Reactive non-sexually related acute genital ulcers associated with COVID-19

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SUMMARY
Acute genital ulcers (AGU), known as Lipschütz ulcers, are painful vulvar ulcers typically affecting non-sexually active girls and women. AGU have been associated with viral infections, namely, Epstein-Barr virus (EBV). Here, we describe a case of AGU in the setting of SARS-CoV-2 in a non-sexually active adolescent girl hospitalised for pain control and urinary retention, who failed a course of oral corticosteroids and then improved with colchicine. Testing for herpes simplex virus, EBV and Behcet’s syndrome were all negative. Testing for SARS-CoV-2 was positive. COVID-19 increases cytokines such as tumour necrosis factor alpha, which has been shown to affect endothelial cell adhesion and neutrophil chemotaxis, leading to aphthosis.

BACKGROUND
Primary acute aphthous genital ulcers, also known as Lipschütz ulcers, ulcer vulvae acutum or acute genital ulcers (AGU), are painful vulvar ulcers without an identifiable aetiology. This rare ulcerative condition occurs most frequently in virginal women and girls and is not associated with sexually transmitted infection. Lipschütz ulcer is a diagnosis of exclusion, after ruling out sexually transmitted infection, Behcet’s syndrome, anogenital Crohn’s disease and other specific ulcerative diagnoses.

AGU have been linked to infection, mainly Epstein-Barr virus (EBV) in the paediatric population,1,2 but also mycoplasma pneumoniae,3 cytomegalovirus (CMV),4 parvovirus B19,5 influenza A and B6,7 and adenovirus.6,8 It is not well understood how these infections may lead to the formation of genital ulceration. Here, we describe a case of primary acute aphthous genital ulcers in the setting of SARS-CoV-2 in a non-sexually active adolescent girl.

CASE PRESENTATION
A 13-year-old Caucasian (Northern European/Italian American) girl presented with severe ulceration and oedema of the vulva. Her vulvar symptoms began with stinging and burning of the external genitalia, with vulvar oedema starting 1 day later, followed by increased swelling, ulceration and severe vulvar pain. She also noted pain with urination. Her symptom began 3 days following systemic symptoms of fevers, chills, sore throat and decreased taste due to COVID-19, for which she and her sister both tested positive. She is not sexually active. Menarche was age 13 and she was not menstruating at that time of symptoms.

Her medical history is significant for a minor deletion of the SHOX gene and she takes human growth hormone. Otherwise, her medical and surgical history is negative. She has no allergies to medications. She has a history of recurrent oral aphthae. Her sister has a history of Lipschütz ulcers from EBV.

INVESTIGATIONS
Physical examination revealed multiple, shallow ulcers with raised and sharply demarcated borders located on the medial aspects of the labia minora. Grey exudate and eschar are noted. The surrounding vulvar tissue was erythematous and markedly oedematous (figure 1).

DIFFERENTIAL DIAGNOSIS
Herpes simplex virus (HSV) type 1 and 2 were negative, as well as rapid plasma reagin screening for syphilis and HIV testing. Evaluation for Behcet’s syndrome was also performed, revealing negative C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and human leucocyte antigen-B51 (HLA-B51). Testing for EBV was negative. A nasopharyngeal swab for SARS-CoV-2 using reverse transcription PCR (RT-PCR) was positive.

TREATMENT
She presented to the hospital emergency department and was initially prescribed a steroid cream and topical lidocaine; however, she was unable to use the steroid cream due to extreme pain and was started on an oral corticosteroid regimen of prednisone 45 mg daily for 4 days, 40 mg daily for 4 days, 20 mg daily for 4 days and then 10 mg daily for 2 days. Six days after initial vulvar symptoms, she began to have severe dysuria for which she started Pyridium. She returned to the hospital on day 7 for pain management and oral steroids. HSV, EBV, HIV and syphilis testing at that time were all negative. She was hospitalised for pain control for 5 days, completing a 14-day course of oral steroids.

She applied topical lidocaine 5% ointment and benzocaine 20% spray for pain control. The genital oedema had decreased, but ulcers and vulvar pain were still present. She was started on colchicine 1.2 mg daily and was noted to have further improvement of oedema and pain within 1 week. Subsequent evaluation by Rheumatology was not consistent with Behcet’s syndrome, revealing negative CRP, ESR and HLA-B51.

