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Authors

Waterman, Christy L

Aronson, Iris K

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Recurrence of non-sexually acquired acute genital ulceration following COVID-19 vaccination

Christy L Waterman MD, Iris K Aronson MD

Affiliations: Department of Dermatology, University of Illinois Chicago College of Medicine, Chicago, Illinois, USA

Corresponding Author: Christy L Waterman MD, 12050 North Michigan Road, Zionsville, IN 46077, Tel: 317-848-2427, Email: Christy.Lee.Waterman@gmail.com

Abstract

There is a rare subset of non-sexually acquired acute genital ulcers, previously called Lipschütz ulcers, that are often preceded by a constitutional prodrome and have been associated with multiple viral and bacterial infections. These ulcers are categorized by some as a variant of complex aphthosis, with one hypothesized etiology involving a non-specific systemic inflammatory response to acute infection or vaccination. Although painful, these lesions resolve over the course of several weeks and recurrence is rare but possible. Recently, there have been reports of genital ulcer development due to either acute infection with COVID-19 or following vaccination against the same. We report a case of non-sexually acquired acute genital ulceration that initially presented in 2008 as Lipschütz labial ulcers associated with acute Epstein-Barr virus infection, with recurrence twelve years later following administration of the second dose of the Pfizer-BioNTech COVID-19 vaccine. This case report and exhaustive literature review challenges widely accepted views regarding the typical age range of patients affected by non-sexually acquired acute genital ulceration, the sexual history of affected populations, the pathophysiology of lesion occurrence, and possibility of lesion recurrence.

Keywords: Lipschütz, recurrence, ulceration, vaccination

Introduction

Given the continually increasing number of patients receiving multiple vaccinations to COVID-19, it is important that clinicians be aware of the cutaneous side effects that may develop following vaccination. Non-sexually acquired acute genital ulceration is an important diagnosis to include in the differential diagnosis of painful labial ulcerations. Clinicians must understand how to exclude other diagnoses, offer treatments to alleviate the physical and social discomforts that accompany genital ulcerations, and provide patients with reassurance regarding the self-limited nature of this adverse vaccine side effect.

Case Synopsis

In 2008, a 16-year-old non-sexually active female with a history of oral aphthous ulcers presented to our dermatology clinic one week after development of multiple painful labial lesions, consisting of punched-out yellow ulcerations of the labia minora (**Figure 1**), [1]. These lesions were accompanied by yellow vaginal discharge, dysuria, inguinal

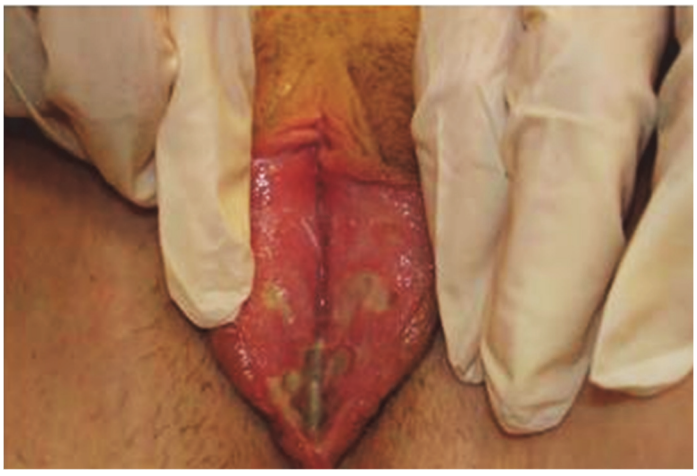

Figure 1. *Initial occurrence of EBV-associated genital ulcers in 2008. The inner surfaces of the labia minora contained multiple deep punched-out ulcerations with a yellow fibrinous base.*

