CASE REPORT

Sweet syndrome: a painful reality

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SUMMARY

Sweet syndrome is a rare disorder that is manifested by constellation of clinical features, including fever, neutrophilic leucocytosis, raised painful plaques on skin and dermal infiltration by neutrophils. Numerous aetiological associations have been reported in the literature, including various haematological malignancies and drugs. Our case was peculiar because of association of capecitabine and Sweet syndrome in rectal cancer. We describe a case of a woman aged 57 years, with recently diagnosed stage III rectal cancer, developed painful erythematous rash over her face along with fever and headache. Skin biopsy was performed which revealed typical findings of Sweet syndrome. She was successfully treated with systemic steroids. Our case was an unusual presentation of Sweet syndrome in a patient with rectal adenocarcinoma treated with neoadjuvant capecitabine.

BACKGROUND

Paraneoplastic syndromes are distinct category of disorders, which are non-metastatic manifestations of underlying malignancy. Sweet syndrome is a rare paraneoplastic syndrome usually seen in haematological malignancies and its association with solid malignancies is extremely infrequent. Sweet syndrome can also be associated with inflammatory conditions as well as medications. It is important to rule out any underlying malignancy if Sweet syndrome is diagnosed without any obvious signs of malignancy. Therefore, it is imperative for any physician to understand the clinical features, diagnosis and management of the Sweet syndrome. The following case represents unusual case of Sweet syndrome likely associated with rectal cancer treated with neoadjuvant capecitabine.

CASE PRESENTATION

A Caucasian woman aged 57 years with recently diagnosed rectal cancer came to the emergency room with severe headache, fever and left-sided facial swelling. Five days before presenting to the hospital, she started having a severe frontal headache with radiation to left temporal area. It was associated with swelling and redness over the left side of the face, including the periorbital area. She denied any preceding upper respiratory infection or any other systemic lesions. Later on, she developed high fevers as well. She had completed neoadjuvant concurrent chemoradiation with capecitabine 4 weeks prior to this presentation. Of note, she did not receive any granulocyte colony-stimulating factor during the neoadjuvant treatment. As far as her history of rectal cancer is concerned, 5 months ago, she was evaluated for persistent weight loss and change in bowel habits. She underwent colonoscopy,

which revealed a rectal mass 5 cm from the anal verge. Biopsy revealed rectal adenocarcinoma and was staged as T3, N1, M0. She completed neoadjuvant concurrent chemoradiation therapy with capecitabine for 6 weeks. She underwent repeat flexible sigmoidoscopy after the neoadjuvant chemoradiation therapy, which showed only rectal ulceration without any mass. Her medical history was also significant for anxiety, depression and 10 pack year of tobacco smoking. She denied any drug abuse history. Her home medications included duloxetine, vitamin D, lorazepam and hydrocodone/acetaminophen. Physical examination revealed tender maculopapular erythematous rash over the forehead, left periorbital and left facial region. Eyes and oral mucosa were intact. Her vital signs revealed a temperature of 102.7°F, heart rate of 128 bpm and blood pressure 138/61 mm Hg.

Figure 1 (A) Dermal infiltration of neutrophils at 10× power. (B) Dermal infiltration of neutrophils at 40× power.

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INVESTIGATIONS

Laboratory findings showed the white cell count of $12.4 \times 10^9/L$ with 88% neutrophils, haemoglobin of 10.9 g/dL, platelets of 374×10^9 , erythrocyte sedimentation rate of 60 mm/hour, creatinine of 0.57 mg/dL and normal liver function tests, including alkaline phosphatase of 112 units/L. Blood cultures remained negative for any growth. Skin biopsy confirmed the diagnosis of Sweet syndrome with evidence of dense dermal neutrophil infiltration as shown in figure 1A, B.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included cellulitis, temporal arteritis and Sweet syndrome. Temporal arteritis was ruled out by negative temporal artery biopsy. Cellulitis was ruled out after biopsy-proved Sweet syndrome.

TREATMENT

A diagnosis of Sweet syndrome was made on the basis of clinical, laboratory and histopathological findings. The patient was started on systemic steroids with prednisone 60 mg/day.

