CASE REPORT

Multi-organ Involvement of Sweet’s Syndrome: A Case Report and Literature Review

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Abstract

The hallmark of Sweet’s syndrome (SS) is the infiltration of mature neutrophils in the upper dermis. We herein report a case of SS with multi-organ involvement. A 32-year-old man presented with fever, anemia and dyspnea. He was given antibiotics, without any improvements. Later, a number of erythematous lesions appeared, accompanied by deteriorating respiratory and cardiovascular functions. A diagnosis of SS was confirmed on a skin biopsy, and the patient was given corticosteroids, the dose of which was reduced after one month. The organ function subsequently deteriorated, and he ultimately died of multi-organ failure. Early recognition of SS with multi-organ involvement is important in patients with SS.

Key words: Sweet syndrome, neutrophils, lung, heart, skin, inflammation

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Introduction

Sweet’s syndrome (SS) is a systemic inflammatory disorder characterized by fever, cutaneous erythematous nodules or plaques, diffuse mature neutrophil infiltration in the upper dermis and a prompt clinical improvement following the administration of systemic corticosteroids (1-3). The first case of SS was reported by Robert Sweet in 1964 and was originally described as acute febrile neutrophilic dermatosis (3). Based on the etiological factors of SS, the condition is now classified into classical/idiopathic, drug-induced and malignancy-associated subtypes (4-11). SS occurs worldwide, with no significant regional or racial differences (12, 13). Cases of SS are mostly detected among patients between 30 and 50 years of age, and some subtypes of SS show significant gender differences. For example, classical and drug-induced cases of SS predominantly occur in women (12, 14), whereas malignancy-associated SS is equally observed in both genders (12, 14).

Cutaneous manifestations of SS typically include red papules, nodules and plaques with an irregular and sharp border. The skin lesions are usually painful, tender and distributed across the face, neck and limbs. In addition to these cutaneous features, SS often presents with involvement in many other organ systems. The most frequently involved extracutaneous organs are the bones, central nervous system, eyes, kidneys, intestine, liver and heart (15-22). Pulmonary involvement is rare. We herein report a case of SS with multi-organ involvement, including the cutaneous, hematological, cardiovascular and pulmonary systems. Due to a delayed diagnosis and the rapid withdrawal of corticosteroids, the patient eventually died of multi-organ failure.

Case Report

A 32-year-old man was admitted to the hospital with a history of a persistent fever and cough lasting for two weeks, with anemia for seven days and dyspnea for two days. His temperature was elevated, at 41°C. He had been previously healthy without a history of any respiratory diseases. There were no skin rashes or other abnormal cutane-
Figure 1. Representative radiological findings of SS on chest CT scans. (A, B) Areas of large, patchy infiltration were observed in the lungs, primarily in the right lung. (C, D) Some lung tissue had become consolidated.

ous signs on the initial physical examination. At that time, the hemoglobin (Hb) level was 89 g/L, and both the white blood cell (WBC) and platelet counts were normal. Chest computed tomography (CT) scan revealed areas of large, patchy infiltration in the right lung. Because a bone marrow biopsy showed changes consistent with chronic myelodysplastic syndrome (MDS), the patient was diagnosed with MDS accompanied by pneumonia and subsequently given antimicrobial and other supportive therapies.

After five days of treatment, the patient’s fever and dyspnea did not improve, and a differential blood cell count showed the following: WBC: 2.7×10^9/L; neutrophils: 0.30×10^9/L (12%); lymphocytes: 17.3%; monocytes: 70%; red blood cells (RBC): 2.47×10^12/L; Hb 84 g/L; platelet count: 178×10^9/L. Two days later, the results were as follows: WBC: 4.7×10^9/L; neutrophils: 75.1%; Hb: 70 g/L. An arterial blood gas analysis showed a pH of 7.44, PaO_2: 80 mmHg, PaCO_2: 33 mmHg. The C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were both within the normal ranges. In addition, a sputum smear, sputum culture and blood and bone marrow cultures were all negative. Meanwhile, a chest CT scan showed that the area of pulmonary infiltration had increased in size and began to involve the left lung (Fig. 1A, B).