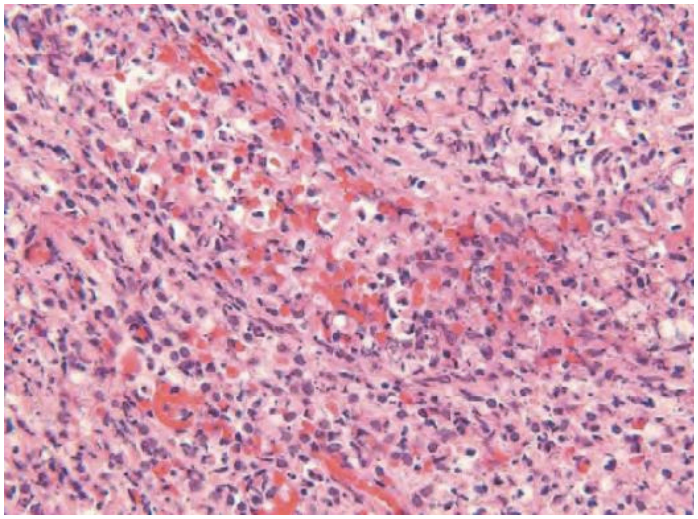

Figure 2. *A vulvar biopsy in 2008 revealed acute suppurative inflammation and reactive changes within dermal small vasculature. H&E, 60×.*

lymphadenopathy, diarrhea, and headache. No oral lesions were present.

Laboratory evaluation at that time was remarkable for elevated liver function tests and elevated Epstein-Barr virus (EBV) early antigen IgG levels. Initial EBV viral capsid antigen IgM levels were within normal limits, but repeat testing showed elevation of these levels, along with a positive monospot test.

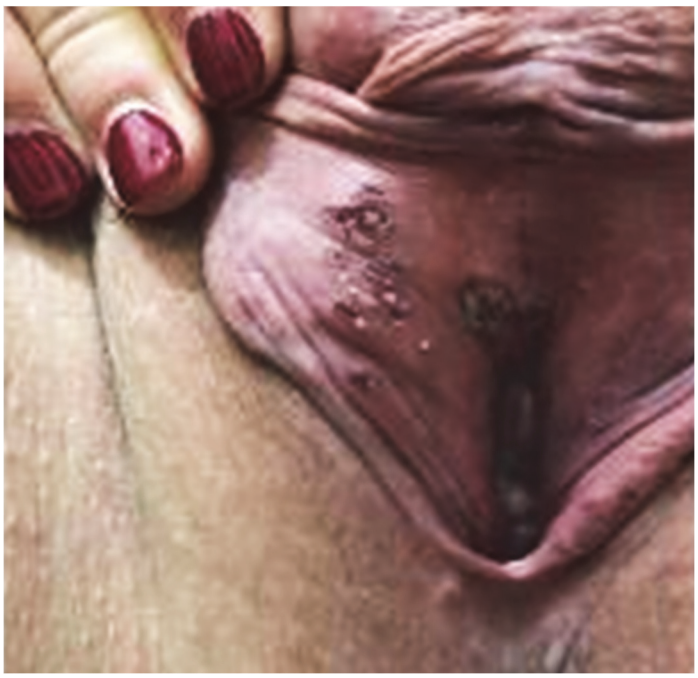

Figure 3. *In 2021, 48 hours after receiving the second dose of the COVID-19 vaccine, painful deep ulcerations formed along the inner aspect of the right labia minora and the inferior border of the left labia minora.*

A vulvar biopsy revealed acute suppurative inflammation and reactive changes within dermal small vasculature (**Figure 2**). Direct fluorescent antibody testing for viral herpes simplex virus (HSV) was negative, along with serum HSV titers. Other causes of vaginal ulceration had been ruled out at that time, including chlamydia, gonorrhea, and cytomegalovirus.

A diagnosis of EBV-associated vaginal ulcerations and acute EBV mononucleosis was made. The patient was treated with a single dose of azithromycin, topical metronidazole gel 0.75% once daily, topical clobetasol gel 0.05% once daily, and topical lidocaine 2% as needed for pain control. Her genital ulcerations resolved over the course of two-four weeks. She remained well for a dozen years without complications from, or return of, her painful genital ulcers.

