A 44-Year-Old Man with Fever, Mucocutaneous Ulcers, and a Rash

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About the Authors

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Summary

We report the case of a 44-year-old man who presented with mucocutaneous ulcers, purpuric rash, fever, pharyngitis, cervical lymphadenopathy, and arthralgias. The patient's symptoms resolved with prednisone treatment. He later experienced recurrence of oral ulcers that responded to colchicine treatment. Behcet's disease is a systemic vasculitis characterized by recurring oral and genital mucocutaneous lesions and accompanying ocular, gastrointestinal, articular, pulmonary, neurologic, or peripheral vascular manifestations. Sweet's syndrome typically presents with flu-like symptoms, fever, neutrophilia, and painful erythematous skin lesions. Along with skin biopsy, classification criteria exist for both conditions, which may help differentiate the two diagnoses on initial presentation.

Résumé

Il s'agit du cas d'un homme de 44 ans qui présente des ulcères cutanéomuqueux, une éruption cutanée purpurique, de la fièvre, une pharyngite, une adénopathie cervicale et des arthralgies. Les symptômes du patient disparurent à la suite de l'administration de prednisone. Plus tard, une récurrence d'aphtes buccaux réagit à l'administration de colchicine. La maladie de Behcet est une vascularite systémique caractérisée par des lésions cutanéomuqueuses buccales et génitales récurrentes accompagnées de manifestations oculaires, gastro-intestinales, articulaires, pulmonaires, neurologiques ou vasculaires périphériques. En comparaison, le syndrome de Sweet se caractérise habituellement par des symptômes pseudo-grippaux, de la fièvre, une neutrophilie et des lésions cutanées érythémateuses douloureuses. La distinction entre les deux diagnostics est facilitée par la réalisation d'une biopsie cutanée et la référence à des critères de classification des deux pathologies dès la présentation.

Case

A 44 year-old man of Chinese descent presented with a one-week history of pharyngitis and fever, followed by oral and genital ulcers, myalgias, and a palpable purpuric rash. He was previously healthy and denied sick contacts, animal or insect exposures, or recent travel. He reported recent unprotected heterosexual contact but denied dysuria, genital discharge, or pruritus. After symptom onset, he had taken Chinese herbal remedies but denied use of any other medications or drugs. Family history was unremarkable.

On examination, the patient looked unwell, was febrile (38.8°C orally), and was diaphoretic. He was initially tachycardic (heart rate [HR] = 120) but responded to intravenous fluids. Examination of the oral cavity revealed painful oral ulcers (Figure 1b) and tonsillar and pharyngeal exudates. He had tender cervical lymphadenopathy and non-tender scrotal and penile ulcers. A palpable, purpuric, non-blanchable, non-pruritic and painless rash (Figure 1c) was present on his lower legs bilaterally, with some lesions displaying central papules. Larger discrete lesions at each wrist had a more nodular appearance with central discolouration (Figure 1a). Lesions

were also present on his upper abdomen and buttock. There were no other skin or nail findings. He had mild peri-articular ankle swelling and right knee stress tenderness with flexion, but no joint effusions. Cardiac, respiratory, abdominal, and neurological exams were unremarkable.

Laboratory investigations revealed a normal white blood cell (WBC) count with neutrophilia, mild anemia (Hb 126), transaminitis, and an elevated erythrocyte sedimentation rate (ESR; 110). The patient was admitted to hospital and given 1 g ceftriaxone and azithromycin 1 g daily for empiric treatment of suspected gonococcal infection and possible chlamydia co-infection. The antibiotics were discontinued after additional investigation results became available and the patient remained febrile despite antibiotics. Bacterial blood and urine cultures were negative, a throat swab was negative for Group A Streptococcus, and the oral lesion swab was negative for herpes simplex virus. The patient was hepatitis B immune. Hepatitis C and HIV 1/2 antibody and p24 antigen tests were negative. Cytomegalovirus, syphilis, parvovirus B12 IgM, EBV monospot and brucella serology testing were negative. Urine testing for Mycoplasma showed no isolates.

