Women's Health Highlight

OPEN

Lipschütz ulcers due to SARS-CoV-2 infection: a neglected diagnosis in emergency room

Ilaria Brambilla, MD, PhD[a], Vittorio Bolcato, MD[b], Martina Volonté, MD[c], Andrea Querzani, MD[d], Carmen Guarracino, MD[a], Enrico Tondina, MD[d], Gian Luigi Marseglia, MD[a,d], Valeria Brazzelli, MD[c,d,*]

ABSTRACT

Background: Primary acute genital ulcers, or Lipschütz ulcers (LU), are nonsexually transmitted, painful, self-limiting, nonrecurrent vulvar ulcers with unclear pathogenesis, representing a challenging diagnosis in emergency setting. LU have recently been described in association with severe acute respiratory syndrome coronaVirus 2 (SARS-CoV-2) infection and vaccination.

Objective: The aim of this study is to describe 2 cases of LU due to SARS-CoV-2 infection, highlighting the diagnostic process, differential diagnosis, disease course, and management options.

Methods: We describe 2 young females (12 and 9 years old) who presented to pediatric emergency room with the sudden onset of well-demarcated, painful, vulvar ulcers with fibrinous necrotic center.

Results: Both patients tested positive to SARS-CoV-2 nasal swab, and, at physical examination, no other lesions were found in other cutaneous or mucosal sites. Sexual abuse was excluded in both cases, as well as infectious and autoimmune diseases. Supportive analgesic therapy was administered, and complete remission of lesions was observed at follow-up visits without evidence of scarring.

Limitations: The main limitation of this work is represented by the small number of cases described.

Conclusion: Even though extremely rare, LU related to COVID-19 are an emerging entity to be considered in the diagnosis of acute genital ulcerations. Multidisciplinary diagnostic workup of genital ulcers must be established in order to exclude sexual child abuse, to ensure patient safety, and to avoid unnecessary treatment and familial anxiety.

Keywords: COVID-19, genital ulcers, Lipschütz ulcer, sexual child abuse

Introduction

Lipschütz ulcers (LU) are a neglected and challenging diagnosis in clinical practice among nonsexually acquired genital ulceration, particularly in emergency setting and in young girls.[1–3] This rare ulcerative condition is most frequently observed in nonsexually active girls, without association with sexually transmitted infections.[1–4] Patients typically present with flu-like symptoms followed by the sudden onset of well-demarcated, painful, vulvar ulcers with a fibrinous, purulent, or necrotic center.[1,3] These lesions usually appear in small number (≤3) on the medial surface of the labia minora and have large dimensions (>10 mm) and a symmetric mirror-like vulvar distribution ("kissing ulcers").[1] In many cases, LU occur concomitantly with an infectious disease and the strongest connection was found with Epstein–Barr virus (EBV) (27%), followed by *Mycoplasma*

What is known about this subject in regard to women and their families?

- LU are self-limiting and extremely painful ulcers typically occurring in young adolescent women who are not sexually active, typically associated with EBV infection.
- Diagnosis of LU derives from the exclusion of more frequently occurring infectious and autoimmune diseases and is associated with considerable anxiety in patients and their family, since they can be a mimicker of child abuse.

What is new from this article as messages to women and their families?

- COVID-19 infection and SARS-CoV-2 vaccination are an emerging trigger of LU to be considered in differential diagnosis of acute genital ulcers.
- A correct diagnostic procedure of genital ulcers in pediatric and adolescent patients must always exclude sexual child abuse through a multidisciplinary approach and the careful search for cutaneous and mucous signs of violent traumatic injury, especially since a rise in child abuse was observed during COVID-19 pandemic.

[a] *Department of Pediatrics, Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[b] *Department of Public Health, Experimental and Forensic Medicine, Fondazione Istituto Neurologico Nazionale C. Mondino I.R.C.C.S., Unit of Legal Medicine, Pavia, Italy*
[c] *Department of Clinical, Surgical and Pediatric Sciences, Institute of Dermatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[d] *Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, Università degli Studi di Pavia, Pavia, Italy*

I.B. and V.B. contributed equally to the work.

** Corresponding author.*

E-mail address: vbrazzelli@libero.it; v.brazzelli@smatteo.pv.it (V. Brazzelli).

International Journal of Women's Dermatology (2024) 10:e122

Received: 26 August 2023; Accepted 23 October 2023

Published online 12 February 2024

DOI: 10.1097/JW9.0000000000000122

spp. (8%), even though in few LU cases, no evidence of infections is detected.[1] More recently, during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, LU cases appear either related to SARS-CoV-2 vaccination or infection.[4–13] Moreover, SARS-CoV-2 pandemic resulted in restricted social and school activities, psycho-physical stress, and work issues that caused a rise in child abuse,[14,15] even if this condition remains underdetected[16]; therefore, clinicians should remain vigilant of sexual child abuse as a mimicker of LU, focusing also on the girl's safety and security, comfortable environment, and psychological support. We describe 2 girls who presented in the pediatric emergency room (ER) with acute vulvar ulcers during SARS-CoV-2 pandemic.

Case reports

Patient 1

A 12-year-old girl came to attention with a 10-day history of burning of the external genitalia, associated with genital ulcers. The girl had no menarche, was not sexually active, and had no previous history of oral or genital ulcers. Two days after symptoms appearance, given the onset of high fever (maximal temperature, 41.2 °C), a SARS-CoV-2 reverse transcription polymerase chain reaction nasal swab was performed and resulted positive. No other COVID-19-related symptoms were reported.