Twelve years after initial ulcer development, the same patient presented with similar painful lesions of the labia minora and majora (**Figure 3**), two days after receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine. Laboratory evaluation revealed an elevated white blood cell count (1.41×10^4/microliter,reference range 0.39-1.2×10^4/microliter) with neutrophilia, neither of which had been present during initial ulcer occurrence. A complete metabolic panel was within normal limits. Further testing showed an elevated EBV viral capsid antigen IgG antibody level of >8.0U (reference range <0.8U), corresponding with prior infection. EBV viral capsid antibody IgM antibody levels were low. C reactive protein (CRP) levels were elevated at 72.1mg/L (reference range <8mg/L). Genital culture speciated normal vaginal flora. A cervical HSV culture was negative, as well as serum HSV1 and 2 IgG.

The patient's genital ulcers enlarged and coalesced over the course of several days, developing the same punched-out appearance as before, topped with yellow fibrinous exudate (**Figure 4**). She did not develop any oral lesions during this episode. She was treated with topical lidocaine ointment 5%, metronidazole gel 1%, and clobetasol ointment 0.05%. She was additionally prescribed valacyclovir one gram orally twice daily for ten days, which was

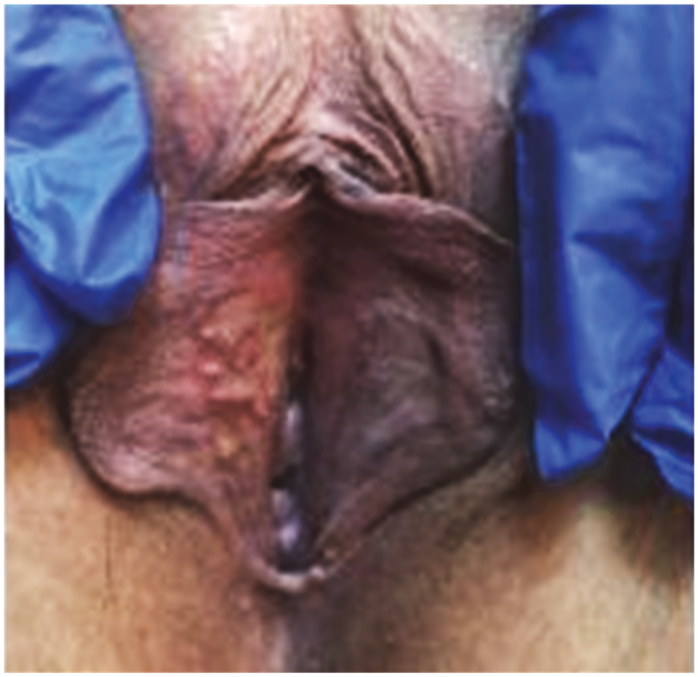

Figure 4. *Seven days after vaccine administration, the deep punched-out ulcers on the right labia minora coalesced. Note the yellow fibrinous base of the ulcers, as well as the purple hue of the corresponding left labia minora.*

discontinued when HSV cultures were negative. The patient's elevated CRP level and leukocytosis resolved within one week. The patient's symptoms improved with these therapies over the course of two-three weeks and she has not experienced additional ulcers since.

Case Discussion

In 1913, Austrian physician Lipshütz proposed three categories for classifying nonvenereal acute genital ulcerations: 1) idiopathic aphthous genital ulcers, 2) ulcers related to Behçet or Crohn disease, and 3) ulcus vulvae acutum, described as sudden, non-relapsing, painful gangrenous genital ulcers that had developed mainly in sexually inactive young females, often accompanied by fever and lymphadenopathy [2]. Genital ulcers in the third category, termed Lipschütz ulcers, were of uncertain origin as no causative agent was identified at that time [3]. In 1977, Brown and Stenchever suggested EBV was associated with the development of Lipshütz ulcers [4]. For the next several decades, the prevailing focus of these acute genital ulcers centered on the connection with acute EBV infection [3,5-9].

