A Fatal Case Of Histiocytoid Sweets Syndrome And Myelodysplasia Unresponsive To Steroid Treatment: A Case And Review Of The Literature

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A Fatal Case Of Histiocytoid Sweets Syndrome And Myelodysplasia Unresponsive To Steroid Treatment: A Case And Review Of The Literature

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Abstract

We describe a fatal case of histiocytoid Sweet’s syndrome in a patient with myelodysplasia that was refractory to multiple therapies, including steroids. Though corticosteroids are classically the initial treatment for Sweet’s syndrome, other factors should be considered. Patients with concurrent myelodysplastic syndrome (MDS), or other hematologic malignancies, are often unresponsive to conventional therapies. We discuss the range of treatment options and importance of the initiation of alternative therapies early in the course of a patient with Sweet’s syndrome who is becoming increasingly resistant to steroids.

Case Presentation

A 44 year-old woman presented to hospital with several episodes of migrating erythematous soft tissue swellings followed by large, erythematous, nodular lesions on all four limbs. The episodes would resolve within several days and were associated with fevers and migrating joint swelling. In the 10 years previously, she had endured a remitting-relapsing course of follicular lymphoma that transformed to diffuse large B-cell lymphoma, and ultimately culminated in autologous stem cell transplantation and eventual remission.

At the time of admission to hospital, the patient was found to have acute renal failure secondary to acute tubular necrosis and the concomitant development of an atypical MDS, and kidney biopsy suggested an ischemic cause for the renal failure. The bone marrow aspirate and biopsy suggested an atypical MDS, and kidney biopsy suggested an ischemic cause for the renal failure. Autoimmune serology was negative, including normal ANCA, ENA screen, ANA, anti-DNA, RF, anti-CCP antibodies, cryoglobulins and complements. She was found to have an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at 140 mm/hr and 127 mg/L respectively. A course of oral corticosteroids was started and the diagnosis of Sweet’s syndrome was entertained; however, skin biopsies at the time were non-diagnostic. The patient was discharged home on a tapering dose of corticosteroids and initially improved, but was re-admitted to hospital one month later with recurrent fever, joint swelling and migratory soft tissue inflammatory lesions. A repeat deep skin biopsy was consistent with a neutrophilic panniculitis with both septal and lobular involvement. She was treated with an increased dose of corticosteroids (60 mg prednisone daily), and was thought to have an atypical Sweet’s syndrome presentation. She was discharged home, but was re-admitted within a week’s time with hypotension, fever and right arm swelling at her indwelling intravenous catheter site. She was treated with pressure support and broad spectrum antimicrobials, yet all cultures were negative. Prednisone was re-started, and hydroxyurea was used to suppress the neutrophilia. Colchicine and potassium iodide, both of which have been shown to be beneficial in Sweet’s syndrome [1, 2], were added after the initial therapies failed. Despite this, she would have recurrent SIRS-like episodes, fevers and intermittent hypotension. Meanwhile, her hemoglobin had continued to fall to 80 g/L and platelets had fallen to 15 X 109/L and chest imaging revealed transient and migratory infiltrates. Her SIRS-like episodes became increasingly severe with recurrent episodes of sudden onset palindromic fever, flushing, acute respiratory decompensation and hypotension resistant to vasopressors. Her unstable condition became increasingly unresponsive to treatment and she was eventually admitted to the ICU.

At the time of admission to the ICU, the medications used to attempt to control herSweet’s syndrome included: prednisone 100 mg PO daily, colchicine 0.6 mg PO TID, and hydroxyurea 500 mg PO daily. Laboratory investigations revealed a white blood cell count of 9.1 X 109/L with neutrophils of 7.93 X 109/L, and severe thrombocytopenia with a platelet count of 33 X 109/L. She had an elevated ESR at 89 mm/hr and a CRP of 244.9 mg/L. IgA, IgG and IgM were all low, and therefore, IVIG was started due to deficient immune status and literary evidence suggesting possible benefit in immunocompromised Sweet’s patients [3].