OUTCOME AND FOLLOW-UP

Her symptoms resolved within a few days and prednisone was tapered over a period of 8 weeks. She successfully underwent laparoscopic low anterior resection of her rectal cancer. She is currently finishing her adjuvant chemotherapy with FOLFOX. The patient remains clinically stable without any evidence of Sweet syndrome.

DISCUSSION

Sweet syndrome was first described in the literature by Dr Robert Sweet in 1964. He described a series of cases with distinct clinical and histological manifestations, including fever, neutrophilic leucocytosis of blood, raised painful plaques on skin and dermal infiltration by neutrophils.¹ Sweet syndrome is also known as acute febrile neutrophilic dermatosis.² There are a number of factors described in the literature that can lead to the development of Sweet syndrome.³ Diagnosis of Sweet syndrome is based on typical clinical, laboratory and histological findings. Diagnostic criteria have been formulated to help clinicians to diagnose the disease.^{4 5} According to these criteria, two major and two minor criteria need to be fulfilled to make the diagnosis of Sweet syndrome (box 1). Sweet syndrome is

associated with various clinical signs and symptoms. Fever is the most common symptom. In some cases, patients report prior upper respiratory infection as well. Skin lesions of Sweet syndrome are typically tender and appear as erythematous papules or nodules. Upper extremities, face and neck are the most common locations for skin lesions. Additionally, Sweet syndrome can be manifested by extracutaneous lesions involving the central nervous system, kidneys, liver, lung and heart.^{3 6}

Sweet syndrome is classified into three distinct categories: classical Sweet syndrome, malignancy-associated Sweet syndrome and drug-induced Sweet syndrome.⁶ Classical Sweet syndrome is also called idiopathic Sweet syndrome and is associated with various conditions with the exception of malignancy and drugs. It is the most common type of Sweet syndrome.⁶ Malignancy-associated Sweet syndrome can be a cutaneous manifestation of undiagnosed malignancy or an initial sign of recurrence of cancer.⁷ Sweet syndrome is associated with haematologic as well as solid malignancies. AML is one of the most common malignancies associated with Sweet syndrome.⁷ A variety of medications have been reported for drug-induced Sweet syndrome, including antibiotics, antineoplastic drugs, colony-stimulating factors and antiepileptics.⁶ In our patient, the underlying aetiology of developing Sweet syndrome could be associated with capecitabine in the setting of rectal cancer. To the best of our knowledge, there is no reported case in the literature of Sweet syndrome in association with capecitabine.

The pathogenesis of Sweet syndrome is not well understood, but there are some mechanisms that have been postulated in the development of the disease. These mechanisms include circulating autoantibodies, dermal dendrocytes, cytokines, immune complexes and genetic susceptibility.^{6 8–10} It may very well be that the pathogenesis of Sweet syndrome is multifactorial, a number of aetiologies playing specific roles in pathogenesis.

The cutaneous manifestations persist for weeks or months if not treated. Although clinical signs and symptoms may spontaneously regress after treating the underlying cause,¹¹ initial supportive treatment is generally required to control the disease. The mainstay of treatment is corticosteroids. The usual initial dose is 1 mg/kg/day and can be tapered down over a period of 4–6 weeks.^{6 12} Alternatively, colchicine and potassium iodide can be used as a first-line therapy for patients who cannot tolerate steroids.^{13 14} Indomethacin, clofazamine, dapsone and ciclosporin can all be utilised as second-line treatment.^{5 15–17}

Box 1 Diagnostic criteria of Sweet syndrome^{4 5}

Major criteria

1. Abrupt onset of painful erythematous plaques or nodules
2. Dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis by histopathology

Minor criteria

1. Fever $>38^{\circ}\text{C}$
2. Association with an underlying haematologic or visceral malignancy, inflammatory disease, or pregnancy, OR preceded by an upper respiratory or gastrointestinal 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 >20 mm/hour; positive C reactive protein; >8000 leucocytes; $>70\%$ neutrophils.

Learning points

- ▶ Sweet syndrome is a rare disorder, which is clinically manifested as fever, erythematous rash and neutrophilic leucocytosis.
- ▶ It is classified into classical, malignancy-associated and drug-induced Sweet syndrome.
- ▶ Sweet syndrome should be differentiated from cellulitis and vasculitis due to similarities in their clinical features.
- ▶ Corticosteroids are the mainstay of treatment of Sweet syndrome.

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