominantly affecting the upper limbs, trunk, neck, and face[1]. First described by Sweet in 1964, this syndrome is characterized by an immune-mediated mechanism and has since borne his name[2]. Lesions typically present as painful plaques, erythematous nodules, or papules. In conjunction with cutaneous manifestations, systemic symptoms such as fever, headache, arthralgia, and leukocytosis may occur[1], and there can be involvement of additional organs, including the eyes, musculoskeletal system, and internal organs. Sweet syndrome is classified into three subtypes based on its etiology: Classical Sweet syndrome, Malignancy-associated Sweet syndrome, and Drug-induced Sweet syndrome[3]. The term "acute febrile

neutrophilic dermatosis" highlights the frequent occurrence of fever exceeding 38°C, which is almost universally present in drug-induced cases, but only seen in 10–20% of patients with classical or malignancy-associated forms[4]. Other common symptoms include arthralgia, lethargy, headache, and myalgia[5]. Inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein levels may also be elevated. Histopathological findings are critical for the diagnosis of Sweet syndrome, necessitating a skin biopsy for confirmation[3]. Histological features typically reveal pronounced edema in the superficial dermis, dense neutrophilic infiltration in the upper and middle dermis, leukocytoclasis, endothelial swelling, and an absence of vasculitis. A few eosinophils may be observed, while older lesions may show sparse lymphocytes or macrophages[6]. Generally, neutrophilic and lymphohistocytic infiltration along with edema are the predominant findings in histopathological examinations[7]. The precise pathogenesis of Sweet syndrome remains poorly understood, with proposed contributing factors including hypersensitivity reactions, cytokine dysregulation, and genetic predispositions [3]. Certain HLA-B alleles have been associated with autoimmune conditions; for instance, HLA-B27 is linked to spondyloarthropathies and joint diseases[8]. HLA-B polymorphism influences antigen presentation to T cells and modulates the immune response to foreign agents[9]. Specifically, HLA-B54 has been associated with Sweet syndrome in Japanese cohorts[10]. Diagnosis relies on clinical, laboratory, and histological criteria, with established diagnostic guidelines facilitating accurate identification of the condition[11,12]. According to these criteria, a diagnosis of Sweet syndrome requires fulfillment of two major and two minor criteria.

Major criteria:

1. Abrupt onset of painful erythematous plaques or nodules.
2. Dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis on histopathology.

Minor criteria:

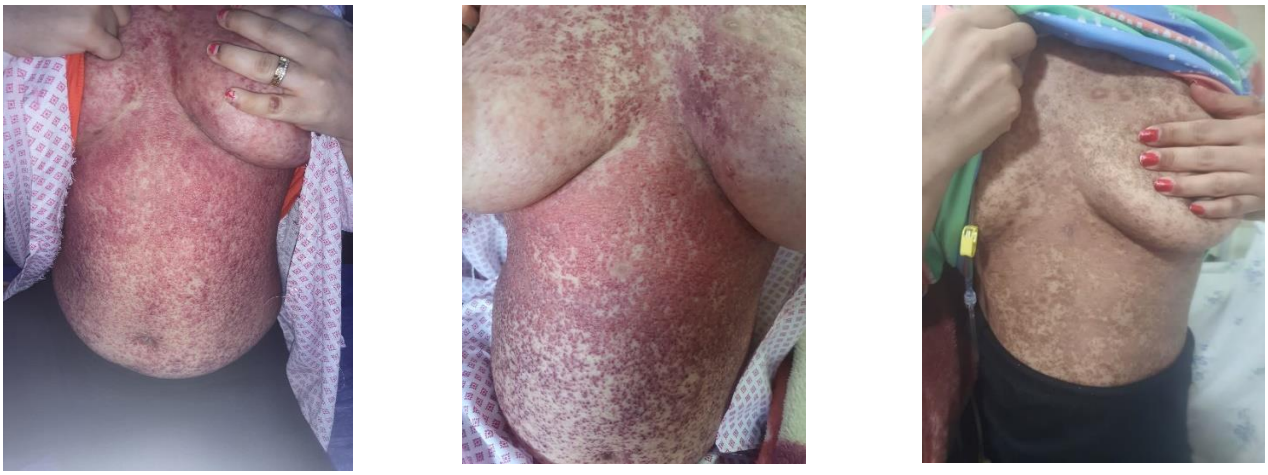
1. Fever >38°C.
2. Association with an underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy, or preceded by an upper respiratory or gastrointestinal infection or vaccination.
3. Excellent response to treatment with systemic corticosteroids.
4. Abnormal laboratory values at presentation (three of four): erythrocyte sedimentation rate >20 mm/hour; positive C-reactive protein; leukocyte count >8000; neutrophils >70% [13].