There are no widely utilized formal diagnostic criteria for Lipschütz genital ulceration. It is a diagnosis of exclusion made after ruling out sexually transmitted infections, Behçet syndrome, extra-genital Crohn disease, and any other specific diagnosis. Therapies are mostly supportive and include anti-inflammatory drugs, topical anesthetics, and corticosteroids. Case reports and studies often emphasize the occurrence of these ulcers in young, typically sexually inactive females and recurrence was previously believed to be rare [2,9,10].

In the past two decades, additional reports and evidence have broadened the scope of our understanding of Lipshütz ulcers. Alternative names have been increasingly common in the literature, including acute genital ulcers [8], acute vulvar ulcers [11], reactive non-sexually related acute genital ulcers [12,13], acute reactive genital ulcerations [14], vulvar aphthous ulcers [15], complex aphthous ulcers [16], and non-sexually acquired genital ulcers [15]. The broad variety of clinical names, as well as the lack of formal diagnostic criteria for inclusion, create confusion when researching and reporting on the topic. We will proceed with the term "non-sexually acquired acute genital ulceration," or NSAGU.

Many authors endeavor to separate genital aphthosis from NSAGUs [8,17], describing genital aphthosis as the development of milder, shallow erosions or ulcers with a clean fibrinous base, with common recurrence, contrasted with the deeper, gangrenous NSAGUs that classically do not tend to recur. In a 2009 descriptive study, major and minor criteria for the diagnosis of NSAGU were proposed [8]. Major criteria included age <20 years, absence of sexual contact in the preceding three months, presenting with a first flare of acute genital ulceration, absence of immunodeficiency, and an acute course of genital ulcers beginning abruptly and healing within 6 weeks without scarring. Minor criteria included the presence of several deep, painful, well-demarcated ulcers with a necrotic or fibrinous center or a bilateral *kissing* pattern of ulcer occurrence on bilateral vulvar surfaces. A diagnosis of NSAGU was made if a patient displayed all 5 of the major criteria and at least one of two minor criteria.

Exclusion criteria included a history of sexually transmitted disease (STD), a history of genital aphthosis, clinical or laboratory evidence of an STD, or immunodeficiency. A history of oral aphthosis was not an exclusion criterion. Importantly, this study excluded patients with a history of prior genital ulcerations, clarifying that genital aphthosis is characterized by recurrence of genital ulcers, while NSAGUs do not tend to recur. The study found that nine out of 13 patients had a history of transient oral aphthae. EBV primary infection was diagnosed in four of 13 patients (31%), with all four of these patients displaying a *kissing* pattern of ulceration. The *kissing* pattern was also displayed in five of the nine remaining patients (56%) not diagnosed with primary EBV infection. No other infectious agents were identified after testing for HSV, cytomegalovirus, toxoplasmosis, HIV, and syphilis.

Conversely, some recent reports have categorized NSAGUs as a variant of recurrent genital aphthosis or complex aphthosis [12,13,15,18]. Oral aphthous ulcers are characterized by painful shallow ulcers with a grey-white base. Minor aphthae are less than one centimeter in diameter (usually three to five millimeters) that heal in seven to ten days, typically without scarring. Risk factors for oral aphthosis include stress, infections, vitamin deficiency, and family history [19]. It is estimated that oral aphthosis affects 20-50% of children and adolescents [20,21] and up to 66% of adults in the United States [18,22]. Larger ulcers greater than one centimeter that require multiple weeks to heal are termed major aphthous ulcers [23]. In complex aphthosis, patients experience recurrent bouts of multiple severe ulcerations, usually of the oral mucosa, although the genital mucosa can be involved [16,24]. These lesions are typically larger and often require four to six weeks to heal. The diagnosis of Behçet disease must be ruled out in cases of complex aphthosis. In 2006, Huppert et al. reported results of a prospective cohort study [18] of twenty females with NSAGUs and found that half of the patients experienced oral aphthous ulcers, which correlates to the expected prevalence of oral aphthae in this age group. Two of twenty were diagnosed with acute EBV infection. One-third of the patients experienced recurrent genital ulcers, meeting the criteria for complex aphthosis. Unlike Farhi et al, Huppert et al. did not exclude patients with a history of recurrent genital ulcers.

