Acute vulvar and upper thigh ulceration associated with primary EBV in an elderly female

Moniyka Sachar1, BA; Afton Chavez2, MD; Lindsey Collins3, MD; Shaofeng Yan4, MD, PhD; Faramarz H. Samie2,3, MD, PhD

**1Alpert Medical School at Brown University, Providence, RI.**

**2Giesel School of Medicine, Dartmouth College, Hanover, New Hampshire**

**3Dartmouth-Hitchcock Medical Center, Section of Dermatology, Department of Surgery, Lebanon, NH**

**4Dartmouth-Hitchcock Medical Center, Department of Pathology and Laboratory Medicine, Lebanon, NH**

**Correspondence: Moniyka Sachar, Brown University, Box G-9038,** Providence, RI 02912, Phone: (510)579-2176, Email: Moniyka\_sachar@brown.edu

Abstract

Epstein-Barr Virus (EBV) infection may cause mucocutaneous ulceration during primary or latent infection. Acute vulvar ulceration and prodromal symptoms are known as Lipschütz ulcers, which are typically seen in young females and are associated with multiple infectious etiologies, including primary EBV infection. In elderly patients, latent EBV infections have been associated with lymphoproliferative ulcerations and immunosenescence or immunosuppression.

We present an immunocompetent 77-year-old female with painful vulvar and thigh ulcers and serologies consistent with a primary or reactivated EBV infection. Histological findings were more consistent with Lipschütz ulcers than latent EBV-associated lymphoproliferative ulcerations, suggesting her ulcers were a manifestation of primary EBV, which is extremely rare in elderly populations. Lipschütz ulcerations primarily affect the vulvar areas of the medial and outer surfaces of the labia minora, and latent EBV-associated lymphoproliferative ulcerations present in the mouth, arms, chest, and gastrointestinal tract, whereas our patient’s ulcers were present on her inner thighs and labium majus. In addition, these ulcerations also took longer to resolve than Lipschütz ulcers of previous reports.

Introduction

Acute genital ulceration with fever and lymphadenopathy was first described in 1913 by Austrian dermatologist Lipschütz [1]. The Lipschütz ulcer, “ulcer vulvae acutum,” is an uncommon, nonsexually transmitted condition typically seen in adolescent females and is characterized by the rapid onset of painful necrotic ulcerations of the vulva or lower vagina, and has been associated with multiple infectious etiologies including cytomegalovirus (CMV), *Mycoplasma pneumoniae*, influenza A virus, Epstein-Barr virus (EBV), and parvovirus B19 (PVB19) [2, 3]. Forty cases of EBV-associated Lipschütz ulcers were reported from 1977 to 2011 [2] and in a literature review summarizing 26 cases of EBV-linked genital ulcers, all except one case occurred in females, with the median age being 14.5 years [4]. Acute EBV-associated ulcers are typically preceded by prodromal symptoms and present as one or few painful, large, deep necrotic vulvar ulcers with purple-red edges and distant lymphadenopathy [4].

We describe a case of painful vulvar and thigh ulcers in an otherwise asymptomatic 77-year-old female with histologic findings consistent with Lipschütz ulcers and serologies consistent with a primary or reactivation of EBV infection. Although latent EBV infection in elderly, immunosuppressed patients has been associated with a lymphoproliferative form of ulcers of the mouth, arms, and chest [5], Lipschütz vulvar ulceration is typically considered a disease of adolescent females, and has been rarely reported in the elderly population [6].

Case Synopsis

A 77-year-old obese Caucasian female nonsmoker with Type 2 diabetes and hypothyroidism initially presented to her gynecologist with two months of painful ulcers on the right upper inner thigh and right labia majus that started as small red papules. The biopsies by her gynecologist showed fibroadipose tissue with marked focal acute and chronic inflammation and fat necrosis. The patient was referred to dermatology.

At the time of dermatologic consultation, the patient was well appearing and otherwise asymptomatic. Her skin history was positive for vulvar lichen sclerosis 7 years prior. She denied previous skin ulcers. She had no personal or family history of gastrointestinal symptoms or Crohn’s. Clinical examination revealed two punched out ulcers with yellow fibrinous material on the right medial upper thigh, one deeper ulcer on the right labia majus, and several small ulcers on the left upper inner thigh (Figure 1). There was no regional or distant lymphadenopathy, tracts, nodules, oral, vaginal, anal, breast, or axillary lesions. A 4 mm punch biopsy taken from the edge of a 1.0 x 0.5 cm punched out ulcer on the left upper thigh showed ulcer and granulation tissue (Figure 2a) with mixed inflammatory infiltrate of neutrophils, lymphocytes, histiocytes and eosinophils. Enlarged activated lymphocytes were also present (Figure 2b). Periodic Acid-Schiff (PAS) stain for fungal hyphae, in situ hybridization for EBV, direct fluorescent antibody (DFA), viral, bacterial, and fungal cultures, and immunostains for varicella zoster virus (VZV), herpes simplex virus 1 (HSV1), and herpes simplex virus 2 (HSV2) were all negative. Specific ulcer etiology was not identified in the biopsy specimen. HIV and syphilis testing was not performed at the patient’s request because she had not been sexually active for years. Complete blood count (CBC) was normal. CMV IgG and IgM antibodies (Abs) were negative. EBV IgM, EBV IgG, and EBV nuclear antigen (EBNA) antibody (Ab) titers were all positive. Other underlying systemic diseases that may be associated with vulvar ulcers include Crohn’s disease, Behcet disease, gluten enteropathy, systemic lupus erythematous, and dermatitis, but these diseases are unlikely given the patient’s lack of other symptoms associated with these conditions. Based on physical exam findings, histopathological analysis, positive acute EBV serologies, and exclusion of other infectious etiologies, the patient was diagnosed with acute ulceration of the upper thighs and labia majus as a manifestation of primary EBV infection. The patient was treated with high potency topical steroids and supportive care with pain management and telephonic follow-up. Lesions were almost completely healed after 4 months with no recurrence at 7 months.