The patient was treated with intravenous antibiotics, including moxifloxacin (0.4 g/d) and micaflugin (100 mg/d), as well as methylprednisolone (80 mg/d, i.v.) and ganciclovir (350 mg/d). After two days of treatment, the patient’s temperature returned to normal, although his dyspnea deteriorated, his blood pressure decreased to 70/36 mmHg and treatment with a vasopressor, dopamine (180 mg/d), was required to maintain a normal blood pressure. In addition, he began to complain of squeezing pain in the anterior chest. The level of a myocardial injury marker, troponin, was 0.36 ng/mL, and the levels of myocardial enzymology markers were increased, as follows: creatine kinase (CK): 54 U/L (normal range, 25-400 U/L); creatine kinase isoenzyme: 37.6 U/L (normal range, 0-25 U/L); lactate dehydrogenase (LDH): 460 U/L (normal range, 109-245 U/L); α-hydroxybutyrate dehydrogenase: 290 U/L (normal range, 72-182 U/L); B-type natriuretic peptide (BNP): 1,119 pg/mL (normal range, 0-100 pg/mL). Cardiac ultrasound showed a slightly enlarged left ventricle and decreased left ventricular systolic function. The left ventricular ejection fraction was reduced, at 37% (Fig. 2), and part of the lung was consolidated (Fig. 1C, D). The patient’s hematological parameters were as follows: WBC: 3×10^9/L; neutrophils: 0.40×10^9/L (14.3%); lymphocytes: 0.3×10^9/L (9.6%); monocytes: 2.3×10^9/L (75.3%); RBC: 2.65×10^12/L; Hb: 90 g/L; platelets: 116×10^9/L. Serological antibodies against mycoplasma, chlamydia and Legionella were all negative, as were a sputum culture and both anti-neutrophil cytoplasmic antibodies (ANCA) and antinuclear antibodies (ANA).

A multitude of annular purple erythematous lesions appeared on the patient’s forehead and back, with edema surrounding the sites of erythema. The lesions measured 1-1.5 cm in diameter, and a skin biopsy revealed that the spinous layer of the skin was slightly thickened, with a moderate
amount of lymphocyte, eosinophil and neutrophil infiltration in the dermis and massive upper dermal edema. SS was confirmed pathologically (Fig. 3), and the patient was also diagnosed with chronic myelomonocytic leukemia. He then received systemic corticosteroid therapy with prednisone (320 mg/d, once/day, i.v.) and meropenem (1 mg, 3 times/day, i.v.). One week after the start of corticosteroid treatment, the patient’s dyspnea and fever began to resolve, although the radiological changes on chest CT showed no improvements. One month after the start of treatment, the dose of corticosteroids was gradually reduced to 40 mg/d. The pulmonary infiltration was subsequently attenuated, as observed on chest CT (data not shown); however, the patient’s temperature rose again, and the WBC and platelet counts continued to decline. Although the dose of corticosteroids was again increased to 160 mg/d, the patient died of multiple organ failure 30 days after the corticosteroid treatment was re-commenced.

Discussion

In recent decades, many etiological factors have been linked to the development of SS, including immunological, inflammatory, infectious, tumorigenic and chemical factors (12, 23, 24). In addition, a mutation in the protein tyrosine phosphatase non-receptor type 6 gene has recently been reported to be implicated in the pathogenesis of some types of neutrophilic dermatoses, including SS (25). Animal models with this mutation present with clinical and histopathological features similar to those of SS. Classical SS is frequently associated with infectious and inflammatory disorders (e.g., immunodeficiency, aseptic meningitis or inflammatory bowel disease), while malignancy-associated SS is frequently associated with myeloid disorders, including acute myeloid leukemia (AML) and MDS. The present patient was initially diagnosed with MDS, followed by chronic myelomonocytic leukemia. Both conditions are frequently reported to be associated with SS (26-28). Adult SS patients usually have a specific medication history; such risk factor medications include granulocyte colony-stimulating factor, minocycline, all trans-retinoic acid agents, sulfamethoxazole and azathioprine (12).

Histopathologically, the striking features of SS are diffuse mature neutrophil infiltration in the superficial dermis and edema in the dermal papillae. Nuclear fragmentation within mature neutrophils, dilation of the small vessels and swelling of endothelial cells are also frequently observed in affected skin lesions. In contrast, vasculitis is usually absent. The skin biopsy in the present case showed the spinous layer of the skin to be slightly thickened, with a moderate amount of perivascular lymphocyte, eosinophil and neutrophil infiltration in the dermis. The detection of infiltration of mature neutrophils in the dermis confirms the diagnosis of SS. Recently, a novel form of acute necrotizing SS was reported (29), characterized by the rapid onset of edematous, erythematous and warm cutaneous lesions, accompanied by neutrophilic infiltration in the deep tissue and necrosis of the soft tissue, with evidence of infection (29).

