A rare case of subcutaneous Sweet's syndrome in a patient with chronic myelogenous leukemia: a case report and review of the literature

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Abstract Subcutaneous Sweet's syndrome (SS) is a rare variant of classic SS characterized by a neutrophilic infiltrate exclusively or predominantly in the subcutaneous tissue, with minimal or absent dermal involvement. We report the case of a patient with a history of chronic myelogenous leukemia who developed subcutaneous SS. Although it has been described in patients with myelodysplastic syndromes and acute myeloid leukemia, this is the first report, to our knowledge, of this rare entity occurring in the setting of a myeloproliferative disorder.

Keywords Subcutaneous Sweet's syndrome · Chronic myelogenous leukemia · Neutrophilic infiltrates · Myeloid disorders

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Introduction

Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, is characterized by the sudden onset of fever, multiple tender erythematous papules and plaques, and the presence of intense neutrophilic infiltrates on skin biopsy that are typically located in the upper dermis. SS is often associated with hematologic disease, and to a lesser extent with solid tumors [1–5].

Subcutaneous SS is a rare variant in which the neutrophilic infiltrate is exclusively or predominantly located in the subcutaneous tissue, with minimal or no dermal involvement [6, 7]. Subcutaneous SS is almost exclusively associated with myeloid disorders. To the best of our knowledge, only 16 cases have been reported in such a setting in the English-language literature to date [8–19], including ten cases with myelodysplastic syndromes (MDS) and six cases with acute myeloid leukemia (AML). We describe the case of a patient with chronic myelogenous leukemia (CML) who developed subcutaneous SS, an association which has not been previously reported.

Case report

The patient is a 43-year-old black female from Bermuda with a history of CML admitted for anemia, thrombocytopenia, fever, fatigue, splenomegaly and abdominal pain, and severe right leg pain. She was diagnosed with CML that was confirmed by the expression of BCR-ABL by FISH, in January 2009. She failed therapy with multiple tyrosine kinase inhibitors including ponatinib. At the time of hospital admission, her hemoglobin was 4 g/dl, platelet count was 5,000/ul, and the white blood cell count was 2,500/ul with 9 % circulating blasts. She received two units of packed red blood cells and two units of platelets. Plain films and MRI of the right hip

joint excluded a pathological fracture. Additionally, Cefepime was started for fever. On physical examination at the time of admission, two firm, tender subcutaneous nodules were noted on the medial side of the right thigh measuring 4×4 and 3×2 cm, respectively. Within 24 h of admission, she developed new left arm pain and worsening abdominal pain. A third nodule developed on the left arm measuring 2×2 cm (Fig. 1). The overlying skin appeared erythematous without fluctuance or pustule. CT scan of the chest, abdomen, and pelvis with contrast showed multiple nodular densities in both lungs as well as hepatosplenomegaly. Micafungin was added for suspected disseminated fungal infection. On day 5 of her hospitalization, two more firm, tender, erythematous nodules were noted on the right arm and forearm. Given the concern for disease evolution and for leukemia cutis, biopsies of the bone marrow and one of the subcutaneous nodules were performed.

Bone marrow biopsy revealed a hypercellular marrow with prominent myeloid hyperplasia, left-shifted granulopoiesis, and markedly decreased megakaryocytic and erythroid precursors. CD34 positive cells comprised 5 % of the marrow. The peripheral blood smear revealed 8 % blasts and 67 % segmented neutrophils. Biopsy of the subcutaneous nodule showed organizing fat necrosis and a dense neutrophilic infiltrate in the lobules, with associated fibrinoid necrosis and numerous macrophages (Fig. 2). There was no significant dermal involvement and no evidence of vasculitis. In addition, no blasts were seen; this was confirmed by the absence of staining for CD34 on immunohistochemistry. Special stains for fungus, acid-fast bacilli, and bacteria were all negative. A diagnosis of subcutaneous SS was made.

During her hospitalization, the percentage of peripheral circulating blasts rose to 18 %. With a concern for disease progression, induction chemotherapy was started with cytarabine and idarubicin (7+3 regimen). The patient had a significant clinical improvement, and she is currently awaiting

Fig. 1 Subcutaneous firm, erythematous nodule on the left arm. Similar nodules were present on the right thigh and right arm (not shown)

Fig. 2 Histological examination showing organizing fat necrosis and dense lobular neutrophilic infiltrate, with associated fibrinoid necrosis and numerous macrophages (hematoxylin-eosin stain; original magnifications: **a**×20, **b**×200)

haploidentical hematopoietic stem cell transplantation. Interestingly, she did not receive steroids, and her nodules responded to chemotherapy. The two nodules on her right arm completely disappeared within a week, and the rest of the nodules decreased in size and became non-tender.

Discussion

Subcutaneous SS is an extremely rare entity. Although it has been described to occur after treatment with vemurafenib, a BRAF inhibitor [20], the majority of reported cases have been associated with underlying myeloid disorders. Following a comprehensive literature search, we identified 16 cases of subcutaneous SS that developed in such a clinical setting. The clinical and histopathologic features of those lesions are tabulated in Table 1.

