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# Acute Genital Ulceration After Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination and Infection

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Reactive, nonsexually related acute genital ulceration, also known as Lipschütz ulcer, is a nonsexually related ulceration involving the vulva, most commonly affecting girls and adolescent women in response to infection. Herein, we describe 3 female patients with acute genital ulceration occurring after severe acute respiratory syndrome coronavirus 2 vaccination or natural infection. *(J Pediatr 2022;246:271-3).*

Reactive, nonsexually related acute genital ulceration, also known as Lipschütz ulcer, is a nonsexually related ulceration involving the vulva, most commonly affecting girls and adolescent women. Although generally a diagnosis of exclusion, acute genital ulceration has been reported following infections, including Epstein–Barr virus (EBV), cytomegalovirus (CMV), influenza A and B, adenovirus, and *Mycoplasma pneumoniae*. Reactive acute genital ulceration has been now reported in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Herein, we report 3 patients with acute genital ulceration presumably triggered by SARS-CoV-2 vaccination or infection.

## Case Report

### Patient 1

A 12-year-old otherwise-healthy female patient presented with painful vulvar ulcerations that had been present for approximately 5 days. Review of systems was positive for dysuria and hematuria. She was initially evaluated by her pediatrician and empirically treated with oral nitrofurantoin, fluconazole, and phenazopyridine for suspected urinary tract infection. She was then referred to pediatric dermatology for further evaluation and treatment due to lack of improvement. She was otherwise healthy and was not taking any other medications, denied any history of sexual activity, and had no previous history of oral ulcers, inflammatory bowel disease, or autoimmune disease. The family reported that the patient had received her second dose of the Pfizer-BioNTech SARS-CoV-2 vaccine approximately 48 hours before symptom onset. The day following vaccination, she also developed subjective fevers, fatigue, and malaise lasting 24 hours.

On physical examination, there were approximately 2 × 2-cm well-circumscribed, shallow ulcers with yellowish sloughing and purulent exudate on opposing surfaces of the bilateral labia minorae. Significant labial edema was present. Her oral mucosae were clear.

Laboratory findings were notable for normal complete blood count and comprehensive metabolic panel and negative urine culture. Urinalysis demonstrated large leukocyte esterase, 20-29 white blood cells per high-power field, and moderate mucus. Lesional herpes simplex virus (HSV)-1 and HSV-2 polymerase chain reaction (PCR), Trichomonas/Gardnerella/Candida DNA probe, EBV antibody panel, respiratory viral panel, and SARS-CoV-2 PCR were negative. These clinical and laboratory findings were supportive of the diagnosis of reactive acute genital ulceration triggered by the SARS-CoV-2 vaccine.

The patient was given topical clobetasol 0.05% ointment twice daily, lidocaine 2% jelly every 4-6 hours as needed, oral acetaminophen and ibuprofen as needed, and sitz baths with improvement of her symptoms. Ulcers healed over the course of 2 weeks.

### Patient 2

A 14-year-old female patient presented to the emergency department with 2 days of severe vulvar pain and ulceration. Onset of symptoms occurred 3 days after the patient received her second dose of the Pfizer-BioNTech SARS-CoV-2 vaccine and was associated with low-grade fevers. This presentation was her second episode of genital ulceration, the first having occurred several months previously following fever, headaches, and body aches. SARS-CoV-2 PCR, EBV serologies, and HSV PCR performed at the time of her first episode were all negative.

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|---|---|
| CMV | Cytomegalovirus |
| EBV | Epstein–Barr virus |
| HSV | Herpes simples virus |
| PCR | Polymerase chain reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |

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Physical examination was notable for left labial swelling and 2 ulcerations on the inner aspects of the left and right labia near the introitus. The left-sided ulcer was approximately 4 cm in diameter with an overlying gray eschar, and the right-sided ulcer was 3 cm. No additional evaluations were performed in the emergency department, as it was felt her presentation and examination were consistent with reactive, nonsexually related acute genital ulceration.

The patient was treated with clobetasol 0.05% ointment twice daily, lidocaine 2% gel, oral acetaminophen and ibuprofen as needed, oral nortriptyline, and vulvar care with sitz baths. She had no improvement at follow up 3 days later, and therapy was changed to lidocaine 5% ointment, and an oral prednisone taper (20 mg twice daily for 5 days followed by 20 mg once daily for 5 days) was prescribed. Her symptoms improved. Four weeks later, the ulcers were nearly healed.

Given the recurrent nature of her symptoms, she was referred for a rheumatology evaluation. Antinuclear antibody profile, rheumatoid factor, myeloperoxidase antibodies, serine protease Immunoglobulin G, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear antineutrophil cytoplasmic antibodies, and complement levels were normal or negative. EBV IgG and IgM antibodies were negative. HLA-B 27 antigen, fecal calprotectin, and eye examination were negative or normal.

Approximately 6 months later, the patient developed a third occurrence of labial ulcers, which occurred 24 hours after testing positive for SARS-CoV-2. Her symptoms included fever, chills, and headaches. She was again treated with topical lidocaine 5% ointment, oral acetaminophen and ibuprofen as needed, and topical clobetasol 0.05% ointment. At 4-week follow up, she was experiencing discomfort, but the ulcers were nearly healed.

