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Labial pain and swelling with fever

Ethan Craig, MD¹, Reza Sedighi Manesh, MD¹, Jonathan D. Cuda, MD², and Allan C. Gelber, MD¹

¹Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

²Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Presentation

A 30-year-old Caucasian woman presented with rapidly progressive and disabling labial pain and swelling associated with rash, fever, generalized arthralgias and headache.

She was in her usual state of excellent health until three days prior to admission, when she developed severe painful vulvar swelling and fatigue. One day later, a tender, pustular rash appeared across her chest, arms and lateral neck. She noted fevers to 38.9°C; arthralgias of the hips, knees, and ankles ensued in association with a severe headache. Over 72 hours, ambulation and urination became increasingly compromised due to progressive pain and swelling affecting the perineum. Her cognition and level of alertness remained intact. She was in a long-term monogamous relationship without current or prior use of illicit drugs. Her family history was negative for any known autoimmune diseases, and her ancestry was Northern European.

Given the high fever with pronounced genital pain and swelling, she was admitted to the Johns Hopkins Hospital for further evaluation and management. Her temperature was 38.3°C, pulse 85 beats per minute and blood pressure 103/62 mmHg. Skin exam showed acneiform lesions across her chest, upper abdomen and back, with target-shaped lesions over the neck (Figure 1A and 1B). There was marked vulvar ulceration and swelling (Figure 2A). Cardiopulmonary and abdominal examinations were unremarkable.

Admission laboratory studies demonstrated a leukocytosis of 22.4 K/mm³ (88% neutrophil, 8% lymphocyte, 4% monocyte). Hemoglobin and platelet count were normal, as were electrolytes, creatinine and liver function tests. Herpes simplex virus and HIV serologies and a treponemal chemiluminescence immunoassay were negative. Punch biopsy of a pustular skin lesion showed folliculocentric dense dermal neutrophil-rich infiltrate (Figure 3A, 3B) containing coccobacilli.

Address for Correspondence: Allan C. Gelber, M.D., Johns Hopkins University School of Medicine, Mason F. Lord Building, Center Tower, Suite 4100, 5200 Eastern Avenue, Baltimore, MD 21224, Ph: (410) 550-2018 Fx: (410) 550-2072 agelber@jhmi.edu.

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Assessment

Full elucidation of her past medical history held the key to uncovering her diagnosis. Inquiry into her earlier health status revealed a first episode with similar phenotypic features 13 years earlier, when she presented as a teenager, with acute onset of an ulcerative vulvar lesion associated with fever, headache, arthralgias, and cervical lymphadenopathy. Extensive evaluation for sexually transmitted infections, including biopsies of the skin and lymph node, was negative. Her symptoms persisted for several months and were quite disabling, though ultimately remitted spontaneously. Another similar episode occurred 5 years prior, and resolved with empiric oral steroid treatment over 2 weeks; an underlying cause was not identified. Workup at that time included a colonoscopy with random biopsies, which was negative for any evidence of inflammatory bowel disease. Between these episodes, she was in excellent health.

Moreover, upon careful review of systems, she described oral aphthous ulcers which recurred 3–4 times annually over the past 15 years. These key features of the past medical history underscore the recurrent nature of her illness and help uncover the underlying cause of the current extreme presentation.

On the basis of the detailed history and physical examination, the patient was diagnosed with Behcet's disease, which is a clinical diagnosis. With the additional revelation of her prior history, her symptoms satisfied the 1990 International Study Group (ISG) criteria for classification of Behcet's Disease,¹ with oral aphthous ulceration, genital ulcers and papulopustular rash (Table 1).

Discussion

Behcet's disease is an autoinflammatory syndrome characterized by recurrent orogenital ulceration, rash, constitutional symptoms, arthritis, and ocular involvement, along with prominent vascular, gastrointestinal and neurologic manifestations.¹ Onset of symptoms typically occurs in early adulthood. Diagnosis of Behcet's disease remains clinical; several classification criteria exist, but the International Study Group (ISG) criteria and International Criteria for Behcet's Disease (ICBD) are most widely utilized (Table 1).^{1,2} Laboratory findings demonstrate inflammation, including an acute phase reactant response. A broad differential diagnosis need be considered.

Many infectious diseases may present with genital ulcerations and fever, including herpes simplex virus, syphilis, chancroid, lymphogranuloma venereum and granuloma inguinale. These diagnostic considerations were remote given her negative screening for sexually transmitted infections and the lack of new sexual contacts. Notably, during each of her prior episodes of genital ulceration, the infectious work-up for sexually transmitted infections was consistently negative. Moreover, the present truncal skin eruption and the appearance and severity of the genital swelling did not suggest disseminated gonococcal or herpes simplex infection.

