INTRODUCTION

Sweet’s syndrome (SS) is the eponym for acute febrile neutrophilic dermatosis and is characterized by a constellation of clinical features and pathologic findings.[1] These include fever, neutrophilia, tender erythematous papules, nodules and/or plaques, and a diffuse infiltrate consisting predominantly of mature neutrophils that are classically located in the upper dermis.[2] Numerous case reports of SS have been published, most of them in association with inflammatory bowel disease, acute leukemia or drug induced. It is very rare to be in association with Chronic Myelogenous Leukemia (CML).

CASE REPORT

A 34-years-old male, a known case of CML, was admitted with complaints of fever on and off and weakness from a fortnight. The patient was positive for BCR-ABL translocation and was taking imatinib 400mg once a day for three years. He gave history of discontinuing imatinib for about a month when he developed typhoid two months back. On presentation, hemoglobin was 4.5 gm/dl, total leucocyte count (TLC) 75,000/mm³ and platelet count 11,000/mm³. Absolute neutrophil count was 30,750/mm³, thus, excluding neutropenic fever. Peripheral blood film (PBF) showed 15% of myeloblasts, 24% of myelocytes and metamyelocytes. Bone marrow aspiration (BMA) revealed 18% blasts suggestive of CML in accelerated phase.

Patient was given transfusion support along with hydroxyurea and allopurinol along with intravenous antibiotics. However, when the blood culture failed to grow any microbe, antibiotics were stopped. Meanwhile there was acute onset of tender, well demarcated erythematous papules and plaques over face and skin of flexor sites of all limbs [Figures 1 and 2]. Lesions rapidly progressed to nodules and a few of them coalesced to form plaques. At some places, pustules were also formed. These were associated with pyrexia of 39.4°C, malaise, headache, and joint pains. The vitals were stable. The cardiovascular system was normal except for tachycardia and no abnormality was detected in his respiratory, abdominal, and neurological examination. No areas of anesthesia, hypopigmented patches or peripheral nerve thickening could be documented. Rest of the skin and mucosa were normal. TLC at this time was...
54,000/mm³ with 77% neutrophils whereas erythrocyte sedimentation rate was 36 mm/hr. The X-ray of the chest, ultrasonogram of the abdomen and pelvis were normal except splenomegaly. Slit skin smear could not identify any acid-fast bacilli and the serum for anti-nuclear antibody was also negative. Skin biopsy was taken from the margin of a lesion on forearm and was referred to an experienced pathologist. The sections showed evidence of marked papillary dermal edema [Figure 3] with extravasation of red blood cells with formation of intraepidermal suprabasal cleavage and nodular and diffuse infiltration by numerous mature neutrophils with karyorrhexis [Figure 4]. Also at some sites, there was evidence of ischemic coagulative necrosis. There was no evidence of vasculitis. These histological features suggested the diagnosis of acute febrile neutrophilic dermatosis.

The patient was prescribed oral prednisolone 60mg per day in divided doses which was tapered over a period of 3 weeks and stopped. Fusidic acid was applied topically at the site of pustules. There was a dramatic response and all the lesions disappeared within a week. Imatinib resistance mutational analysis was performed by nested RT-polymerase chain reaction (PCR) and Sanger’s sequencing. However, it failed to reveal any mutation in ABL kinase domain of BCR-ABL transcript. Repeat PBF and BMA revealed 17% myeloblasts; thus, excluding possibility of frank development of acute leukemia. He was prescribed nilotinib in view of unidentified mutation. He is on follow up and there has been no recurrence of skin rash till 4 months. However, there has been poor hematological response to nilotinib. The patient is being evaluated for allogenic stem cell transplantation.

DISCUSSION

SS was originally described by Dr. RD Sweet in 1964 as an acute febrile neutrophilic dermatosis.[2] Cohen et al., documented sixth case of SS in association with CML in 1989.[3] SS can present in several clinical settings: Classical (or idiopathic), drug induced, and malignancy associated.[4]
Classical SS occurs most frequently in women in the age group of 30-60 years in association with infection (upper respiratory or gastrointestinal), inflammatory bowel disease, or pregnancy. Recurrence of the dermatosis is noted in nearly one-third of the individuals. Behcet's disease, erythema nodosum, sarcoidosis, sterile osteomyelitis, rheumatoid arthritis, and Grave’s disease are some of the other reported associations. Diagnostic criteria are outlined in Table 1.

Su and Liu reported the first patient with drug-induced SS in 1986 and the associated medication was trimethoprim-sulfamethoxazole. The most frequently implicated drug is granulocyte-colony stimulating factor. Others include all trans-retinoic acid, minocycline, and oral contraceptive drugs. Recurrence of the dermatosis is common when the patient is rechallenged with the offending drug. The disease manifestations frequently improve with discontinuation of the drug.