Among the 16 previously reported cases, different terms have been used, including neutrophilic panniculitis [11–13, 16, 18], SS-like (Sweet's-like) neutrophilic panniculitis [14], and Sweet's panniculitis [10]. In all the cases, the patients had either MDS or AML and presented with multiple erythematous nodules that frequently involved the limbs, especially the lower extremities [8–19]. Most of the nodules were accompanied by fever, and some were painful. On histological examination, all lesions showed an extensive neutrophilic infiltrate

Table 1 Summary of subcutaneous Sweet's syndrome associated with myeloid disorders

Reference	Age/ sex	Myeloid disorder	Clinical manifestations of the lesion	General symptoms	Histopathologic findings of the lesion	Clinical course
8	52/F	Preleukemic state evolving to acute myeloid or myelomonocytic leukemia	Multiple erythematous nodules (2–3 cm) on the arms and inner thighs	Low-grade fever	Dense, patchy neutrophilic infiltrate in the subcutaneous lobules	Resolved spontaneously; developed classic SS 11 weeks later, and was diagnosed with AML
9	48/F	MDS	Recurrent cutaneous nodules on the legs	Fever, arthralgia	Dense neutrophilic infiltrate in the fatty tissue; nuclear segmentation anomalies in 25 % of the neutrophils	Controlled by oral prednisolone; later developed RAEB
10	65/F	MDS transforming to AML	Tender, inflamed plaques on the right cheek and left supraclavicular fossa	Spiking fever	Dense neutrophilic infiltrate and leukocytoclasia in subcutaneous adipose tissue	Controlled by prednisolone 50 mg/day
11	74/F	MDS (RARS)	Multiple tender, erythematous nodules and plaques on the left forearm and left leg	Spiking fever; edematous legs	Dense, patchy subcutaneous neutrophilic infiltrate spreading out from septa to lobules	Responded to prednisolone 30 mg/day
12	59/ M	MDS (RAEB)	Numerous, tender, small pustular lesions and erythematous papules randomly distributed over entire body	High fever, malaise	Dense subcutaneous neutrophilic infiltrate with a lobular distribution	Rapid improvement after oral prednisolone 40 mg/day
13	57/ M	MDS	Multiple subcutaneous tender, erythematous nodules on the legs, arms and trunk	Spiking fever	Neutrophilic infiltrate in the fat lobules	Rapid improvement after oral prednisone 60 mg/day
14	19/ M	APML on ATRA	1 cm, discrete, erythematous nodule on the right shin	N/A	Subcutaneous neutrophil-rich lobular infiltrate with admixed lymphocytes, histiocytes, and immature myeloid cells	Resolved spontaneously
15	64/ M	AML (M6) on G-CSF	Edematous plaques on the upper eyelids, right auricular area and the chest wall; subcutaneous indurations with mild erythema on the buttock	High fever	Dense, predominantly lobular neutrophilic infiltrate	Began to regress before induction of methylprednisolone
16	66/ M	MDS on G-CSF	5×3 cm tender, firm, erythematous nodule on the left anterior upper arm; 1-year history of tender, erythematous nodules in varying locations	Afebrile	Dense neutrophilic infiltrate predominately in subcutaneous septae; few neutrophils exhibited abnormal segmentation	N/A
17	78/ M	MDS	Multiple non-tender, small, indurated, erythematous to violaceous nodules in submental region	Recurrent and episodic fevers (>38 °C)	Neutrophilic infiltrate involving septae and lobule with prominent leukocytoclasia	N/A
18; two cases	47/ M	MDS (RCMD) on AZA	Multiple erythematous nodules on lower extremities	Fever	Marked lobular neutrophilic infiltrate	Responded to corticosteroid
19; four cases	62/F 53/ M	MDS (RCMD) on AZA AML	Tender, erythematous lesions at AZA injection sites (abdomen) Tender subcutaneous nodules on the buttock and thigh	Fever High fever, fatigue, dyspnea	Marked subcutaneous neutrophilic infiltrate extending to the lower dermis Predominantly lobular neutrophilic infiltrate	Prompt response to corticosteroids Resolved spontaneously
	53/F	AML	Multiple tender, indurated, erythematous and edematous plaques (3–7 cm) on all the extremities	Fever	Predominantly lobular neutrophilic infiltrate with occasional hypersegmentation and leukocytoclasia	Resolved spontaneously
	41/ M	AML-M2	Several tender nodules on the arms and thighs (1–3 cm), no erythema or surface changes		Predominantly septal neutrophilic infiltrate with leukocytoclasia and focal fat necrosis	Resolved spontaneously

Table 1 (continued)