Biopsy of her pustular skin lesion demonstrated coccobacilli, which could raise a question of an infection. However, while Behcet's Disease lesions are classically described as sterile,

Hatemi et al recently studied 70 biopsies from 58 patients with known Behcet's Disease and found that a majority were positive for at least one microorganism.³ In this series, 58.6% of the cultured pustules cultured grew *Staphylococcus aureus*.³ When examining only those pustules from locations unusual for acne vulgaris, such as the leg and arm, 85.7% of lesions were positive for *S. aureus*.³ The microbiology was similar to that seen among patients with acne vulgaris, though the patients with Behcet's disease had higher rates *S. aureus* and *Prevotella*, and lower rates of culture for coagulase-negative Staphylococci.³ The role of these bacteria in the pathogenesis of Behcet's disease is not clear; whether these bacteria are involved in initiation of cutaneous lesions, or are rather mere colonizers and as such non-pathogenic, remains to be determined. The papulopustular lesions of Behcet's Disease are otherwise indistinguishable on histopathology from acne vulgaris. The distribution of lesions, however, differs between the two entities. Behcet's disease often involves the arms and legs, an unusual distribution for acne vulgaris.³

Beside papulopustular skin lesions, which are found in up to 83% of patients at presentation,⁴ Behcet's disease has been described to cause numerous other cutaneous manifestations which may overlap in presentation with other disease entities. Mucocutaneous lesions including oral ulcerations and genital ulcerations have long been considered the hallmark of Behcet's. Erythema nodosum is an important cutaneous manifestation, with up to 62.4% of patients may have this finding at presentation.⁴ The pathergy reaction, an exaggerated inflammatory response leading to formation of a pustule at the site of needle prick to the skin, has been included in several diagnostic criteria.^{1,2} Other reported manifestations include Sweet syndrome (acute febrile neutrophilic dermatosis), pyoderma gangrenosum, erythema multiforme-like lesions and purpura.⁵

It is important to note, however, that none of these skin lesions is pathognomonic for Behcet's disease, and each of them may occur in a wide variety of other systemic processes. For example, the differential diagnosis of Behcet's disease commonly includes inflammatory bowel disease. These two inflammatory disorders share several common features, including arthritis, oral ulcerations, uveitis and enteritis. In addition, inflammatory bowel disease can be associated with several cutaneous lesions which may be confused for Behcet's Disease. "Metastatic Crohn's disease," a non-caseating granulomatous lesion which can involve almost any area of the skin, can involve the genitalia; and vulvar pyoderma gangrenosum associated with inflammatory bowel disease has also been described.^{6,7}

Lumbar puncture was strongly considered given the concern for *Neisseria meningitidis* as a cause of fever, headache and rash. However, the sharpness of her mental faculties and the follicular and acneiform nature of her skin eruption, were not well-explained by bacterial meningitis. We suspect the severe headaches were the consequence of aseptic meningitis, a neurologic sequela of Behcet's disease-mediated inflammation of the central nervous system.

Much of the morbidity from Behcet's disease appears to accrue early in the disease course. In a longitudinal cohort of 387 Turkish patients, about 83% of ocular involvement occurred within the first 5 years.⁴ The prevalence of orogenital ulcerations, skin lesions, and arthritis all declined over time following diagnosis.⁴ It should be noted, however, that other

manifestations including vascular disease and neurologic disease in this same cohort did not as clearly downtrend over time.⁴

Management

Due to the severity of this patient's genital ulcerations and systemic features, intravenous methylprednisolone @1 mg/kg daily was begun. The following day her fevers, rash and labial swelling had dramatically improved (Image 2B). The genital ulcerations gradually healed over several weeks. She was tapered off of steroids entirely, and during six months of follow-up, she had no recurrence of symptoms and felt entirely asymptomatic.

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Figure 1.

Figure 2.

Figure 3.

Table 1

Diagnostic Criteria for Behcet's Disease

International Study Group Criteria ¹	International Criteria for Behcet's Disease ⁴
Recurrent oral ulceration (at least 3 times in previous year) AND at least 2 of:	4 points from following:
• Recurrent genital ulceration	• Ocular lesions - 2 points
• Eye lesions including retinitis, uveitis	• Genital aphthosis - 2 points
• Skin lesions (erythema nodosum and/or papulopustular lesions)	• Oral aphthosis - 2 points
• Positive pathergy reaction	• Skin lesions - 1 point
	• Neurologic manifestations - 1 point
	• Vascular manifestations - 1 point
	• Positive pathergy reaction - 1 point