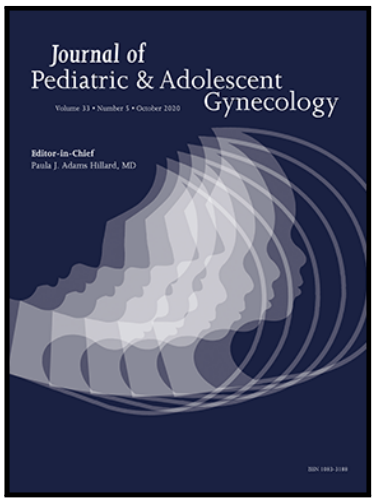

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Vulvar Aphthous Ulcers in Perimenarchal Adolescents After COVID-19 Vaccination: A Multicenter Case Series

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Abstract

This case series from three academic hospital-based pediatric and adolescent gynecology services outlines the temporal association between vulvar ulcers in female adolescents and

COVID-19 vaccination. We identified eight cases and describe each patient's presentation, differential diagnosis, diagnostic work up, complications, treatment modalities, and overall course of illness. All cases seek to illustrate the clinical experiences of patients and providers interfacing with vulvar aphthous ulcers and contribute to the emerging literature exploring the novel association between vulvar aphthous ulcers and COVID-19 vaccination. To date, this is the largest described case series of this association in the literature.

***Keywords**:* COVID-19, vaccine, aphthous ulcers, vulva, adolescent

Introduction

Vulvar aphthous ulcers (also known as Lipschutz ulcers) have been described since the early 1900s. These non-sexually acquired genital ulcers typically appear in the perimenarchal population as one to three painful ulcers that spontaneously resolve within 21 days. Etiology is not completely understood but there is believed to be a large immunologic component given a high association with a recent viral or bacterial infection.[1-5] Most recently, several case reports and case series have been published describing the development of vulvar ulcers during infection with SARS-CoV-2 as well as after COVID-19 vaccination.[6-15] In this report, we describe a series of eight cases of perimenarchal adolescent females who developed vulvar aphthous ulcers subsequent to COVID-19 vaccination without evidence of prior SARS-CoV-2 infection. This case series contributes to the emerging literature describing vulvar ulceration after COVID-19 vaccination and further elucidates typical clinical features, optimal treatment modalities, and overall course of this novel association.

Methods

A pediatric and adolescent gynecology provider at each of the three centers searched their clinical practice records and collected their encounters for all cases of female adolescents

presenting with vulvar aphthous ulcers after COVID-19 vaccine from April 2021 to September 2021. For each case identified, the provider reviewed the electronic medical record (EMR) to identify the age of the patient, menarchal status, date, brand and dose of vaccine received, date of clinical presentation, time to initial symptoms and resolution of symptoms, clinical description of average lesion(s), work up, treatment, follow up and recurrence. This de-identified data was sent to the lead author to collate and analyze in a personal health information-compliant data storage service. The patients' treating physicians obtained patient and guardian verbal assent for publication of de-identified clinical information and photographs. Written consent was obtained for published photographs.

Results

Eight cases of adolescents with vulvar aphthous ulcers were identified who had received the Pfizer-BioNTech COVID-19 vaccine within one or two days of the appearance of the ulcers (Table 1 & Figure 1). The ages of the adolescents ranged from 12 to 17 years with a mean age of 14.6 and all except one were post-menarchal (Table1). Seven of the eight adolescents developed the ulcers after the second dose of the vaccine. Only one adolescent, notably with a prior history of vulvar aphthous ulcers, presented with symptoms after the first vaccine dose. None of the patients had a known history of COVID-19 or a recent exposure to SARS-CoV-2. In addition, there were no reported recent symptomatic viral illnesses. Table 1 highlights clinical characteristics, management, and outcomes for each of the eight reported patients with ulcers following vaccination.

Most patients reported systemic symptoms including fevers, headache, and myalgias after vaccination prior to vulvar symptoms. Average symptom onset of vulvar pain and dysuria was two days after the second dose of vaccination with peak symptoms ranging from day two to day

five from vaccination. All physical exams were consistent with aphthous ulcers, demonstrating multiple violaceous ulcerations with yellow fibrinous exudate, surrounding erythema and necrotic islands (Fig 1).

Symptom resolution varied from 10 to 24 days. One patient was hospitalized for urinary retention in the setting of labial edema and found to have genital cultures positive for *Corynebacterium* and *Bacteroides fragili*s. Different institutions and physicians employed their own diagnostic plans. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) testing was performed in two patients and all tests were negative. Three patients were tested for herpes simplex virus (HSV) and found to be negative. Half of the patients had microbiology performed with fungal and bacterial cultures, with two patients exhibiting positive cultures. The patient with the vulvar culture positive for *Corynebacterium* and *Bacteroides Fragili*s was treated with a course of cephalexin. Another patient with a vulvar culture positive for *Staphylococcus* aureus was managed as an outpatient with amoxicillin.

