CASE REPORT

Strange case of dimorphic skin rash in a patient with cirrhosis: atypical herpes simplex and sweet's syndrome

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SUMMARY

A middle-aged man with decompensated cirrhosis and a dimorphic multisite skin rash is diagnosed with rare atypical herpes simplex infection, manifesting Sweet's syndrome (SS) in the absence of other described associations. SS, an acute febrile neutrophilic dermatosis, has three common forms—classical or idiopathic, malignancy associated and drug induced. Systemic autoimmune, connective tissue diseases and infections are also strong associations. The latter is commonly described in Gram-positive bacteria, salmonellosis and *Yersinia*. Herpes infections are a rare cause of SS, reported only thrice in literature, one with concomitant lupus, the second with associated mycobacterial infection and third, in metastatic breast disease in contrast to our patient. Atypical rash, especially if dimorphic, warrants histopathological evaluation to confirm underlying disease.

BACKGROUND

Sweet's syndrome (SS) or acute febrile neutrophilic dermatosis encompasses clinical symptoms, physical features and pathological findings that include fever, neutrophilia, tender erythematous papules, nodules or plaques and a diffuse upper dermal infiltrate of predominantly mature neutrophils.¹ The classical form of SS affects women in the third to the fifth decade and is preceded by an upper respiratory tract infection with recurrence seen in one-third. SS can be a paraneoplastic manifestation of acute myelogenous leukaemia and solid tumours. Drug-induced SS is seen with granulocyte-colony stimulating factor and other medications such as older antibiotics, chemotherapy agents or analgesics.² Rare association of isolated herpes simplex virus (HSV) infection, in a patient with cirrhosis, has not been described before. We emphasise on the histopathology of atypical skin lesions even in patients with advanced cirrhosis for confirmation of diagnosis for timely medical management.

CASE PRESENTATION

A 48-year-old man, a diagnosed case of decompensated alcoholic cirrhosis, was admitted to the emergency room in a disoriented state. Three days before, the patient developed high-grade fever without chills and rigours that settled with 500 mg of acetaminophen. Later, he developed reversal of sleep pattern and difficulty in comprehending

simple commands. One day prior to arrival in the emergency, he developed multiple reddish blisters localised over both hands that increased in number and size rapidly. His drug history included multi-vitamin supplements, protein supplements, rifaximin, carvedilol, torsemide and spironolactone. On examination, the patient was not oriented to time, place and person. Icterus was evident, and right-sided posterior auricular lymph nodes were palpable. There was no pallor, cyanosis, clubbing or bilateral pitting pedal oedema. Skin examination revealed large reddish blisters interspersed between erythematous papulonodular lesions over the thenar region of both hands (figure 1). Signs of peripheral digital gangrene were absent. Abdominal examination revealed firm hepatomegaly and splenomegaly without ascites. The patient was put on mechanical ventilation. During the next 12 hours, new lesions erupted over the hands sparing other parts of the body. Blood investigations revealed white cell count of $18 \times 10^9/L$ (polymorphonuclear cells 68%), platelet count of $44 \times 10^9/L$ and C reactive protein of 158 mg/L (normal 0–5 mg/L); liver function tests showed total bilirubin 6.8 g/dL (upper limit of normal (ULN) <1.0) with direct fraction 4.6 g/dL (ULN <0.3), alanine aminotransferase 108 U/L (ULN 68), aspartate aminotransferase 84 U/L (ULN 37), alkaline phosphatase 160 U/L (ULN 117) and serum procalcitonin was >2 to <10 ng/mL. Central and peripheral blood and urine cultures were sterile, and chest X-ray did not suggest parenchymal lesions. Serum carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 19-9 and prostate-specific antigen were within normal limits. Ultrasound of the thyroid and abdomen was normal. Cultures from endotracheal aspirate on multiple occasions showed no growth. On the third day after admission to the intensive care unit, he developed confluent nodular lesions over the right and left (right greater than left) superior orbital regions. These lesions were polymorphic, with blisters containing clear and creamy fluid (figure 2). Other areas were spared. Considering eruptive viral dermatopathy, serology for herpes simplex, varicella, cytomegalovirus, HIV and Epstein-Barr virus was sent. Tzanck smear was unremarkable. The patient's condition deteriorated with new-onset hypotension and non-oliguric acute kidney injury. A decision was made to biopsy the atypical lesions over the face and the haemorrhagic