OUTCOME AND FOLLOW-UP
Ulceration and oedema resolved within 6 weeks; however, she was noted to have agglutination of
patients were controlled by oral pain medications.13 Necessary in cases of acute urinary retention and severe pain not associated with COVID-19 are hospitalisation.

Positive nasopharyngeal swab for SARS-CoV-2 using RT-PCR in four patients hospitalised due to AGU. Hospitalisation is often necessary in cases of acute urinary retention and severe pain not controlled by oral pain medications.

EBV is noted to be the most cited infectious aetiology for AGU, followed by CMV infection.1 2 3 4 5 Over 40 cases of AGU have been linked to EBV in the literature and it is estimated that EBV is implicated in about 30% of AGU cases.1 2 3 4 There have been two hypotheses regarding the mechanism of genital ulceration in the setting of viral infection. The first is formation of immune complex deposition causing a type III hypersensitivity reaction that leads to microthrombosis and necrosis in the genital area. The second is virus-provoked cytolysis resulting after haematological spread of virus-infected lymphocytes, autoinoculation through self-contact or, in the case of sexually active patients, through genital–genital or oral–genital contact.1 2 3 4 Cases of AGU have also been described in influenza A and B virus and adenovirus,5 6 but at the time of publication, there have been no described cases of AGU associated with SAR-CoV-2.

Oral aphthous ulcers have been reported in four patients related to COVID-19 in Spain.17 All four patients presented with typical COVID-19 symptoms, including anosmia, fever, headache, malaise and dyspnoea. COVID-19 was confirmed with a positive nasopharyngeal swab for SARS-CoV-2 using RT-PCR. Testing for secondary causes of aphthosis, including HSV, syphilis, hepatitis, HIV, EBV and CMV, were all negative in these cases. Dominguez-Santas et al17 postulated that COVID-19 increases cytokines, inciting tumour necrosis factor alpha (TNF-alpha), leading neutrophils to disrupt the oral mucosa. Elevated TNF-alpha has been found in patients with recurrent aphthae and affects endothelial cell adhesion and neutrophil chemotaxis.17 18

In addition, one report describes COVID-19 identified in a vulvar lesion by RT-PCR in a pregnant patient.19 The lesion was described as a 3 mm ulceration on the right posterior fourchette of the vulva; however, the report did not describe pain associated with the lesion, only vaginitis symptoms consistent with vulvo-vaginal candidiasis. In this case, a viral swab was collected from a vulvar lesion and inadvertently tested positive for SARS-CoV-2 RNA and Pan-SARS RNA. The vulvar lesion tested negative for HSV-1 and HSV-2. The patient had upper respiratory symptoms, including cough, fatigue, myalgias and anosmia, consistent with SARS-CoV-2.

The second is virus-provoked cytolysis resulting after haematological spread of virus-infected lymphocytes, autoinoculation through self-contact or, in the case of sexually active patients, through genital–genital or oral–genital contact.1 2 3 4 Cases of AGU have also been described in influenza A and B virus and adenovirus,5 6 but at the time of publication, there have been no described cases of AGU associated with SAR-CoV-2.

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COVID-19 infection at the time of diagnosis. This case demonstrates SARS-CoV-2 viral shedding detected in a vulvar lesion.²³ However, it is unclear whether the lesion was associated with concurrent COVID-19 infection or whether viral shedding may occur in any disruption of the mucous membrane of any origin, and it happened to be detected with testing. AGU are a self-limiting condition. Treatment generally involves supportive care and symptomatic pain relief in the form of oral and topical medications.²⁰ ²¹ In general, non-steroidal anti-inflammatory drugs are avoided, as they have been associated with recurrent oral and genital aphthous ulcers in one case.²² A course of systemic corticosteroids is often used in treatment. In the case series of non-sexually active girls with AGU described by Rosman et al, there were insufficient data to determine whether oral corticosteroids shortened the course of AGU; however, ultraptotential topical steroids, such as clobetasol propionate 0.05% ointment, have shown benefit in the treatment of oral aphthous ulcers and may also be beneficial for AGU.¹³ ¹⁰ ²¹ Colchicine has been reported as a treatment for AGU associated with EBV infection in the setting of previously failed treatment, including topical and systemic corticosteroids and topical imiquimod.¹³ Colchicine has been used in other ulcerative conditions, such as recurrent aphthous stomatitis and Behçet’s disease.²³ ²⁴ The proposed mechanisms of action are through inhibition of chemotaxis and phagocytosis of neutrophils.²³

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