Reference	Age/ sex	Myeloid disorder	Clinical manifestations of the lesion	General symptoms	Histopathologic findings of the lesion	Clinical course
				Fever, diffuse swelling of the extremities		
	62/F	MDS	Violaceous plaques on the legs	N/A	Dense neutrophilic infiltrate within the superficial subcutis, some neutrophils appeared hyposegmented	Resolved after oral prednisone
Present case	43/F	CML	Five subcutaneous firm, tender, erythematous nodules on medial right thigh and arms (up to 4 cm)	Fever, fatigue, pain in abdomen and extremities	organizing fat necrosis and dense lobular neutrophilic infiltrate associated with fibrinoid necrosis and numerous macrophages	Responded to chemotherapy with idarubicin and cytarabine

AML acute myeloid leukemia, *APML* acute promyelocytic leukemia, *ATRA* all-trans-retinoic acid, *AZA* azacitidine, *CML* chronic myelogenous leukemia, *G-CSF* granulocyte colony-stimulating factor, *MDS* myelodysplastic syndrome, *N/A* not available, *RAEB* refractory anemia with excess blasts, *RARS* refractory anemia with ringed sideroblasts, *RCMD* refractory cytopenia with multilineage dysplasia, *SS* Sweet's syndrome

that was exclusively or predominantly located in the subcutaneous tissue. Although most of the cases described showed a lobular distribution [8, 12–15, 18, 19], the infiltrate may also dominate the septa [16, 19], or both [11, 17]. By definition, to be called subcutaneous SS, there should be no associated vasculitis or other cause of panniculitis. Clinically, the lesion may resolve spontaneously or be successfully treated with corticosteroids. It may also respond to chemotherapy, as in our patient. Since the cases shared similar clinical and pathological manifestations and all occurred in patients with myeloid disorders, they should all be classified as subcutaneous SS [6, 19].

The etiology of subcutaneous SS is still unknown. It has been postulated that uncontrolled release of pro-inflammatory mediators may contribute to the development of subcutaneous SS [11]. Indeed, increased level of granulocyte colony-stimulating factor (G-CSF) and all-trans retinoic acid (ATRA) chemotherapy have been linked to the disease [14–16]. G-CSF induces neutrophil mobilization by increasing the production of macrophage inflammatory protein 2 (MIP-2) in the bone marrow [21]; and ATRA has been shown to induce gene expressions of a number of CXC and CC chemokines in acute promyelocytic leukemia cells [22].

Interestingly, subcutaneous SS may occur prior to the acute transformation of the underlying myeloid disorders. Cooper et al. reported a patient with MDS and subcutaneous SS who developed AML 11 weeks after the skin lesion appeared [8]. Cullity et al. described a case of “Sweet’s panniculitis” occurring on a patient with MDS transforming to AML [10]. The present case demonstrated a clear association between the course of the skin lesion and the underlying CML, in which the nodules occurred prior to the patient entering a presumed accelerated phase and regressed after starting chemotherapy. It has been shown that high expression of CXC chemokine ligand 4 (CXCR4) and activation of the CXCR4-CXCL12 axis can promote leukemogenesis and the progression of AML [23]. On the other hand, increased cytokines/chemokines will lead to the activation or recruitment of macrophages/neutrophils which may play a role in the pathogenesis of subcutaneous SS.

A diagnosis of subcutaneous SS should be made only after ruling out other possible conditions [24]. Leukemia cutis is an important differential, as both entities may occur in a similar clinical setting. Microscopically, leukemia cutis typically shows a perivascular and/or periadnexal leukemic infiltrate or a dense interstitial/nodular infiltrate involving the dermis and subcutis. Immunohistochemistry, in most cases, is very helpful in confirming a diagnosis of leukemia cutis [25]. Erythema nodosum (EN) may be indistinguishable from subcutaneous SS, both clinically and histologically. EN is the most common form of panniculitis. EN is a hypersensitivity reaction with a spectrum of histologic features that is related to the morphologic chronology of the disease [26]. The

prototypical lesions present as a septal panniculitis with a mixed cellular infiltrate comprising lymphocytes, neutrophils, histiocytes, giant cells, and variable eosinophils. Occasionally, EN may demonstrate a predominant neutrophilic component [27]. The presence of Miescher radial granulomas is thought to be relatively specific for EN [7, 19]. However, it has also been reported in SS, Behcet's disease, and necrobiosis lipoidica [28]. Additionally, several other conditions that can lead to subcutaneous neutrophilic inflammation should be excluded, including infection, pancreatic panniculitis, alpha-1 antitrypsin deficiency, rheumatoid arthritis, with inflammatory bowel disease, and local reaction secondary to injection [6, 19, 24].

In conclusion, we report the first case of subcutaneous SS occurring in the setting of CML. Subcutaneous SS is a rare entity associated with MDS, AML, and CML. In our opinion, it is important to recognize and differentiate subcutaneous SS from other diseases and conditions, as subcutaneous SS may be a warning sign of progression of the underlying myeloid disorder.

Conflict of interest The authors declare that they have no conflict of interest.

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