Fatal Systemic Sweet's Syndrome

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Background

- Sweet's Syndrome is a rare disease manifested by an acute febrile neutrophilic dermatosis of painful erythematous and purpuric papules and nodules. There are 2 major and 4 minor criteria used to formally define the disease (Table 1).[1]

- Sweet's Syndrome is classified into three types: classical (associated with upper respiratory tract infection, inflammatory bowel disease or pregnancy), malignancy-related and drug induced.[1] However, to date, there are only 4 cases in the literature of an association with systemic inflammatory response syndrome.

Major Criteria	Minor Criteria
(1) Abrupt onset of painful erythematous plaques or nodules. (2) Histopathological evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis.	(1) Fever > 38°C (2) Association with an underlying hematologic or visceral malignancy, inflammatory disease, or pregnancy, OR preceded by an URTI, GI infection or vaccination (3) Excellent response to treatment with systemic corticosteroids or potassium iodide (4) Abnormal laboratory values at presentation (three of four): erythrocyte sedimentation rate > 20mm/hr, positive C-reactive protein, > 8000 leukocytes, > 70% neutrophils

Table 1: Diagnostic criteria for classical Sweet's Syndrome. Two major and two of four minor criteria must be present to establish a diagnosis.

Methods

- We describe a case of a 44 year old woman with follicular lymphoma in remission, who developed myelodysplastic syndrome and a severe acute illness consistent with systemic Sweet's Syndrome manifesting with recurrent, recalcitrant fever, arthralgias, skin manifestations, and ultimately palindromic severe inflammatory response syndrome (SIRS). After multiple remissions and relapses, her condition ultimately proved fatal.

Presentation of the Case

- A 44 year old woman with follicular lymphoma transformed to diffuse large B-cell lymphoma (in remission, on maintenance rituximab) developed fever with migratory joint swellings, cold sore outbreaks and painful, pruritic large erythematous nodules and plaques on both legs.

- These symptoms continued on a recurrent and relapsing course for 2 months, ultimately culminating in hospital admission when she further developed easy bruising secondary to anemia and thrombocytopenia.

- During this admission, she had renal failure secondary to acute tubular necrosis, unexplained transient skin rashes and migratory arthralgias with persistent anemia and thrombocytopenia.

- Skin biopsy was non-diagnostic; bone marrow biopsy demonstrated myelodysplastic syndrome. She was started on a course of oral corticosteroids, and due to a positive response, a diagnosis of Sweet's Syndrome was considered.

- Her initial autoimmune serology was negative including normal complements but acute phase reactants were extremely elevated with ESR of 140 and a CRP of 127. Rituximab was held due to marrow failure and she was discharged on a four week tapering course of oral corticosteroids.

- Three weeks hence she relapsed with recurrent fever, arthritis and skin lesions, necessitating re-admission. Deep skin biopsy demonstrated neutrophilic panniculitis, leading to a diagnosis of atypical systemic Sweet's Syndrome.

- Acute phase reactants were markedly elevated: CRP 244.9 mg/mL, ESR 92 mm/hr, Ferritin 1928 µg/L and C3 was low at 0.72 g/L. Anemia and thrombocytopenia persisted with a marked neutrophilia. ANCA's, ENA panel, ANA, anti-DNA, RF, anti-CCP and cryoglobulins were negative.

- Corticosteroids again produced resolution of symptoms and she was discharged, however, once tapering began she became acutely unwell and hypotensive, requiring readmission only 3 days after her discharge.

- Extensive culturing never demonstrated organisms. Her clinical course was complicated by deep venous thrombosis (DVT) of her arm secondary to a PICC line. Her condition was unstable; she suffered recurrent episodes of palindromic fever, hypotension requiring vasopressors, and acute respiratory decompensation, associated with transient and migratory infiltrates on imaging.

- Laboratory investigations demonstrated persistent anemia, thrombocytopenia, neutrophilia and markedly elevated acute phase reactants.

- Again she received corticosteroids and broad spectrum antimicrobials despite negative cultures, but with no response. Hydroxyurea was added in an attempt to suppress her neutrophilia, and colchicine, a first to second line therapy for Sweet's Syndrome was added also.

- Cutaneous lesions resolved, but systemic manifestations persisted. Deterioration continued, with each palindromic flare more severe than the last, ultimately requiring intubation and continuous epinephrine infusion support.

- Potassium iodide and pulse high-dose methylprednisolone were added, producing a temporary stabilization, but upon first taper she deteriorated once again. Immunomodulatory doses of IVIG treatment were unhelpful, and she died after 3 weeks of aggressive ICU therapy.

- Cause of death on autopsy findings indicated multi-organ failure with bilateral acute bronchopneumonia, and multiple palpable erythematous epidermal lesions on arms bilaterally; microscopic examination revealed neutrophilic dermatosis with no evidence of infection consistent with Sweet's Syndrome, and finally splenomegaly with multiple subcapsular infarcts and acute splenitis.

- Minor findings included ascites, hepatomegaly with congestion, and reactive lymphadenopathy with no evidence of residual or recurrent lymphoma.

Discussion

- Sweet's Syndrome was first described by Dr. Robert Sweet in 1964 as an "acute febrile neutrophilic dermatosis".[2] Since then, several hundred cases have been reported which expanded the clinical and pathological features of the disease.[1]

- Our patient was found to have myelodysplastic syndrome associated Sweet's Syndrome and, during the course of her illness, had satisfied all major and minor diagnostic criteria. Anecdotally, MDS-associated Sweet's Syndrome appears to be generally harder to treat.

- Fever is the most common symptom associated with the skin manifestations of Sweet's Syndrome. Arthralgias, malaise, and myalgias are also reported.[1,3-5] Sweet's Syndrome associated with systemic inflammatory response syndrome is generally rare. Indeed, we could only identify four cases in the literature,[6-9] two of which were not in English journals, but both reporting fatalities from the same[6,8]

- Other extracutaneous manifestations of Sweet's syndrome have been well documented, including lung involvement with pulmonary infiltrates and edema,[6,10] cardiac failure,[11] hepatomegaly,[1] and splenomegaly;[12] the latter two were also features in our patient. The most commonly laboratory findings are an elevated ESR and peripheral leukocytosis with neutrophilia.[3]

- Circulating auto-antibodies, cytokines, immune complexes may all play a role in the pathogenesis of Sweet's Syndrome.[1] An etiologic role for pro-inflammatory cytokines,[3,13] especially granulocyte colony stimulating factor (G-CSF), has been shown in several cases of Sweet's Syndrome.[14-16] Indeed, Sweet's Syndrome is a recognized complication of G-CSF administration.[20-22]

- Most cases of Sweet's Syndrome respond rapidly to systemic corticosteroids,[7] or one of the other first line agents such as colchine and potassium iodide. Corticosteroid-resistant[23] or intolerant[24] cases are rare, but cases have been described of successful rescue therapy with the administration of anti-TNF therapy (infliximab, etanercept). After such a prolonged ICU stay with concomitant high dose corticosteroids, however, we presumed infection was complicating her clinical picture and did not attempt this therapy.

Conclusion

- **Although the extracutaneous involvement of Sweet's Syndrome is well documented, there are to date only 4 cases of Sweet's Syndrome associated with systemic inflammatory response syndrome, only two of which proved fatal; these latter 2 only being published in the non-English literature**
- **Sweet's Syndrome is an evolving dermatosis with each new reported case adding information to our understanding of the condition.**

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