CLINICAL VIGNETTE

Aphthous Genital Ulcers: An Uncommon Manifestation of New-Onset Systemic Lupus Erythematosus (SLE)

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Introduction

Aphthous genital ulceration can be reactive in response to infection or systemic autoimmune disease, and is often mis-diagnosed as a sexually transmitted infection.[1] These ulcers are classically associated with Behcet's and Crohn's disease, and are commonly associated with oral ulceration.[2] However, genital ulcers are a rare manifestation of systemic lupus erythematosus (SLE), and few cases have been documented in the literature.[3] We present a 20-year-old woman who presented with a myriad of worsening symptoms including genital ulcers leading to a new diagnosis of SLE.

Case Presentation

A 20-year-old woman with a history of asthma and migraine was admitted to the hospital with one week of worsening symptoms including fever, chest pain, dyspnea, headache, visual disturbance, diarrhea, shoulder and neck pain, bilateral lower extremity pain and weakness, and vaginal pain. She had been hospitalized four months prior for fever, pericarditis, and myocarditis, and at that time was found to be seropositive for parvovirus B19 IgG. Her symptoms were attributed to viral illness and self-resolved within days. During the previous hospitalization, she also developed painful genital ulcerations believed to be secondary to chancroid, as the patient was sexually active with a male partner and her pain improved with antibiotics.

The patient remained asymptomatic until one week prior to admission, where she began to develop neck and shoulder myalgias, along with worsening of her usual migraine headaches and visual distortion. She denied blurry vision, neck stiffness, nausea, and vomiting. She then developed bilateral knee and ankle pain, watery diarrhea, and intermittent fevers up to 39.4 C. One day prior to admission, she developed positional, non-exertional, non-pleuritic chest pain, worse when lying on her side and improved when lying on her back. She also developed shortness of breath noticed when laughing and speaking quickly. The same day, she developed vaginal pain and dysuria similar to the pain felt during her prior hospitalization. Review of systems was also positive for dry eyes and dry mouth. She denied any sick contacts or recent travel. The patient's most recent sexual encounter occurred three months prior to admission in the context of a monogamous relationship with an asymptomatic male partner. During the encounter, the patient did not use a condom or other contraception.

On examination, she was afebrile, with normal heart rate, blood pressure of 118/72 and 100% oxygen saturation. No rashes were present on examination. Mucous membranes were moist without oral ulceration. The patient was found to have mild warmth and swelling of the bilateral knees as well as pain with flexion and extension. The knee joints were non-erythematous and non-tender to palpation. Neurological exam was notable for 4/5 strength with knee flexion and extension but was otherwise unremarkable. Genitourinary exam was notable for ulceration of the clitoral hood exquisitely tender to palpation, as well as several internal vaginal ulcerations. White vaginal discharge was noted. In addition, mild nontender pelvic lymphadenopathy was present bilaterally.

Initial labs were notable for thrombocytopenia relative to baseline, with a platelet level of 93,000/ul. Additionally, troponin-I level was elevated and peaked at 0.60 ng/ml, aspartate aminotransferase was elevated at 122 U/L and creatine kinase was 2718 U/L. Urinalysis was notable for 1+ hematuria, 1+ proteinuria, trace leukocyte esterase, and negative nitrites, and urine bacterial cultures showed no significant growth. ECG on admission showed sinus rhythm and borderline diffuse ST segment changes compared to prior ECG concerning for possible pericarditis. Chest x-ray was notable for mild pulmonary vascular congestion concerning for possible myocarditis.

