Disseminated Lyme Disease Presenting With Nonsexual Acute Genital Ulcers

Justin J. Finch, MD; Jenna Wald, MD; Katalin Ferenczi, MD; Saima Khalid, MD, MPH; Michael Murphy, MD

Report of a Case

A previously healthy woman in her 50s presented to the dermatology clinic with a 3-week history of rapidly expanding painful vaginal ulcers, neck and back pain, fever, malaise, and a tender “sunburn” on her shoulders. Skin evaluation 10 days prior at her primary care clinic revealed similar smaller genital ulcers and an annular erythematous patch on her abdomen with a “central raised mole.” Lyme titer testing had negative results. The patient denied sexual activity in more than 12 years. She had no history of sexually transmitted infection including genital herpes; no ocular symptoms including eye pain, redness, or visual changes; no oral ulcers or any previous history of genital ulcers. She took no long-term medications. The ulcers continued to progress despite treatment with oral ciprofloxacin (for a concomitant urinary tract infection), oral prednisone (6-day tapering protocol beginning at 24 mg/d), and topical neomycin ointment.

On examination, she had multiple well-defined, punched-out, painful, 2- to 12-mm diameter purulent ulcers on her labia minora (Figure 1). Symmetrically distributed across her shoulders and arms was a large, poorly demarcated tender erythematous patch consistent with a sunburn. Her oropharynx was normal. Multiple biopsies of her vaginal ulcers were performed, and she was prescribed lidocaine hydrochloride gel, 5%, and triamcinolone gel, 0.1%, twice daily.

Biopsies of vaginal ulcerations showed an epidermal ulcer with adjacent polymorphous inflammatory infiltrate. There were no viral cytopathic features or changes of vasculitis. Immunohistochemical and special stains for fungal elements, bacteria, parasites, spirochetes, and herpes simplex virus (HSV) had negative results. Direct immunofluorescence testing had negative re-
results. Tissue cultures were negative for bacteria and viruses. Additional laboratory tests demonstrated a positive result for HSV-2 IgG, elevated serum C-reactive protein level (186 mg/L; reference value, <5 mg/L [to convert to nanomoles per liter, multiply by 9.524]), and weakly positive antinuclear antibody test result (1:40). Normal laboratory values were obtained for rapid plasma reagin, tests for *Chlamydia* and *Neisseria gonorrhoeae*, complete blood cell count, and tests for antibodies to *Borrelia burgdorferi*, *Babesia*, *Ehrlichia*, human immunodeficiency virus (HIV) types 1 and 2, HSV-1, and double-stranded DNA. Serologic testing for Epstein-Barr virus was not performed.

Two weeks later, the patient presented with worsening fatigue, myalgias, neck and back pain, and new-onset headaches. Her fevers had waned, and the treated vaginal ulcers had improved slightly. Skin examination now demonstrated multiple 5- to 20-cm diameter pink, annular patches on her back and shoulders (Figure 2).

The patient was prescribed doxycycline 100 mg twice daily for suspected secondary Lyme disease, and within 48 hours, she noted resolution of all symptoms including fatigue, neck pain, and rash and rapid improvement of the vulvar ulcers. Repetition of the Lyme enzyme-linked immunosorbent assay and Western blot test now revealed positive results. A punch biopsy of the edge of a patch showed interstitial histiocytic dermatitis with focal interface changes. Additional laboratory testing at this time included a nutrition panel, which had unremarkable results. A pathergy test was performed and had negative results. Her vaginal ulcers completely resolved without scarring, and she had not experienced any recurrence of the ulcers at 12-month follow-up.

### Discussion

Nonsexual acute genital ulceration (NAGU), formerly referred to as Lipschütz ulcers, is characterized by acute onset of singular or multiple painful vaginal ulcers with no identifiable etiology and nonspecific pathologic analysis in women and girls with no prior history of oral or genital ulcers. Most women with NAGU exhibit nonspecific systemic symptoms, such as myalgias or fever. This suggests an infectious etiology, but in more than 75% of patients, no pathogen is identified. In other cases, NAGU has been associated with systemic infection due to Epstein-Barr virus, *Mycoplasma*, aerobic bacteria, HIV, mumps, cytomegalovirus, influenza A, and *Toxoplasma gondii*. To our knowledge, this is the first reported case of NAGU associated with Lyme disease.