### Patient 3

A 29-year-old female patient with a history of asthma was referred to the Dermatology Clinic by infectious diseases consultants for recurrent genital ulcers, to assess for Behçet disease. The patient endorsed a history of 2 preceding episodes of genital ulceration, the first occurring 8 years before presentation and the second approximately 1 year previously. The latter episode was associated with a positive rapid antigen SARS-CoV-2 test.

The patient was initially evaluated in the Infectious Diseases Clinic after developing ulcers of the labia minorae, each measuring up to 1 cm in diameter, that began 24 hours following her first dose of Moderna SARS-CoV-2 vaccine. She also complained of fevers and chills for 2 days following her vaccination. Lesional specimens for HSV-1 and HSV-2 PCR were negative. Per the patient, EBV and CMV IgG had been positive in 2013; repeat testing was not obtained during this presentation. She denied any history of penetrative vaginal intercourse. She had a history of oral aphthosis and HSV but denied a history of inflammatory bowel disease, pathergy at sites of needle sticks performed to draw blood, or ocular symptoms.

After her second dose of the Moderna-SARS-CoV-2 vaccine, approximately 5 weeks after her first dose, she presented to the Dermatology Clinic for evaluation of 2 genital lesions that started within 48 hours of vaccination and requested a skin biopsy to exclude infection. On her labia minorae, there were 2 erythematous, small erosions measuring 2 mm and 5 mm with surrounding white hyperkeratosis. Given the onset of symptoms that day, early evolving ulceration was suspected. Biopsy was performed and revealed spongiotic dermatitis with a mixed infiltrate of lymphohistiocytic cells, neutrophils, and plasma cells in the dermis. In situ hybridization for EBV encoding region was negative. CMV, Gram, and Periodic Acid Schiff with digestion stains were also negative. The patient was treated symptomatically with clobetasol 0.05% ointment twice daily, and the lesions resolved. She was encouraged to use L-lysine for her recurrent oral aphthous ulcers.

Of note, the patient considered changing from Moderna to the Pfizer BioNTech SARS-CoV-2 vaccination before her third dose. Given case reports in the literature of acute genital ulceration seen after Pfizer BioNTech vaccination, she opted to continue with Moderna. At follow up, she did report minor genital ulcerations following her booster but did not seek care due to the mild severity of symptoms.

## Discussion

Acute genital ulceration most commonly affects peripubertal and adolescent female patients. The ulcers are usually well-demarcated, deep, and tender to palpation. Classically, they present in a bilateral and symmetric pattern, often described as "kissing" lesions. These lesions are painful and can lead to urinary retention, and patients may require hospitalization for pain management and indwelling Foley catheter. Fortunately, acute genital ulceration is a self-limited condition and is rare. Treatment is primarily supportive with local wound care, sitz baths, and pain management with oral analgesics and topical anesthetics. Topical steroids and short courses of oral steroids may be considered in refractory cases.[1] Given its appearance and relative rarity, reactive acute genital ulceration often is misdiagnosed as a sexually acquired disease, which can lead to significant psychological distress, especially in patients who may not be sexually active. The differential diagnosis for acute genital ulceration includes infectious etiologies such as syphilis or HSV, autoimmune conditions such as Behçet disease or inflammatory bowel disease, and other inflammatory conditions such as erosive lichen planus, lichen sclerosus, or fixed-drug eruption.

Acute genital ulceration has been linked to several infections, including EBV, CMV, influenza A and B, adenovirus, and *Mycoplasma pneumoniae*. Falkenhain-López et al described the first reported case of painful genital ulcers along with a single oral aphtha in a 41-year-old woman in the setting of PCR-confirmed SARS-CoV-2 infection.[2] Symptoms resolved following a course of oral prednisone. Additional cases of acute genital ulceration presenting in

adolescent girls associated with SARS-CoV-2 infection have been reported by Krapf et al and Christl et al, respectively.[1,3] In the latter patients, symptoms were refractory to oral corticosteroid therapy, and patients required hospitalization for pain control and immunosuppressants, before resolution of symptoms.[1,3]

There have been a variety of dermatologic conditions reported in association with SARS-CoV-2 infection, as well as in response to SARS-CoV-2 vaccines. Specifically, mRNA vaccines against SARS-CoV-2 have been linked to injection site reactions, urticaria, angioedema, pernio, pityriasis rosea-like eruptions, bullous pemphigoid, erythromelalgia, and morbilliform eruptions.[4] A review of the literature reveal 3 cases of vulvar aphthous ulcers following the Pfizer-BioNTech SARS-CoV-2 vaccine.[5-7] These patients initially experienced mild, flu-like symptoms following administration of the vaccine and subsequently developed vulvar ulcers within one week, with unremarkable evaluations for infectious and autoimmune causes.

We report 3 patients with acute genital ulceration presumably triggered by SARS-CoV-2 infection or mRNA vaccination against SARS-CoV-2. Given the current environment of misinformation and distrust surrounding vaccines, it is important to accurately report adverse side effects related to the SARS-CoV-2 vaccine. Adding more information to the medical literature regarding potential side effects of SARS-CoV-2 vaccines will allow providers to be better equipped to counsel patients should symptoms occur, including the self-limited nature of acute genital ulceration, as well as to avoid potentially unnecessary diagnostic evaluations. Moreover, given the possible repercussions of misdiagnosing this condition, health care providers should be aware of acute genital ulceration and its possible rising incidence, given the prevalence of both natural SARS-CoV-2 infection and vaccination. ■

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