Similarly, a 2010 case review [12] by Lehman et al. examined 10 cases of NSAGU and found that 70% of the patients had either a history of oral aphthous ulcers or had active oral lesions at the time of presentation with genital ulcerations, several percentage points above the expected prevalence of aphthous ulcers in this adolescent population. Six of the 10 patients reported to have experienced recurrent genital ulceration, with the average time to ulcer recurrence being 10 months. The authors noted that both aphthous ulcers and NSAGUs tend to be preceded by a febrile illness or other acute systemic illness. Due to these similarities, these authors hypothesized that NSAGUs should be classified as a form of complex aphthosis. Again, it is important to note that patients with recurrent genital ulceration were included in this study but were excluded in others.

Associations with acute viral infections other than EBV have been made, including cytomegalovirus [25], mumps [10], influenza A virus [26], influenza B virus [26], mycoplasma pneumoniae [28], salmonella [29], and more recently COVID-19 infection [14,15]. Despite these associations, in the majority of cases, the cause of NSAGU is not discovered, remaining idiopathic in nature [8,12,18].

For decades, it was widely accepted that NSAGU occurred most commonly in young non-sexually active girls in the peripubertal age period [8,12,18]. The average age of onset of NSAGUs was found to be 11.5 years in a 2010 case review [12] which limited the population of interest to females under the age of 18 years. Farhi et al. found an average age of onset to be 16.6 years; importantly, one of the major inclusion criteria for this study was age less than 20 years. However, a 2016 analysis [28] challenged previous findings regarding the average age of the patient population affected by NSAGU, as this analysis did not exclude participants based on age and patients with recurrent genital ulceration were included. In this analysis the mean age of the patient population was 29.1 years, and 84% of participants

had been or were sexually active; HSV had been ruled out in all 33 cases. There are several explanations for these age discrepancies. First, the fact that many studies limit the age of the study population to individuals under the age of 18 or 20 years old completely excludes older individuals from even being considered to develop NSAGU. Second, individuals who are sexually active and develop genital ulcers may mistakenly be diagnosed with a sexually transmitted disease and treated as such, without appropriate confirmatory testing. The lack of sexual activity in the younger population may prompt further expansion of the differential diagnosis and further investigation into the etiology of genital ulcers. Third, the lack of definitive diagnostic criteria and the confusion surrounding the role that aphthosis may or may not play in NSAGU leads to ambiguity regarding what should be included or excluded in the category of NSAGU.

Although the exact pathophysiologic mechanism of NSAGU formation is unknown, several hypotheses have been formed. Pelletier et al. in 2006 described a case of NSAGU in the setting of acute infection with paratyphoid fever and proposed that the pathogenicity of genital ulcer formation involved cytotoxic T lymphocytes recruited in response to systemic viral illness, leading to non-specific inflammation and genital ulceration [29]. Conversely, Sardy et al. proposed in 2011 that immune complex formation during acute infection could lead to immune complex deposition in the genital mucosa, causing localized vascular immune complex deposition and a hypersensitivity reaction leading to tissue destruction and ulcer formation [9]. Both hypotheses rely on the presence of acute systemic inflammation in response to acute illness with an infectious process. Yet for the majority of patients described in most studies, no infectious process could be readily identified.

Epstein-Barr virus is the causative agent of infectious mononucleosis. It has been estimated that up to 95% of adults worldwide have been infected with EBV [6], many of whom likely had an asymptomatic infection during childhood, with only a small percentage displaying symptoms of infectious mononucleosis. EBV preferentially infects B lymphocytes and, although it is typically transmitted through oral secretions, EBV DNA has been isolated by polymerase chain reaction (PCR) from male and female genital tracts of both healthy individuals and people who are acutely infected with EBV. The role of EBV DNA found the genital tract is poorly understood [5,7].