Throughout the ICU admission, pulse doses of methylprednisone were administered, but the patient
continued to have episodes characterized by acute, sudden and profound hypotension, hypoxia, face and neck flushing requiring multiple pressors and responding predominantly to epinephrine, steroids and diphenhydramine. Allergic and carcinoid work-ups were negative and there was no evidence of either mastocytosis or basophilic leukemia in the bone marrow or in multiple peripheral smears. Several bronchoscopies were performed, all of which were clear. Her hypotensive and hypoxic episodes became increasingly unresponsive to treatment and eventually culminated in her death.

Approval of this case study was awarded by the Queen's University Health Sciences Research Ethics Board and the need for informed consent was waived.

Pathology

Post-mortem examination of skin lesions revealed a focal area of spongiosis and edema within the epidermis accompanied by a mild mixed inflammatory infiltrate which included neutrophils and lymphocytes. The epidermis was otherwise uninvolved. The dermis exhibited a nodular, dense, inflammatory infiltrate with extension to the subcutaneous adipose tissue (Figure 1A). There was edema in the papillary dermis. There was no evidence of vasculitis and gram stain did not reveal any microorganisms.

The inflammatory infiltrate consisted predominantly of mononuclear cells with variably-shaped, vesicular nuclei with inconspicuous nucleoli and scant eosinophilic cytoplasm (Figure 1B). These cells outnumbered the accompanying inflammatory infiltrate that consisted of neutrophils, lymphocytes, and mature histiocytes. The monocytic cells were strongly immunoreactive to myeloperoxidase (Figure 2A and 2B) and also expressed the histiocytic markers CD68, CD43 and lysozyme. The morphology and immunoreactivity of the infiltrating cells were consistent with histiocytoid Sweet's syndrome as described by Requena et al [4].

Given that the patient had MDS, she was considered to be at risk for transformation to an acute myeloid leukemia (AML), and thus, the possibility that the infiltrating cells represented a cutaneous manifestation of AML was considered. However, bone marrow and multiple peripheral blood smears showed no evidence of AML, nor did the infiltrating dermal cells express blast markers CD117 or CD34. Based on morphology and immunoreactivity, the infiltrating cells are best considered immature myeloid cells and because of the patient’s MDS, the cells would be expected to be clonal in nature.

Discussion

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, was first described in 1964 by Robert Douglas Sweet [5]. It is a disorder of unknown etiology characterized by the acute onset of painful, erythematous, and asymmetrically distributed cutaneous plaques and nodules with fever, leukocytosis and neutrophilia. Patients with Sweet's syndrome often report suffering from arthralgias, arthritides and myalgias. Though the etiology of the syndrome has not been clearly defined and most cases are idiopathic in nature, there is a known association of Sweet's syndrome with systemic disease of an inflammatory or neoplastic nature, with MDS being one of the most frequent malignancies occurring in patients with Sweet's syndrome [6-8].

Histologically, Sweet's syndrome cutaneous lesions typically consist of a dense, nodular or diffuse infiltrate of neutrophils in association with papillary dermal edema. Notably, however, Requena et al [4] have reported that in some patients, the dominant dermal infiltrate is composed of histiocyte-like immature myeloid cells and not polymorphonuclear leukocytes. The variant was hence named histiocytoid Sweet's syndrome and reveals an expanded histopathologic spectrum of the condition. Both classic Sweet's syndrome and histiocytoid Sweet's syndrome generally respond well to systemic corticosteroids [4, 9].

We describe a fatal case of histiocytoid Sweet's syndrome with immature myeloid cells in a patient with MDS that was refractory to steroid treatment. This patient's lesions were only partially responsive to systemic corticosteroids and became progressively more refractory. The patient's symptoms were also unresponsive to other treatments previously demonstrated to provide clinical improvement of Sweet's lesions, including colchicine, potassium iodide and IVIG [1, 2, 3].

There have been similar reports of Sweet's syndrome occurring in conjunction with MDS in which the disease was only partially responsive to systemic corticosteroids and failed to respond to other treatment options. Tomasini et al [10] report a case of a patient whose cutaneous lesions initially responded to corticosteroids treatment but became progressively unresponsive with subsequent recurrences. In these cases, alternative and experimental therapies should be considered. Browning et al [11] report a patient whose lesions completely resolved with thalidomide therapy after only a partial response to steroids, while
Haliasos et al [3] describe a pediatric case of Sweet’s syndrome associated with immunodeficiency that was responsive to IVIG therapy and dapsone. Both our case and a paper by Tomasini et al [10] report Sweet’s syndrome with immature myeloid cells, a rare feature seen occasionally in conjunction with MDS [12, 13]. In both of these cases, the patients failed to respond to several forms of treatment, suggesting the additional factor of an immature myeloid cell MDS variant confers resistance to traditional therapies.