Consistently increased values of ESR and peripheral leukocytes, in particular, an increased percentage of neutrophils, are the major laboratory findings in SS patients (30). A reduced level of Hb and/or abnormal platelet count are also often observed in these patients (31). The eosinophil count may range from rare to abundant (32). The present patient exhibited an increasingly reduced Hb level and significantly increased WBC and neutrophil counts. Clearly, obtaining a complete blood cell count and documenting evidence of cellular differentiation is essential for diagnosing SS.

Although SS is frequently reported to involve multiple extracutaneous organs, pulmonary involvement is uncommon.
Radiological changes of SS in the lungs include the presence of nodular, reticular or patchy infiltration, with or without effusion (20, 33). Some patients have been confirmed to have pulmonary involvement based on transbronchial lung biopsies. Histopathologically, SS is characterized by interstitial inflammation, edema and mild fibrosis, in which a large number of neutrophils and occasional lymphocytes, macrophages and eosinophils infiltrate the alveoli (19). Our patient demonstrated such pulmonary infiltrates, as revealed on chest CT (20, 33). Unfortunately, because he was very ill, we were unable to perform a transbronchial lung biopsy in order to pathologically confirm infiltration of the lung with neutrophils.

Cardiovascular involvement was also noted in this patient with SS. He complained of chest pain and exhibited abnormal myocardial enzymology. In addition, cardiac ultrasound showed a slightly enlarged left ventricle, decreased left ventricular systolic function and reduced left ventricular ejection fraction. Aortic stenosis, aortitis, cardiomegaly, coronary artery occlusion and myocardial infiltration with neutrophils have all been previously reported to occur in patients with SS (21).

SS often presents as an upper respiratory tract infection with flu-like symptoms in its early stages. Fever is the most common symptom in SS patients and may precede the development of skin lesions by days or weeks. The current patient demonstrated a persistent fever during the entire course of disease, and painful red skin eruptions appeared days after the onset of fever. As the clinical manifestations of SS are easily misinterpreted as indicating either infection or exacerbation of the underlying disease, the diagnosis of SS is frequently missed or delayed in clinical practice. In the present report, the patient originally presented with both respiratory and hematological symptoms, whereas the cutaneous symptoms were not obvious. He was therefore initially misdiagnosed with pneumonia and given antibiotics for 10 days; the major reason for this error was that we were unable to recognize SS in its early stages. The symptoms of fever and cutaneous erythematous lesions are very common in patients with infectious, rheumatological, neurological and autoimmune diseases; therefore, SS should be differentiated from these disorders. In particular, the occurrence of fever in SS should be differentiated from that resulting from infection. In addition, the presence of cutaneous lesions, negative cultures and lack of response to antibiotics, with hypersensitivity to systemic corticosteroids, is helpful for making the diagnosis.

Based on our experience with the present patient, we emphasize that following points: 1) providing early recognition of SS is critical, particularly in patients who present with extracutaneous symptoms as the first sign; 2) conducting a careful physical examination is essential (a few small areas of skin rashes appeared on the current patient when he was initially hospitalized; however, this important sign was neglected until further erythema appeared days later); 3) confirming the pathogen is important for treating infectious disease (in patients treated empirically with antibiotics without confirmation of the underlying pathogen, clinicians should pay more attention to the efficacy of antibiotic therapy and modify the diagnosis and therapy in a timely manner); and 4) administering aggressive treatment is necessary. Systemic corticosteroid infusion is often used to treat SS, with rapid and reliable effects. The clinical symptoms of SS usually resolve rapidly following the initiation of steroid therapy. However, the prognosis of SS depends heavily on the etiology of the disease and the severity of the involved organ systems. In the present case, we were unable to save the patient’s life. In addition to the development of multi-organ involvement and increasing organ failure, the rapid withdrawal of corticosteroids may have been an important cause of the patient’s demise.

SS is characterized by fever and neutrophilia in addition to the presence of cutaneous erythematous plaques and/or nodules and diffuse infiltration of the dermis by mature neutrophils. Although pulmonary involvement is relatively rare, providing early recognition of SS in patients with multi-organ involvement is important for the prompt administration of treatment.

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