It is unclear how EBV virus comes to exist in the genital tract and the pathophysiologic mechanisms behind genital ulcer formation are not known. It has been hypothesized that EBV virus may exist in the genital tract in squamous epithelial cells, in lymphocytes, or in cell-free form [30]. Possible mechanisms of viral spread to genital epithelial cells include direct inoculation with infected saliva, circulating B lymphocytes, or hematogenous spread [7]. It has been suggested that migration of lymphocytes to genital epithelia is the causative mechanism of ulcerations [6]. Interestingly, prolonged viral shedding of EBV from epithelial cells may occur for months after resolution of symptomatic mononucleosis infection, and, in highly concentrated salivary samples of seropositive individuals, the virus can be identified in up to 100% of healthy participants, suggesting that the virus is likely never latent [31]. Interestingly, the focus of studying genital ulceration specifically in pediatric populations may lead to a selection bias towards a connection with EBV because in developed nations the peak incidence of primary infection with EBV is 15-19 years of age [22,32].

There has been only one clearly reported case in the literature of EBV-associated NSAGU recurrence. In 2009, Leigh and Nyrijesy described a 14-year-old female with a history of oral aphthous ulcers that was diagnosed with EBV-associated vaginal ulcers, whose genital ulcers recurred one year after initial presentation and resolved within several days with a course of oral prednisone [7]. Although previously linked to multiple acute viral and bacterial infections, we present an interesting case of NSAGU initially attributable to primary EBV infection with acute recurrence 12 years later triggered by vaccination against COVID-19. We hypothesize that one possible mechanism of ulcer recurrence involves the reactivation of ulcer activity during periods of

physiologic stress, similar to HSV recurrence with increased life stressors. Interestingly, unlike the timeline often seen in aphthosis, our patient did not experience multiple bouts of recurrent genital ulceration. Instead, our patient's initial ulcerations resolved and did not recur for a full dozen years. An alternative hypothesis of ulcer recurrence pathophysiology involves the reactivation of ulcer activity during periods of increased immunologic systemic inflammatory activity, such as in the days following contraction of a viral or bacterial infection or after receiving a vaccination.

Recently, there have been increasing reports of genital ulcers associated with both acute COVID-19 infection [14,15] and vaccination against COVID-19 [34-36]. Most reports were classified as genital aphthous ulcers, with others labeled as acute genital ulcerations. All reported cases resolved within several weeks, with supportive care being the mainstay of treatment after ruling out other etiologies. Vaccinations have been reported to cause a wide array of side effects and complications, such as the development of lichen planus or a lichenoid drug eruption after receiving vaccination to hepatitis B, influenza, herpes zoster [37-39], tetanus-diptheria-acellular pertussis [40], and rabies [41]. The influenza vaccine has been associated with development of multiple other disease states, including Sweet syndrome [42], pemphigus vulgaris [43], bullous pemphigoid [44], papular acrodermatitis of childhood [45], and lichen planus [46]. Our case of NSAGU recurrence in the 48 hours following COVID-19 vaccination supports the hypothesis that ulcer formation is a result of increased immunologic systemic inflammatory activity. Continued publication of additional reports on the topic should be encouraged so comparison of case details may be performed, and broader conclusions may be observed [47].

Conclusion

Our case report, in concert with similar recent reports, serves to communicate ongoing observations from frontline clinicians. This report challenges widely accepted views regarding the typical age range of patients affected by non-sexually acquired acute genital ulceration, the sexual history of affected populations, the pathophysiology of lesion occurrence, and possibility of lesion recurrence.

Given the continually increasing number of patients receiving multiple vaccinations to COVID-19, it is important that clinicians be aware of this diagnosis, understand how to exclude other diagnoses, offer treatments to alleviate the physical and social discomforts that accompany genital ulcerations, and provide patients with reassurance regarding the self-limited nature of this adverse vaccine side effect.

Potential conflicts of interest

The authors declare no conflicts of interest.

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