Two patients had a prior episode of aphthous ulcers and underwent a rheumatologic workup given the recurrence. One of these patients was hospitalized for urinary retention and uncontrolled pain. The other underwent outpatient vulvar biopsy of the ulceration and the pathology demonstrated chronic inflammation (Fig 2). Work up revealed negative testing for antiphospholipid antibody, systemic lupus erythematosus, Behcet's disease, and ANCA associated vasculitis in both these patients referred to rheumatology.

Five patients required only symptomatic support, three received a course of oral steroids, and two received a course of antibiotics for positive vulvar cultures.

For the three patients who received oral steroids, full resolution without evidence of further lesions ranged from 14 to 21 days. For those who received symptomatic treatment only,

documented full resolution of lesions ranged from 10 to 25 days. Symptomatic treatment included non-steroidal anti-inflammatory drugs, acetaminophen, zinc oxide barrier cream, sitz baths, and topical lidocaine.

One patient in this case series was identified to have a recurrence of ulceration after her Omicron booster vaccination. She received her booster twelve months after her initial COVID-19 vaccination. Her symptoms began two days after the booster at which time she was started on an oral prednisone taper. Her physical exam and overall course were notably milder with complete resolution of ulceration seven days later.

Discussion

The differential diagnosis of vulvar ulcers in adolescents is extensive and includes infectious (bacterial, viral, and fungal) as well as autoimmune and inflammatory associated causes of genital or oro-genital ulcerations such as Behçet's disease, Crohn's disease, and complex aphthosis. Most vulvar aphthous ulcers, however, are idiopathic with a negative infectious work-up and are most likely secondary to an immunologic response to infection or other source of inflammation that is commonly preceded by prodromal symptoms including fever, chills, fatigue, and malaise.[3, 7, 16] Previously reported infectious triggers include EBV, *Mycoplasma pneumoniae*, CMV, influenza A and B, mumps virus, *Salmonella*, parvovirus B19, adenovirus, *Toxoplasma gondii*, and; most recently, SARS-CoV-2 infection.[2, 3, 6, 8-10, 12, 14]

These eight cases illustrate the temporal association of vulvar ulcers with the Pfizer-BioNTech Covid-19 Vaccine in adolescent females and support the increasing number of case reports with similar findings.[7, 10, 13, 14] Thus, COVID-19 vaccination may be a novel etiology for vulvar aphthous ulcers.

While pathogenesis of vulvar aphthous ulcers remains uncertain, it is posited that a cell-mediated immune response to the acute phase of an infection results in a type 3 hypersensitivity reaction characterized by intravascular deposition of immune mediated complexes with subsequent complement activation and formation of microthrombi in dermal vessels and tissue necrosis.[3, 9] Given that COVID-19 vaccination elicits a strong immunogenic reaction, it is possible that this systemic non-specific inflammatory response also contributes to the development of vulvar aphthous ulcers after vaccine administration. Indeed, studies have demonstrated that the Pfizer-BioNTech vaccine incites a robust immune response via activation of CD4+ and CD8+ T cells and cytokine production, specifically interferon gamma.[14, 17] Given these findings, the presented cases further support the long-held hypothesis that vulvar aphthous ulcers are an immunologic response rather than a sign of a genital infection themselves. Additionally, this case series supports the multifaceted immune response from the COVID-19 mRNA based vaccine. Effective treatment has been shown in this case series as well as in other case reports and systematic literature reviews to include steroids, targeted antibiotic treatment for superinfected ulcers, and analgesia.[18] While there does not seem to be documented evidence of decreased time to resolution with a course of steroids in our cases, our series is limited by its retrospective nature, reliance on EMR documentation, and inconsistent utilization of steroids as part of the treatment pathway. Additional limitations of our case series included lack of longitudinal follow up for all patients to determine if patients subsequently tested positive for SARS-CoV-2 after resolution of ulceration, experienced recurrent ulcerations, or had aphthous ulcers following booster vaccinations. Lastly, not all cases had available photos for publication to include in our case series.

While steroids have been used to treat severe aphthous vulvar ulcerations and have become a mainstay of COVID-19 treatment pathways, there is the potential for steroids to mitigate the COVID-19 vaccine's intended activation of the immune system for antibody production against SARS-CoV-2 infection. Future investigation is needed to understand optimal treatment modalities for vaccine-associated ulcers that do not interfere with the necessary immune response and thus vaccine efficacy and protection against SARS-CoV-2 infection. With expected increased vaccine uptake in this age group and the subsequent possible increased incidence of acute vulvar ulceration following vaccination, our case series will allow providers to be better equipped in counseling and managing patients who present with similar symptoms thus reducing misdiagnoses and delay to treatment.

Disclaimers/Conflicts of Interest/Affiliations:

None for all authors

Location studies conducted:

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Declaration of Competing Interest

The authors have no financial disclosures or conflicts of interest.