Cohen and Kurzrock found that 21 percent of the patients with SS had either a hematologic malignancy or a solid tumor. Shapiro et al., reported the first patient with solid tumor-associated SS, a 58-year-old man with testicular carcinoma, in 1971. Dermatosis-related solid tumors include carcinomas of the genitourinary organs, breast, and gastrointestinal tract. In men malignancy associated SS occurs as frequently as in women and less often preceded by an upper respiratory tract infection. The onset of SS can precede, follow or appear concurrently with the diagnosis of cancer. Indeed, the dermatosis can be the cutaneous harbinger of either an undiagnosed malignancy in a previously cancer-free individual or an unsuspected recurrence in a known oncology patient. Most common cancer association is with acute myelogenous leukemia. However, in patients with hematologic disorders, SS can occur in one or more of the following forms: A paraneoplastic syndrome, a drug-induced dermatosis, or a condition whose skin lesions concurrently demonstrate leukemia cutis. Ayirookuzhi et al., reported a case of imatinib-induced SS in a patient of CML in 2005, as the dermatosis developed shortly after instituting imatinib therapy and also recurred after restarting targeted therapy. However, in the case under discussion, dermatosis developed when the patient was already on imatinib for three years and had entered the accelerated phase of CML; thus indicating paraneoplastic aetiology in this case. Also, some may argue that hydroxyurea was a newly administered drug in the patient and thus, it could be a case of hydroxyurea induced SS. At this juncture, the authors would like to clarify that hydroxyurea was continued after development of dermatosis in view of high counts along with prednisolone. The patient also received hydroxyurea after stopping steroid therapy and no recurrence was observed. Kaune et al., reported a case of SS in association with CML complicated with pneumonitis. They presumed the causative agent to be nilotinib. However, there was no recurrence of the lesion despite continuation of nilotinib.

The exact pathogenesis of SS remains undefined. However, altered immunological reactivity in the form of hypersensitivity to bacterial, viral, or tumor antigens, or circulating auto anti body and immune-complex reaction and cytokine deregulation are the proposed aetiopathological factors. An increase in the frequency of HLA Bw54 in Japanese patients with SS has been reported by Mizoguchi et al.

Skin lesions of SS are typically tender, red or purple-red, papules or nodules often distributed asymmetrically. Larger lesions may develop into plaques. The most frequent lesion locations are the upper extremities, face, and neck. The lesions have a transparent, vesicle-like appearance because of the pronounced edema in the upper dermis. Central clearing may lead to annular or targetoid pattern in latter stages. In patients with malignancy-associated SS, the lesions may appear bullous, become ulcerated and/or mimic the morphologic features of pyoderma gangrenosum. Mucosal involvement of the mouth, appearing as oral ulcers, is uncommon in patients.

### Table 1: Diagnostic criteria for classical SS versus drug-induced SS

<table>
<thead>
<tr>
<th>Classicala</th>
<th>Drug-inducedb</th>
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<tr>
<td>Abrupt onset of painful erythematous plaques or nodules</td>
<td>Abrupt onset of painful erythematous plaques or nodules</td>
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<tr>
<td>Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis</td>
<td>Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis</td>
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<tr>
<td>Pyrexia &gt;38℃</td>
<td>Pyrexia &gt;38℃</td>
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<td>Association with an underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy, OR preceded by an upper respiratory or gastrointestinal infection or vaccination</td>
<td>Temporal relationship between drug ingestion and clinical presentation, OR temporally-related recurrence after oral challenge</td>
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<tr>
<td>Excellent response to treatment with systemic corticosteroids or potassium iodide</td>
<td>Temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids</td>
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<td>Abnormal laboratory values at presentation (three of four): Erythrocyte sedimentation rate&gt;20 mm/hr; positive C-reactive protein; &gt;8,000 leukocytes; &gt;70% neutrophils</td>
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aThe presence of both major criteria (1 and 2), and two of the four minor criteria (3, 4, 5, and 6) is required in order to establish the diagnosis of classical SS; the patients with malignancy-associated SS are included with the patients with classical SS in this list of diagnostic criteria. All five criteria (A, B, C, D, and E) are required for the diagnosis of drug-induced SS.
with classical SS. However, dermatosis-related oral lesions occur more frequently in SS patients with hematologic disorders.

Farmakiotis et al., reviewed the medical records of 195 leukemia patients who underwent skin biopsy for new lesions and clinical suspicion of infection over four years. In 39% of the patients, infection was identified via skin biopsy. SS was third most common non-infectious diagnosis after leukemia cutis and drug reactions. It is important to differentiate between SS and infection, and that is an additional reason to always confirm the diagnosis by skin biopsy, since administration of corticosteroids can have a very adverse impact on infectious syndromes, particularly fungal infections, which are very common in this patient population.

A dense, perivascular, neutrophilic infiltrate is the hallmark of SS. Fragmented neutrophil nuclei (referred to as karyorrhexis or leukocytoclasia), swollen endothelial cells, and dilated small blood vessels may also be present. The overlying epidermis is normal and changes of primary leukocytoclastic vasculitis such as fibrin deposition or neutrophils within the vessel walls are usually absent. The inflammatory cells form a band-like infiltrate in the papillary dermis. An important concept that authors would like to highlight is that SS is characterized by infiltration of mature neutrophils in dermis whereas in leukemia cutis, under a close differential diagnosis, diffuse infiltrate of immature myeloid cells were observed. Hematologic malignancy associated SS can, thus, be visualized as a more differentiated variant of leukemia cutis. Also SS can be observed anytime in accelerated growth of myeloid cells, which infiltrate extramedullary tissue.

First-line agents in the treatment of SS include oral prednisolone, potassium iodide, cholinicaine, and IV methylprednisolone. Usually, there is dramatic response to systemic steroids. However, rarely there may be a need to institute second-line drugs in resistant or steroid-dependant cases. These include indomethacin, clofazimine, dapsone, cyclosporine, and cyclophosphamide.

Thus, to conclude, SS is a rare cutaneous manifestation of CML; however, it may occur in patients with CML who have lost hematological response to imatinib. Skin biopsy must be undertaken to confirm the diagnosis in patients of CML with cutaneous manifestations.

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REFERENCES


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