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Figure 1 Clinical examination of the hands. Skin examination revealed the presence of occasional large reddish blisters interspersed between multiple erythematous papulonodular lesions over the thenar region of both hands.

nodular lesions over the hands after coagulation correction utilising thromboelastography—targeting platelets above $50\,000/\text{mm}^3$ and fibrinogen $>120\text{ mg/dL}$ ³ for histopathology and routine cultures. The biopsy from the weeping facial nodule

Figure 2 Clinical examination of the face. Large confluent nodular lesions over the right side of the face greater than left side, along the superior orbital regions, are noted. These lesions were flat-topped and polymorphic, with surface blistering with weeping clear and creamy fluid.

revealed complete focal necrosis of the epidermis with dense neutrophilic infiltrate of the dermis and fibrinoid necrosis of the vessel wall with endothelial swelling and occasional multinucleated epithelial cells—possibly due to herpes infection (figure 3A–C). Meanwhile, the patient was started on intravenous acyclovir as per standard guidelines, and blood for IgM herpes simplex was positive. The biopsy of the haemorrhagic lesion over the hand showed mild basal vacuolation and subepidermal bulla with neutrophilic infiltrate. The dermis showed dense interstitial and perivascular neutrophilic infiltrate with leucocytoclasia without inclusions, thrombi or vasculitis—these features are suggestive of SS (figure 3D–F). Tissue cultures did not show any bacterial or fungal growth. A final diagnosis of severe herpes infection and associated SS leading to fulminant sepsis and multiorgan failure was made. Even though the patient had transient clinical improvement, secondary bacterial sepsis intervened during the long intensive unit stay leading to death from multiple organ failure 4 days after the final diagnosis.

INVESTIGATIONS

In a patient with cirrhosis, acute worsening of chronic decompensation warrants aggressive search for treatable causes of the acute insult. In our patient, after ruling out common causes of severe sepsis and in the absence of systemic autoimmune, connective tissue diseases (antinuclear antibody, rheumatoid

Figure 3 Histopathology of the skin lesions. Biopsy from lesion of the face showing complete focal necrosis of the epidermis (A, H&E stain, 10 $\times$) with dense neutrophilic infiltrate of the dermis (B, H&E stain, 20 $\times$) and fibrinoid necrosis of the vessel wall with endothelial swelling and occasional multinucleated (C, H&E stain, 40 $\times$) epithelial suggestive of viral aetiology; the biopsy of the haemorrhagic lesion over the left hand showing mild basal vacuolation and subepidermal bulla with neutrophilic infiltrate (D, H&E stain, 10 $\times$); the dermis showing dense interstitial and perivascular neutrophilic infiltrate (E, H&E stain, 20 $\times$) with leucocytoclasia (F, H&E stain, 40 $\times$), features suggestive of Sweet's syndrome.

factor, cryoglobulin level and extractable nuclear antigens) or malignant diseases, further evaluation of the atypical skin lesions revealed two different pathologies—herpes simplex infection and associated SS.

DIFFERENTIAL DIAGNOSIS

A multitude of skin conditions can mimic SS. These include acral erythema, drug eruptions, rosacea fulminans, cellulitis, erysipelas, herpes zoster virus, pyoderma gangrenosum, systemic mycoses, tuberculosis, viral exanthem, leukaemia cutis, lymphoma, metastatic tumour, erythema multiforme, erythema nodosum, urticaria, lupus erythematosus, vasculitis, erythema elevatum diutinum, granuloma faciale, leucocytoclastic vasculitis and periarteritis nodosa.⁴ However, most of these can be easily ruled out on the basis of histopathology—for example, in erythema, elevated diutinum younger lesions show leucocytoclastic vasculitis, whereas older lesions have dermal fibrosis and mucin; in granuloma faciale, the dense diffuse neutrophilic infiltrate is associated with microscopic features of leucocytoclastic vasculitis and numerous eosinophils; in leukaemia cutis, the dermal infiltrate consists of immature neutrophils; in leucocytoclastic vasculitis, vessel wall destruction and extravasation of erythrocytes along with fibrinoid necrosis of vessel walls, karyorrhexis and neutrophils in the vessel wall are seen and in purpura fulminans, a very close diagnosis, there is involvement of small vessels at the junction of dermis and subcutaneous fat characterised by thrombi within the lumina of the vessels, a sparse infiltrate of neutrophils around the vessels, extravasation of erythrocytes, oedema of the dermis and epidermal necrosis with subepidermal blister formation, all of which were classically lacking in our patient.⁵ Another condition, a variant of SS, is neutrophilic dermatosis of the dorsum of hand that can present with classical features of SS, but lesions are located on the dorsal surface of the hand, which was not the presentation in our patient.⁶