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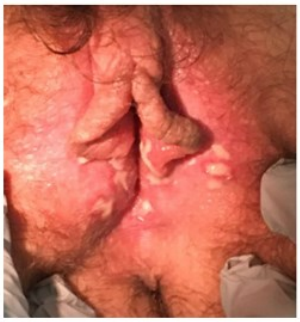

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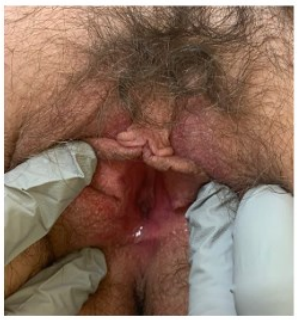

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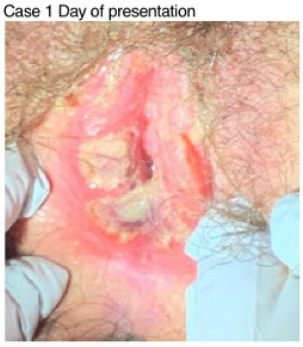

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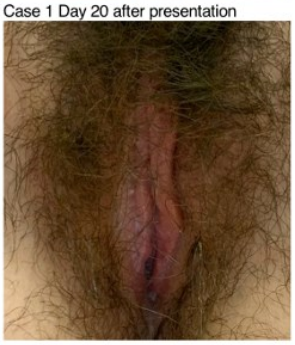

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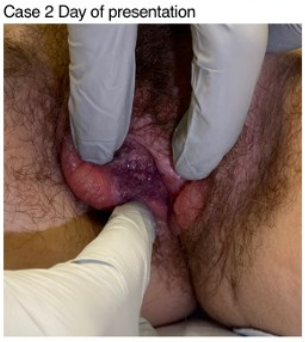

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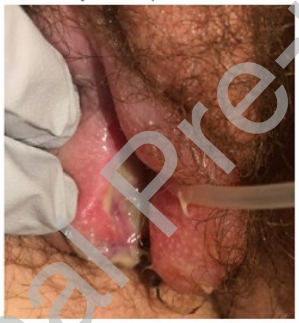

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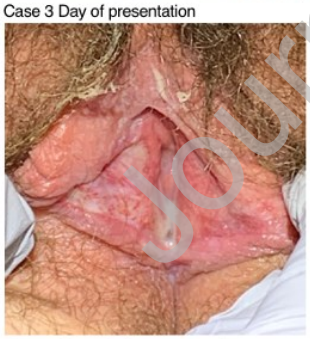

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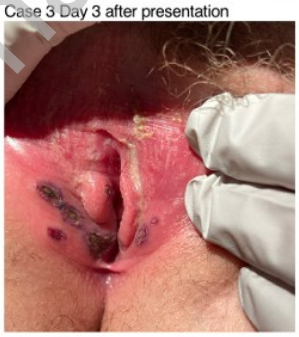

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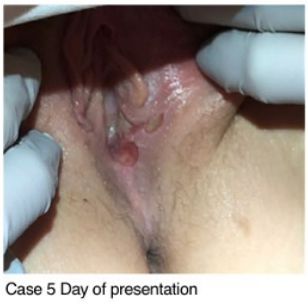

Case 5 Day of presentation

Fig 1. Vulvar Ulceration and Resolution following COVID-19 Vaccination

Table 1 Characteristics, management, and outcomes for each patient with ulcers following vaccination

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age at diagnosis	17	14	13	12	14	15	16	16
Dose	2nd	1st	2nd	2nd	2nd	2nd	2nd	2nd
Time to onset of vulvar ulcer from vaccine (Days)	2	2	1	1	2	2	2	2
Prior history vulvar lesion	0 episode	1 episode	1 episode					
Time to resolution (Days)	20	25	14	21	21	21	10	10

Treatment	Methylprednisolone taper, Amoxicillin, 5% lidocaine ointment, tylenol/NSAIDs, sitz baths	Lidocaine 2% jelly, tylenol/NSAIDs	Prednisone taper, Cephalexin, 2% lidocaine jelly, tylenol/NSAIDs, sitz baths	oral steroids			zinc oxide, NSAID, xylocaine 2% spray	zinc oxide, NSAID, xylocaine 2% spray
Menarchal status	Post-menarchal	Post-menarchal	Post-menarchal	Pre-menarchal	Post-menarchal	Post-menarchal	Post-menarchal	Post-menarchal
Serologies/ Culture								
HSV	negative	neagtive	negative	x	x	x	x	x
EBV	ordered but not completed	x	x	negative	ordered but not completed	negative		
CMV	ordered but	x	x	negati	order	negati		

	not completed			ve	ed but not completed	ve		
Genital culture	4+ Staphylococcus aureus	x	4+ Corynebacterium species, 1+ Bacteroides fragilis				negative	negative
Biopsy	x	Chronic Inflammation	x	x	x	x	x	x
Referals/Consults	x	Rheumatology	Rheumatology	x	x	x	x	x