Given the patient's constellation of findings, a broad rheumatologic and infectious workup was initiated. Rheumatologic laboratory studies were notable for a positive antinuclear antibody (speckled, 1:1280), rheumatoid factor (32 IU/ml), lupus anticoagulant and anti-SSA antibody (120 U), along with a mildly elevated urine protein/creatinine ratio (0.5). Echocardiography completed after resolution of chest pain showed mild mitral valve and tricuspid regurgitation improved from prior hospitalization, but no evidence of pericardial effusion. MR shoulder and femur showed small joint effusions without evidence of myositis. Infectious studies were notable for a negative parvovirus B19 PCR. Evaluation for HIV, syphilis, gonorrhea, chlamydia. trichomoniasis, bacterial vaginosis and vaginal fungal infection was unremarkable, and bacterial culture and gram stain of the ulcerative lesions grew normal

vaginal flora. HSV PCR was not obtained but was negative from her prior admission. Biopsies of the ulcers were not performed given exquisite tenderness of the lesions on exam. Results from laboratory testing are summarized in Table 1.

Table 1: Summary of infectious and rheumatologic laboratory evaluation during hospitalization

Infectious Studies	Rheumatologic Studies
HIV negative	**ANA positive (1:1280)**
RPR negative	**Rheumatoid factor positive (32 IU/ml)**
Chlamydia/Gonorrhea negative	**Lupus anticoagulant positive**
HSV negative*	**Anti-SSA antibody positive (120 U)**
Trichomonas antigen negative	**Urine Protein-to-Creatinine Ratio elevated (0.5)**
Bacterial vaginosis screen negative	C3/C4 within normal limits
Fungal stain negative	Anti-dsDNA negative
Bacterial culture lesion: normal vaginal flora	Anti-Smith negative
Urine culture: no growth	Anti-cardiolipin negative
Parvovirus negative	Anti-β2 glycoprotein negative
	Anti-SSB negative
	Anti-CCP negative
	p-ANCA, c-ANCA negative
	Myositis panel negative

* from prior hospitalization

The patient was diagnosed with systemic lupus erythematosus (SLE), meeting 5 of 11 American College of Rheumatology criteria for diagnosis (serositis, arthritis, thrombocytopenia, positive ANA, positive lupus anticoagulant). Initially, the genital ulcers were thought to be infectious given the presence of white discharge on exam, and the infection was thought to be potentially triggering her lupus flare. However, STI screening was non-contributory, and the patient's most recent sexual encounter was three months prior to admission, making chancroid and other infectious causes of genital ulceration unlikely. Given the temporal association of her genital ulcerations with her other symptoms, the ulcers were ultimately thought to be a manifestation of the patient's newly diagnosed lupus. Symptomatic improvement with antibiotics were believed to be a consequence of superimposed bacterial infection of ulcerated mucosa.

She was started on prednisone 40mg and hydroxychloroquine 400mg in the hospital in addition to supportive care and her symptoms improved. She was seen by rheumatology two weeks after discharge for optimization of prednisone dosage. She was also seen by Obstetrics & Gynecology and her primary care physician for continued follow-up of symptoms.

Discussion

Genital involvement in SLE has been documented on few occasions in the literature. Vulvar plaques have been reported in patients with both discoid lupus as well as SLE.[4] Genital ulceration in SLE is rare, with Fresko et al. finding no genital ulcerations in a sample of 48 women with SLE.[5] To our knowledge, this is the fourth case report to document genital ulceration as a manifestation of SLE. Aphthous ulceration has also been documented in related autoimmune conditions such as primary Sjogren's syndrome.[6]

The pathophysiology of recurrent aphthous ulceration in the setting of immune dysregulation remains largely unknown. Histologic examination of recurrent aphthous ulceration shows mixed inflammatory infiltrate.[7] The mechanism of inflammation likely involves activation of T cells by mast cells and macrophages, as well as release of tumor necrosis factor alpha (TNF-alpha). Inflammation may result from the action of TNF-alpha in promoting leukocyte adhesion to endothelial cells and neutrophil chemotaxis.[8] Further characterization of the immune processes involved in aphthous stomatitis may lead to the development of more targeted therapies in the future.

Determining the cause of genital ulceration presents a clinical challenge particularly in sexually active individuals. However, in the setting of various coinciding symptoms and in the absence of evidence of STI, it is important to consider systemic conditions such as lupus erythematosus.

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