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Adolescents with Vulvar Ulcers: COVID-19 disease, COVID-19 Vaccines, and the Value of Case Reports



Precis: Despite their limitations, case reports can be valuable additions to the medical literature. We should encourage frontline providers to submit case reports. Although a single case report cannot be used to draw inferences, a collection of high-quality case reports can inform hypotheses which can be tested in larger studies and can sometimes be synthesized into evidence to inform decision-making.

“Good case reporting demands a clear focus, to make explicit to the audience why a particular observation is important in the context of existing knowledge” (Vandenbroucke 2001).¹

COVID-19 and Aphthosis

Most scientific insights stem from an initial observation. We know from neuroscience that our brains are “difference seeking machines”,² so when a case is unusual, it sticks out. Long before we conduct a formal study of a disease, we need a frontline provider to notice, pay attention, and write it down. This power of observation is the most remarkable tool in medicine. Individually or collectively, we gather our experiences and move from an anecdote to a case series. When we ruminate on the linked cases, we develop hypotheses, which we can sometimes test with an observational trial or even a randomized controlled trial (RCT).

Recently, the *Journal of Pediatric & Adolescent Gynecology* (JPAG) has published 3 case reports of vulvar ulcers, 1 temporally associated with COVID-19 disease and 2 temporally associated with receiving the COVID-19 vaccine.³⁻⁵ We are not entirely surprised by these reports. Vulvar ulcer research in Cincinnati began with an astute clinician (Paula Hillard, MD) who served as a one-woman pediatric gynecology referral service for a tristate area. She discussed her unusual cases with a national network at annual JPAG meetings. When, as a fellow working with Dr Hillard, I saw my first case of non-sexually transmitted vulvar ulcers in 2002, Dr Hillard directed me to search her medical records for other cases.⁶ As we began receiving many referrals, we set up a protocol and collected prospective data to address the hypothesis that the ulcers were causally linked to an unknown viral infection with seasonal variation.⁷ By hand searching the medical literature for similar cases, we uncovered the original 1913 reference to Lipschütz ulcers⁸ and the dermatology literature describing deep, complex oral aphthoses with occasional vulvar manifestations.⁹ Our results convinced us that there was no seasonality or infectious etiology for vulvar aphthosis, and we altered our clin-

ical practice to add topical and oral corticosteroids to our care regimen.

Between us, we have cared for dozens of young girls affected by these ulcers. By continuing to publish similar case reports, we share our experience and are better able to provide supportive care, avoid extensive diagnostic workups, and offer reassurance about the self-limited nature of most cases of vulvar aphthosis. Although I no longer have a clinical practice, I still get occasional emails and messages on social media from young women and parents seeking answers about this unusual condition.

Although we cannot infer causality from case reports, we are not surprised that either COVID-19 disease or COVID-19 vaccination might be temporally associated with a vulvar ulcer. The pathogenesis of complex oral or vulvar aphthosis is still uncertain but likely involves a cell-mediated immune response. Aphthosis can be triggered by a long list of factors, such as local trauma, viral infections, and drugs. Thus, a viral disease such as COVID-19, or a vaccine that elicits a strong immune response, is a plausible trigger for vulvar aphthosis. As these and other case reports demonstrate, such reactions are rare, are self-limited, and should not be construed as definitive adverse reactions to the vaccine.

The Case for Case Reports

These recent publications highlight the role that case reports play in advancing medical knowledge and the reasons we should encourage more of them. Cases can provide an early warning of an intervention’s side effects or a novel presentation of disease.¹⁰ A well-written case report contains rich details that are not available in electronic databases or medical records. The discussion section can help to generate new hypotheses, link disparate fields, and spark further investigation. Cases can be synthesized to summarize pertinent details that help clinicians with diagnosis, treatment, and prognosis of rare conditions.