In 1993, a review of multiple retrospective studies indicated that 25 of 118 patients with Sweet syndrome (21%) had hematologic malignancies or solid tumors[14]. Malignancy-associated Sweet syndrome constitutes a significant subset of cases[15]. No significant difference was observed in histopathological features between patients with and without hematologic malignancies[16]. Sweet syndrome can be associated with hematological malignancies, including acute myeloid leukemia (AML)[17]. In cases associated with AML, Sweet syndrome may manifest in atypical clinical forms that exhibit aggressive behavior and are frequently associated with subcutaneous involvement. Although chemotherapy for AML may play a crucial role in the development of Sweet syndrome, the exact mechanisms remain unclear. This condition is often considered steroid-resistant, with genetic abnormalities potentially influencing its atypical presentation[18]. Leukemia is a malignant neoplasm affecting the hematopoietic system. Following a phase of dissemination in the bone marrow and the emergence of leukemic cells in peripheral blood, extramedullary manifestations may occur in various organs, including the skin. Leukemia cutis represents an extramedullary manifestation of leukemia, with rare presentations including erythematous macules, blisters, and ulcers, which may occur individually or in combination[19]. Histopathological examination reveals infiltration of the epidermis, dermis, or subcutaneous tissue by neoplastic leukocytes or their precursors, resulting in clinically recognizable skin lesions. Leukemia cutis may develop before, after, or concurrently with the diagnosis of systemic leukemia [20].

In 2023, a case report published a 44-year-old woman diagnosed with AML who underwent chemotherapy. Following treatment, she developed painful skin rashes on her chest that spread centrifugally, accompanied by neutropenic fever unresponsive to broad-spectrum antimicrobial medications. A biopsy of the rashes confirmed the diagnosis of Sweet syndrome, revealing dense neutrophilic infiltration in the dermis. Systemic steroid treatment was initiated, resulting in rapid resolution of fever and improvement of the skin rashes. This case illustrates that Sweet syndrome can present with significant neutrophilic infiltration, even in the context of chemotherapy-induced neutropenia[21]. In 2021, another case involving Sweet syndrome was reported in a patient with AML and myocarditis, with skin lesions improving following treatment with the 7+3 chemotherapy regimen; examination of the bone marrow on day 28 indicated remission of AML [22]. In 2020, a 55-year-old woman with AML characterized by an FLT3 mutation, treated with Gilteritinib, developed skin rashes on her limbs. Histopathological analysis confirmed Sweet syndrome due to neutrophil infiltration, and her skin lesions improved after discontinuation of Gilteritinib, suggesting a potential drug-induced etiology[23]. These cases indicate that Sweet syndrome may present variably and at different intervals in patients diagnosed with AML, warranting careful attention from clinicians. If the underlying disease is not treated, skin manifestations may persist for weeks or months. Although clinical signs and symptoms may resolve spontaneously following treatment of the underlying disease, additional therapeutic interventions are typically necessary to manage the condition. The primary treatment modality is corticosteroids, with a standard initial dosage of 1 mg/kg/day, which can be tapered over a period of 4-6 weeks [4, 24].

Consent

Regarding the publication of the patient's condition and the publication of the patient's images in the form of an article, the patient was discussed and written consent was obtained.



A B C

Figure 1. A) Before treatment B) during treatment C) after the nadir phase

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