OUTCOME AND FOLLOW-UP

In a patient with cirrhosis with severe sepsis leading to extrahepatic organ failures, a syndromic condition termed acute on chronic liver failure (ACLF) is described. The more the organ failures, the higher is the mortality associated with ACLF. In the presence of multiple organ failures, timely treatment of the acute event in our patient did not prove beneficial and ultimately led to mortality, an event that is dependent on multiple factors other than acute insult (such as grade of liver disease severity, model for end-stage liver disease score or presence of hepatic encephalopathy) in ACLF.⁷

DISCUSSION

SS is characterised by clinical symptoms, investigational features and pathological findings (fever, elevated neutrophil count, tender erythematous lesions and a diffuse infiltrate consisting predominantly of mature neutrophils typically located in the upper dermis). Skin lesions of SS are red or purple-red, papules or nodules that may develop into asymmetrical plaques. It presents as either a single lesion or multiple lesions, and the most frequent locations include the upper extremities, face and neck.⁸

Choi and Chung in 1999 first described the association of SS with HSV in a patient with systemic lupus erythematosus (SLE). However, SLE itself is strongly associated with SS as described in a case series by Barton and colleagues and so, the relationship of SS with herpes was not very strong in the presence of confounding factors.^{9 10} Coskun *et al* in their report showed

an association of herpes virus with SS in a patient with metastatic breast disease and tumour infiltration of the bone marrow. However, even this description was confounded by the fact that solid metastatic disease can be associated with SS.¹¹ In the third case reported in the association between SS and herpes virus, Theng and colleagues described a patient with active *Mycobacterium chelonae* and HSV infections.¹² Whether SS was associated with mycobacterial infection or herpes virus is, however, not clear. The age, clinical presentation and blood investigations were not suggestive of underlying malignancy in our patient. The medications review did not conform with drug-induced SS.⁴

The definitive diagnosis of herpes is by demonstrating the presence of the virus in the affected area, by either isolation or antigen detection. Serological testing (for IgM) is useful in symptomatic patients when direct methods show negative results and in asymptomatic patients to determine the present infection. HSV infection causes typical cytopathic changes in epithelial cells with the formation of multinucleated cells. This test can be performed when an urgent result is needed, and no alternative test is immediately available. In our patient, the clinical presentation was catastrophic, and we required immediate results to rule out a viral pathology and hence used IgM and histology testing for herpes infection which were high yielding in a smaller lab set-up.¹³ The histology of lesions on the face and hands was distinct from each other (giant cell formation and epidermal changes in viral-associated skin disease and leucocytoclasia, intense neutrophilic dermal infiltrates and preserved epidermis in SS).

In our case, the fourth report in the world literature concerning this association, we show that isolated herpes simplex infection in the absence of other infections, malignancy, autoimmune and connective tissue disease can be associated with SS and a novel description in a patient with cirrhosis. Patients with cirrhosis have dysregulated immune functions and cytokine metabolism. Circulating autoantibodies, cytokines, dermal dendrocytes, human leucocyte antigen serotypes and immune complexes related mechanisms are all postulated to contribute to the pathogenesis of SS.¹⁴ In the presence of severe viral sepsis, cirrhosis could have been an added risk factor for the development of SS due to herpes virus infection in our patient.

Learning points

- ▶ Sweet's syndrome (SS) could be associated with herpes simplex infection in the presence of an underlying immune dysregulation such as cirrhosis.
- ▶ SS should be a differential diagnosis in a patient with cirrhosis presenting with rapidly evolving skin lesions in the presence of severe sepsis.
- ▶ Close differential diagnosis such as purpura fulminans, leucocytoclastic vasculitis and drug-induced dermatopathy can be clinically difficult to differentiate and requires histopathology for confirmation even in advanced cirrhosis.
- ▶ An active and aggressive search for infectious causes of SS is warranted in patients with multiple organ failures and rapid clinical deterioration.

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