The best reason to write case reports, perhaps, is that they resonate with readers. Medical education has long been based on apprenticeship and case-based learning. Adult learning theory supports that most of us learn best by experience. More than that, case reports are stories that are easy to read. Some medical educators report that story-based material is easier to retain than simple text.¹¹

Although case reports as a category are valuable, not all case reports are created equal, and their quality can vary. Recognizing this, an international group of experts developed the CARE (CAse REports) guidelines to increase

the accuracy, transparency, and usefulness of case reports.¹² This guidance provides an outline of information that should be collected and included in each case report. However, not all journals adhere to these guidelines, and a review of COVID-19 case reports found that compliance was uneven.¹³

The CARE guidance is directed to authors of case reports. A single case report cannot be used to draw inferences; however, a collection of high-quality case reports can inform hypotheses that can be tested in larger studies and can sometimes be synthesized into evidence to inform decision-making. To compile information from case reports, evidence synthesis experts need a tool to assess their quality (ie, risk of bias). As such, Murad et al recently proposed an 8-item checklist to examine the methodologic quality of case reports and case series.¹⁰ Two other recent tools (JBI and Guo) include similar questions.^{14,15} Any high-quality systematic review that uses case reports should clearly state which tool was used to assess the quality of included studies.

The typical hierarchy of evidence places the RCT as the “gold standard” of rigorous, unbiased scientific evidence. In many situations, RCTs or well-designed observational studies might not be available or might not be appropriate to answer the question at hand. Nevertheless, experts need to summarize whatever evidence is available to help frontline clinicians make decisions.

Case reports often vastly outnumber more rigorous study designs. This is especially true for obstetrics, where pregnant women are often excluded from RCTs; for surgical conditions, where it is difficult to achieve blinded group assignment and assessment; and for rare conditions (such as vulvar aphthosis), where it is hard to enroll an adequate sample size to permit comparisons. Even when other study designs are published, authors can use case reports to supplement the available evidence. For example, in a systematic review of treatments for headache in pregnancy, the authors included 19 case reports as supplemental evidence, as these cases might be the first signals of rare harms of new treatments.¹⁶

Our recent experience with the COVID-19 disease demonstrates the power of case reports in rapidly discovering disease characteristics, treatments, and outcomes. In a simple search of PubMed, using the search term “COVID” and filtering by article type, more than 14,000 articles were identified between January 1, 2020, and September 23, 2021, of which 70% were termed “case reports,” 26% were deemed “systematic reviews,” and 4% were classified as “randomized controlled trials.” The pandemic highlights how case reports and case series can be synthesized into systematic reviews to improve medical care long before we can set up well-designed trials. The same is true in the case of vulvar aphthosis, although the time course has been much longer than for COVID-19. In PubMed (searching “ulcer AND vulva*” in all fields and filtering by article type), I found over 800 articles published since 1932. Of these, 54% were case reports and 1% were RCTs or systematic reviews, with the balance being “other types.”

Recently, 2 teams synthesized the case reports of vulvar aphthosis into systematic reviews. An Austrian team

summarized 21 articles published between 2001 and 2019 and describing 60 patients.¹⁷ They developed a diagnostic algorithm that supports the one we suggested in 2006.⁷ A review by a Swiss team used slightly different search terms and a longer window (1965 to present) to uncover 108 articles describing 158 women.¹⁸ The authors concluded that management should include reassurance, local hygiene, wound care, and pain control but not systemic corticosteroids. The methodologic quality of both of these systematic reviews is only fair (based on the AMSTAR¹⁹ tool). Both were rated down for not publishing an a priori protocol, searching only a single database, using limited search terms, lack of dual data abstraction, not providing a list of excluded articles (and reasons for exclusion) and for not incorporating the scientific quality of the included studies into the conclusions. Of personal interest, both reviews cite a clinical review article that I wrote, but neither included either of our 2 case series.^{6,20} Without a list of excluded studies, I cannot tell if they missed these articles because of the limited search terms that they used or if the studies were excluded for other reasons.

In summary, at present, there are too few cases reporting aphthosis after COVID disease or COVID-19 vaccination to infer a statistical association. However, case reports are a valuable source of rich details about conditions that are difficult to study with more rigorous designs and can be synthesized to help guide medical care. It is now time for someone to produce a high-quality systematic review of vulvar aphthosis so that we can incorporate the existing evidence into decision-making and best care for our patients.

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