Figure 1. a–c) Skin and oral manifestations at presentation; e) neutrophilic dermatoses on skin biopsy; d,f) skin manifestations after 13 days of prednisone therapy.

Autoimmune work up (ANA, RF, ANCA, anti-ds DNA, complements) was negative. Skin lesion biopsy demonstrated a neutrophilic dermatosis, with fibrin deposition and small vessel vasculitis in the deep dermis and no eosinophils (Figure 1e). A sub-corneal follicular pustule was present in the biopsy fragment. Skin pathergy test was negative. The patient was started on prednisone 40 mg daily for a presumptive diagnosis of Behcet’s disease (BD) and was discharged afebrile after clinical improvement. Follow-up appointments with rheumatology and ophthalmology were arranged for the patient; there was no evidence of uveitis during the admission. Chest x-ray, electrocardiogram, and echocardiogram performed in hospital were within normal limits.

The patient was seen in clinic 11 days after discharge and exhibited almost complete resolution of his oral ulcers, as well as improvement in the rash (Figure 1d, f) and genital ulcers. Five months after his initial presentation, he presented with recurrent oral ulcers that responded to colchicine treatment.

Discussion
Neutrophilic Dermatoses

Sweet’s syndrome is classically characterized by fever, neutrophilia, painful erythematous skin lesions with neutrophilic infiltrate in the upper dermis, and immediate response to systemic corticosteroids.¹ It typically presents in middle-aged women² and may be associated with upper respiratory tract and gastrointestinal (GI) infections, pregnancy, inflammatory bowel disease, and malignancy (often hematologic), or it can be drug-induced.¹ Generalized flu-like symptoms are common in Sweet’s syndrome, as are joint manifestations.² Involvement of mucous membranes, with oral ulcers and ocular lesions, as well as ears, bone, central nervous system (CNS), and intra-abdominal and intra-thoracic organs has been reported.¹ In most cases, there is a leukocytosis with elevated neutrophils.²

In Sweet’s syndrome, the typical skin lesions are tender erythematous papules and nodules that may coalesce into irregular plaques.¹ Most frequently they occur on the face, neck, and arms.⁴ Pathergy may be present.¹ Pustular lesions are rarely observed and, when present, primarily occur on the extensor surfaces of the distal arms (neutrophilic dermatosis of the dorsal hands) in patients with ulcerative colitis.⁴

Histopathological findings typical of Sweet’s syndrome are a major diagnostic criteria (Table 1). On histopathology, the neutrophilic infiltrate in the dermal layer is separated from the epidermis by edema.² Although vascular lesions may be present, there is no true vasculitis² in Sweet’s syndrome, with fibrin deposition and neutrophilic vasculitis typically

being absent.¹ Drug-induced Sweet’s syndrome may show an inflammatory infiltrate with eosinophils.¹ In contrast, “pustular lesions on purpuric bases” or “pustular vasculitis” have been used to describe BD, which is characterized by a neutrophilic vascular reaction. Thus, male sex, presentation, and distribution of non-tender cutaneous lesions, absence of leukocytosis, morphology of the neutrophilic dermatosis, and recurrence of oral ulcers favours a diagnosis of BD over Sweet’s syndrome (with neither major diagnostic criteria being met).

Behcet’s Disease
Epidemiology

BD is a systemic vasculitis characterized by chronic recurrent clinical symptoms of oral and genital mucocutaneous lesions and ocular, GI, articular, pulmonary, neurologic, and peripheral vascular manifestations (Table 1). BD has roughly equal distribution among men and women,⁵ and typical age of onset is 20–40 years.⁶ Younger age at diagnosis and male sex are worse prognostic features, with higher mortality and increased ocular morbidity.⁷ The disease has the highest incidence in ethnicities found along the Silk Road, including regions in the Middle East, the Mediterranean basin, and Asia (between 30 and 45 degrees northern latitude) and is uncommon in developed countries; reasons for these geographic differences are unknown.⁷

Pathogenesis

The etiology of BD is unknown. Although believed to be an autoimmune process, it has not been associated with any autoantibodies.⁸ An association of HLA-B51 and BD has been established; however, the specific role of HLA-B51 in the pathogenesis of BD has not been elucidated, as it only explains 20% of disease heritability.⁸

Table 1. Proposed Diagnostic Criteria for Sweet’s Syndrome.