Several other medications have been shown to result in clinical improvement of Sweet’s lesions. Colchicine was first proposed as a treatment for Sweet’s syndrome by Suehisa and Tagami [14, 15] who achieved good results in a limited number of patients. It has since been further studied with one trial achieving a very good response in 90% of patients in whom fever subsided, cutaneous lesions attenuated and arthralgias disappeared [1]. The success seen in this study was found to be independent of severity of disease, without relapse and with limited adverse effects.

Indomethacin has been shown to produce a good response in Sweet’s syndrome patients treated with 150 mg/day for first week and 100 mg/day for two additional weeks [16]. Jeanfils et al achieved a good response in 17 of 18 patients with no relapses. The patient who did not achieve response had AML, highlighting the resistant-nature of Sweet’s associated with hematological malignancies. Potassium iodide and aspirin have also been associated with benefit in a limited number of cases [2, 17], while chlorambucil has been suggested as a means of maintaining remission in one case [18]. In one case of severe Sweet’s associated with MDS, whose skin lesions responded to high doses of systemic steroids but recurred on dose reduction, cyclosporine was used with good results in clearing skin lesions and stabilizing blood counts [19]. Overall, it appears as though more complex cases of Sweet’s syndrome, such as those complicated by MDS or immunodeficiency, may require consideration of more aggressive treatment.

There is little known about why Sweet’s syndrome in association with hematologic malignancies is resistant to therapy. One theory suggests that high levels of chemotactic factors secreted by neoplastic cells may be associated with the lack of efficacy of indomethacin in a patient with AML [16]. Another thought is that inappropriate cytokine secretion and defective intracellular signaling associated with MDS may play a role [20]. It is possible that these same chemotactic factors or defective intracellular signaling may be what not only caused treatment-resistance in our patient, but may have also been related to the patient’s recurrent SIRS-like episodes. In fact, there have been rare cases of patients presenting with SIRS-like episodes in which the diagnosis of Sweet’s syndrome was eventually made [21-23]. In one of these cases, the idiopathic chronic SIRS proved to be fatal despite attempted treatment with many of the medications described above [23]. It is possible that this clinical presentation of SIRS in the context of Sweet’s syndrome may predict treatment-resistance and it has been speculated that an unknown antigen trigger may be the cause of SIRS in such cases [23].

Given the numerous reports of lack of efficacy of both traditional and novel treatments in non-classic Sweet’s cases, alternative methods such as thalidomide, IVIG, or cyclosporine should perhaps be initiated more promptly in these complex patients. When managing clinically suspected steroid-resistant Sweet’s syndrome associated with underlying MDS, the possibility of skin lesions being due to a leukemic infiltration of the skin should be considered. The continued administration of steroids in this setting could be harmful, and alternative therapies should be considered promptly.

**Conclusion**

Though corticosteroids are classically the initial treatment for Sweet’s syndrome, other factors should be considered. Patients with concurrent MDS, or other hematologic malignancies, are often unresponsive to conventional therapies. The range of treatment options should be discussed and initiation considered early in the course of a patient with Sweet’s syndrome who is becoming increasingly resistant to steroids.
Illustrations

Illustration 1

Histopathologic features of Sweet's syndrome. Dermal band-like inflammatory infiltrate involving the superficial and mid-dermis with extension into the subcutaneous tissue. Hematoxylin-Phloxine-Saffron stain (x 10).

Illustration 2

Histopathologic features of Sweets syndrome. The predominant cell type in the infiltrate is composed of vesicular nuclei with sparse cytoplasm. Hematoxylin-Phloxine-Saffron stain (x 800)
Illustration 3

The infiltrating cell population shows strong immunoreactivity for myeloperoxidase (x 40).

Illustration 4

The infiltrating cell population shows strong immunoreactivity for myeloperoxidase (x 800).
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