The differential diagnosis of vaginal ulcerations is long and includes sexually transmitted infections, inflammatory diseases (most notably Behçet disease and complex aphthosis), systemic illness, and drug reactions. Our patient took no medication and had no sexually transmitted infections. Although her HSV-2 IgG serologic test had positive results, she had no history of genital herpes, and lesional tissue demonstrated negative viral culture results, absence of viral cytopathic changes, and negative HSV-2 immunostaining. In the absence of any oral or ocular lesions, gastrointestinal disorder, autoimmune disorder, or pathergy, Behçet disease is unlikely. Complex aphthosis is a diagnosis of exclusion, sometimes associated with nutritional deficiencies, which were not identified in our patient. Unfortunately, Epstein-Barr virus serologic analyses were not performed.

The simultaneous onset of acute genital ulcers with Lyme disease, worsening with progression of Lyme disease, and dramatic improvement without recurrence on treatment of Lyme disease support the diagnosis of Lyme-associated NAGU. In retrospect, the patient’s “sunburn” was probably an ill-defined patch of erythema migrans, and it is possible that the “raised mole” found at her visit to a different clinic was a tick located in the center of her primary erythema migrans.

Although the etiology of NAGU is unknown, the vulvar ulcers may result from an exuberant immune response to infection. Immunologic phenomena are not foreign to *Borrelia* infection: lymphocytoma cutis is a well-recognized manifestation of tick bite, and reports of immunologic manifestations of Lyme disease include lichen sclerosus et atrophicus, Behçet disease, morphea, Parry-Romberg syndrome, cutaneous B-cell lymphoma, eosinophilic fasciitis, granuloma annulare, infantile poplar acrodermatitis, and urticarial vasculitis.

### Conclusions

With the case presented herein, we can consider NAGU among the protean immunologic manifestations of Lyme disease. Lyme titer analysis should be considered for women presenting with genital ulcers of unclear etiology.
A Disease With Many Names

Leishmaniasis is known by a myriad of popular names: Aleppo boil, Aleppo button, and Aleppo evil; Baghdad boil; Biskra button and Biskra nodule; Calcutta ulcer; chiclero ulcer; Delhi boil; Jericho button; Kandahar sore; Lahore sore; Oriental button and Oriental sore; Pian bois; Uta for cutaneous leishmaniasis; black fever; dum-dum fever; and Kala-azar for visceral leishmaniasis.1

Cutaneous leishmaniasis—or Oriental sore—is an ancient disease from the Old World. The first reference was found in the Ebers Papyrus (2000 BC), an Egyptian medical papyrus in which “Nile furuncle” is named. Furthermore, cutaneous leishmaniasis may be 1 of the 12 plagues of Egypt described in the Old Testament. In the 10th century, the Persian writer Avicenna described what he called “Balkh sore” in northern Afghanistan. There is also other evidence from various places in the Middle East of an entity as “white leprosy.” In Central America (Belize, Guatemala, Mexico), cutaneous leishmaniasis is also other evidence from various places in the Middle East of an entity known as “Baghdad boil” or “Jericho button.” In India, visceral leishmaniasis was known by the term Kala-azar (“black fever” in Hindi), indicative of the terrifying effect of the disease. In 1756, Alexander Russell clinically described the cutaneous disease in a Turkish patient and called it “Aleppo boil” owing to the ugly scar that remained after its healing. In 1885, David Douglas Cunningham, a physician of the Indian Army in Calcutta, India, described what he thought to be the spores of an ulcer of “Delhi boil.” He postulated, therefore, that cutaneous leishmaniasis had a fungal etiology. In 1898, Peter Borovsky, a Russian military surgeon working in Tashkent Military Hospital (in what is now Uzbekistan), discovered the protozoan responsible for “the Oriental sore.” Three years later, William Leishman, a Scottish army doctor, identified peculiar bodies in the spleen pulp of a soldier who had died of “dum-dum fever,” and in 1903, he published his work “On the Possibility of the Occurrence of Trypanosomiasis in India” in the British Medical Journal. In the same year, Charles Donovan, professor of physiology at Madras University in India, reported similar findings and concluded that Leishman bodies were a new parasite distinct from Trypanosoma. British physician Ronald Ross sought the link between these organisms and Kala-azar and named them Leishmania donovani.

In the New World, the disease is believed to be autochthonous; in fact, some pre-Colombian sculptures depict comparable, erosive lesions. Moreover, Incan texts from the 15th and 16th centuries mention the presence of skin ulcers on seasonal agricultural workers returning from the Andes. The lesions were attributed to the “valley sickness” or “Andean sickness,” and later, because of the resemblance with leprosy, they were also known as “white leprosy.” In Central America (Belize, Guatemala, Mexico), cutaneous leishmaniasis is considered an occupational disease. It is known as chiclero ulcer because it is endemic among forest workers who collect the chicle latex from which chewing gum is produced.2

Author Affiliations: Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.

Corresponding Author: Gianluca Nazzaro, MD, Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Via Pace 9, 20122 Milan, Italy (gianluca.nazzaro@gmail.com).