Major Criteria
- Abrupt onset of tender or painful erythematous or violaceous plaques or nodules
- Predominantly dermal neutrophilic infiltration without leukocytoclastic vasculitis
Minor Criteria
- Preceding fever or infection
- Accompanying fever, arthralgia, conjunctivitis or underlying malignancy
- Leukocytosis
- Good response to systemically administered corticosteroids and not to antibiotics
- Increased erythrocyte sedimentation rate
Definitive diagnosis requires 2 major and 2 minor criteria.
Modified from (3)

Clinical Features

The original descriptive triad of BD included recurrent oral ulcers, genital ulcers, and uveitis as hallmark features of the disease. Aphthous ulcers less than 1 cm in diameter are the most common type of oral ulcer in BD, with 85% prevalence.⁷ They may be present anywhere on the oral mucosa, with the lips being the most frequent site.⁹

Genital ulcers are also common (found in 85% of cases), and distribution usually involves the scrotum. GI tract involvement includes mucosal ulceration, mainly in the ileum and colon, and symptoms of colicky abdominal pain and diarrhea. Skin involvement includes nodular lesions resembling erythema nodosum, papulopustular lesions similar to acne vulgaris, superficial thrombophlebitis, and positive pathergy test. Pustulosis, a vasculitis consisting of a sterile pustule on a rounded erythematous-edematous or purpuric base, is the most frequent skin lesion in BD.⁹

Ocular involvement is usually in the form of bilateral relapsing uveitis. Musculoskeletal symptoms include myositis, non-erosive peripheral arthritis, and arthralgias. The most serious symptoms of BD and major causes of mortality include vasculitides of major vessels and neurologic manifestations. In nationwide Iranian surveys of patients with BD, Davatchi and colleagues⁹ found that oral and genital aphthosis and skin manifestations were the most common symptoms among 1,996 patients (93%, 76%, and 69%, respectively), with ocular manifestations found in only 35%, joint involvement in 30%, and phlebitis, CNS, and GI involvement being relatively uncommon (6.5%, 8.8%, and 5.3%).

Diagnosis

Fifteen different classification systems or diagnostic criteria have been proposed for BD, with the latest one being the International Criteria for Behcet's Disease (ICBD).⁹ In Davatchi and others' review of all 15 BD criteria using a disease registry in Iran (where BD prevalence is high), the ICBD (Table 2) was found to be the most accurate, with an accuracy of 93.8%, sensitivity of 96.1%, and specificity of 88.7%.⁹ The patient in this case meets BD diagnosis by having 4 points on the ICBD system.

Treatment

Various double-blind, randomized controlled trials have been performed with patients with BD, using agents such as methylprednisolone, azathioprine, thalidomide, colchicine, dapsone, cyclosporine, and azapropazone.⁷ There is no clear first-line agent considered the overall standard of care for BD, and despite the common use of oral steroids, no clear evidence on their efficacy for BD has been published.⁷ In 2008,

Table 2. Revised International Criteria for Behcet's Disease (traditional format).

Criteria	Points
Oral aphthosis	1
Skin manifestations	1
Vascular lesions (thrombosis, aneurysm)	1
Pathergy phenomenon	1
Genital aphthosis	2
Ocular lesions	2
Diagnosis requires 3 or more points.	
Modified from 9	

the European League Against Rheumatism developed nine recommendations for managing BD based on expert opinion and uncontrolled evidence, further highlighting the need for controlled trials.¹⁰

Key Points

- Sweet's syndrome and Behcet's disease should be considered in the differential for patients presenting with fever, rash, and mucocutaneous ulcers.
- Behcet's disease typically presents in younger patients and is more common in ethnicities found along the Silk Road.
- Oral and genital ulcers and skin manifestations are common features of Behcet's disease, while Sweet's syndrome may be preceded by infection and/or associated with malignancy.
- Skin biopsy is helpful in narrowing the diagnostic differential and guiding treatment.

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