Discussion

Acute genital ulceration is a rare manifestation of primary EBV infection that typically occurs with symptoms of infectious mononucleosis and primarily affects adolescent females [2,4].Histological analysis of these Lipschütz ulcers is nonspecific and shows ulceration with fibrinoid crust and extensive perivascular, mixed inflammatory infiltrate resulting in severe, local, nonspecific necrotizing vasculitis [4]. The diagnosis of EBV-associated ulcers should also be based on exclusion of other infectious agents such as CMV, HSV, VZV, human immunodeficiency virus (HIV) and syphilis. EBV virus may be detected directly in lesional swab samples or biopsy specimens using polymerase chain reaction (PCR) or detection of viral DNA and proteins in EBV-associated ulcers, though in situ hydridization can be negative [2,4,8].

Nearly all patients suffering from primary EBV infection have EBV IgM and IgG Abs. In some cases, serology may be negative when the ulcer first appears and therefore repeat testing is recommended in cases of uncertainty. Peak IgM Abs occur around the second week of illness, but may persist for several months after an acute infection and may also reappear during EBV reactivation. Peak IgG levels occur slightly later, and then decline to lower levels that persist for life and appear to be associated with permanent immunity. EBNA Abs first appear in a minority of patients in the third or fourth week following onset of EBV infection, and persist for life. The presence of EBV IgG and EBV IgM in the absence of EBNA indicates acute infection. The presence of EBV IgG and EBNA in the absence of EBV IgM is typical of past infection [7].

In elderly patients, EBV-positive mucocutaneous ulcers have been recently identified as a rare, distinct clinicopathologic lymphoproliferative disorder in patients with persistent latentEBV infection. These ulcers form as a result of uncontrolled B-cell transformation and proliferation when latent EBV virus becomes unchecked due age-related immunosuppression. Histological analysis of these ulcers typically shows atypical large Hodgkin/Reed-Sternberg (HRS)-like cells with a polymorphous inflammatory background, mimicking classical Hodgkin lymphoma (cHL) [5].

In summary, EBV-associated ulcers traditionally are thought to present as Lipschütz ulcers--vulvar ulcers afflicting adolescent females during acute primary EBV infection, or as lymphoproliferative ulcers of the mouth, arms, chest, or gastrointestinal tract in elderly patients due to immunosuppression and latent EBV. The authors of this case report present a patient who displayed findings atypical for both the latent and acute EBV-associated manifestations. The lymphoproliferative, latent-EBV ulcers would be more expected given the patient’s old age, however her histological findings were more similar to those seen in primary EBV infection. This patient had an uncommon serologic pattern of simultaneous expression of EBV IgM, EBV IgG, and EBNA which is seen in only approximately 5% of normal routine laboratory practices, and can indicate late primary infection or reactivation. Further testing such as trending of Ab titers or exclusion of false positive EBV IgM Abs by testing for heterophile Abs, parvovirus B19, *Toxoplasma gondii*, hepatitis A, autoantibodies, rheumatoid factor, and IgG avidity may be conducted to definitively determine a primary infection versus reactivation, however reactivation is still relatively rare and generally considered of no clinical significance in immunocompetent patients [7]. This patient’s clinical presentation was unusual for a primary EBV infection because she had no prodromal symptoms; however, although primary EBV infection is typically associated with symptoms of infectious mononucleosis [2],genital ulceration may rarely be the presenting or dominating symptom of EBV, and not all patients with EBV-associated genital ulcers develop prodromal symptoms [4]. The vulvar and upper thigh ulceration sites on this patient were atypical for Lipschütz ulcers and latent EBV-associated ulcers. Most Lipschütz ulcers primarily affect the vestibule, medial, and outer surfaces of the labia minora [2].The labia majora is rarely involved [3],and upper thigh involvement such as in our patient has not yet been reported. Finally, this patient’s lesions took approximately 4 months to resolve, which is longer than the reported 18-day mean healing time [4] and longest reported healing time of 10 weeks for Lipschütz ulcers [9], and may be related to her older age, diabetes and obesity.

Conclusion

The traditional view of Lipschütz ulcers should be reevaluated to consider that they may affect any age demographic, not just young females. Consistent with our findings, a very recent 2015 retrospective analysis of 33 Lipschütz ulcers found that 27.3% of affected patients were 35 years or older (range 10-79 years). Of the 33 Lipschütz ulcers the authors reported, two were associated with EBV, however further details of these individual cases such as patient age, EBV serologies, and ulcer histology were not reported in the study [3].In addition, in cases of uncertainty regarding the acuteness or latency of EBV infection and the associated ulcerations, dermatologists should be familiar with the range of histologic and serologic findings that may occur. Dermatologists should be aware of and able to recognize the wide spectrum of clinical manifestations of EBV.

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