At physical examination, vulvar area appeared erythematous and mildly edematous. Two extremely painful, symmetrical, fibrin-coated lesions were evident in the inner surface of labia minora (Fig. 1). The girl also presented with urinary retention. Sexual child abuse was excluded due to the contextual presence of prodromal symptoms and the absence of other traumatic lesions in the clinical examination. She was hospitalized in the pediatric COVID ward for diagnosis and pain control. Blood tests showed a normal cell count and negative inflammatory markers (C-reactive protein and procalcitonin). The main autoimmunity markers (anti-nuclear antibodies, anti-tissue transglutaminase immoglobulin antibodies, and type 1 diabetes–related antibodies) resulted negative. Serum antibodies for the most common pathogens (EBV, cytomegalovirus, virus varicella zoster, herpes simplex virus, human herpes virus 6, human herpes virus 7, *Mycoplasma pneumonia*) were negative, except for a previous contact with herpes simplex virus 1 (positive IgG and negative IgM). Cultural examinations on vaginal, pharyngeal, and lesional swabs resulted negative for fungi and bacteria. Finally, the patient proved negative for human leukocyte antigen-B51. A diagnosis of LU was made.

A nonsteroidal anti-inflammatory double-therapy was prescribed, with rapid pain relief. Ulcers were treated with local application of 2% eosin aqueous solution, alternating with betamethasone/gentamycin cream and gauze dressing containing hyaluronic acid.

Edema disappeared within the first week. Ulcerations resolved completely at first follow-up control, 25 days after first appearance, with no evidence of scarring of the labia minora.

Patient 2

A 9-year-old prepubescent girl presented to pediatric ER in February 2022 for the appearance of painful ulcers on labia minora, with vulvar edema associated with difficulty in walking (Fig. 2). No clear prodromal of fever or other flu-like symptoms were reported in recent anamnesis. On physical examination, oral mucosa was normal. On gynecological examination, the external genitalia were morphologically normal, besides the presence of 2 symmetrical ulcerative lesions on the labia minora

Fig. 1. Patient 1 clinical presentation of genitalia at emergency room

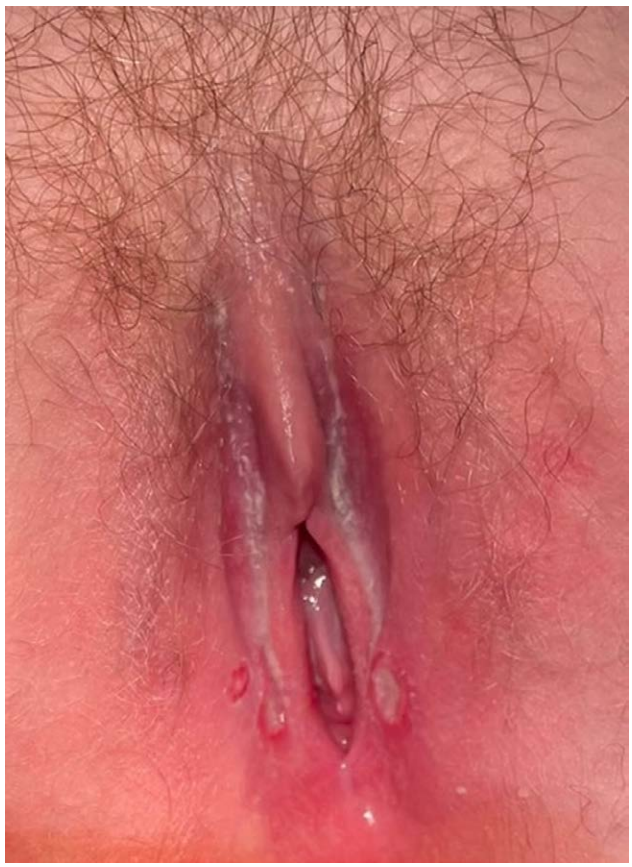

Fig. 2. Patient 2 clinical presentation of genitalia at emergency room

(diameter 4–5 mm), with the typical "kissing pattern." No other skin and mucosal lesions were found, and personal history was negative for sexual activity or previous ulcerative manifestations. SARS-CoV-2 reverse transcription polymerase chain reaction nasal swab resulted positive. Biochemical analysis showed no elevation of inflammatory indexes and no significant alterations in blood count. After hospitalization, anti-nuclear antibodies, celiac disease, and type 1 diabetes–related antibodies resulted negative. Furthermore, a serologic screening for the most common pathogens was performed: EBV, herpes simplex virus 1, herpes simplex virus 2, *M. pneumonia*, papillomavirus proved negative; a previous contact with cytomegalovirus was detected (positive IgG and negative IgM). Microbiological culture for bacteria and fungi on mucosal swabs resulted negative. Urine biochemical test exhibited presence of bacteria, leukocytes, and leukocyte esterase. Molecular analysis for human leukocyte antigen-B51 was negative. A diagnosis suggestive of LU was made.

Immediate intravenous nonsteroidal analgesia was administrated, and betamethasone/gentamycin cream was applied topically. Given the obtainment of pain control, the patient was discharged, with prescription of oral nonsteroidal anti-inflammatory drugs for pain management and local application of 2% eosin aqueous solution alternating with betamethasone/gentamycin cream and gauze dressing containing hyaluronic acid. A rapid remission of pain and progressive lesion healing were seen since the first follow-up control. Three weeks after, vulvar mucosa lesions were completely remitted without scarring.

Discussion

Pediatric LU diagnosis in emergency setting represents a complex, but interesting challenge to direct first investigations, therapy, and hospitalization.[2,13] Even though extremely rare, in the last years of COVID-19 pandemic, an increase in case reports of

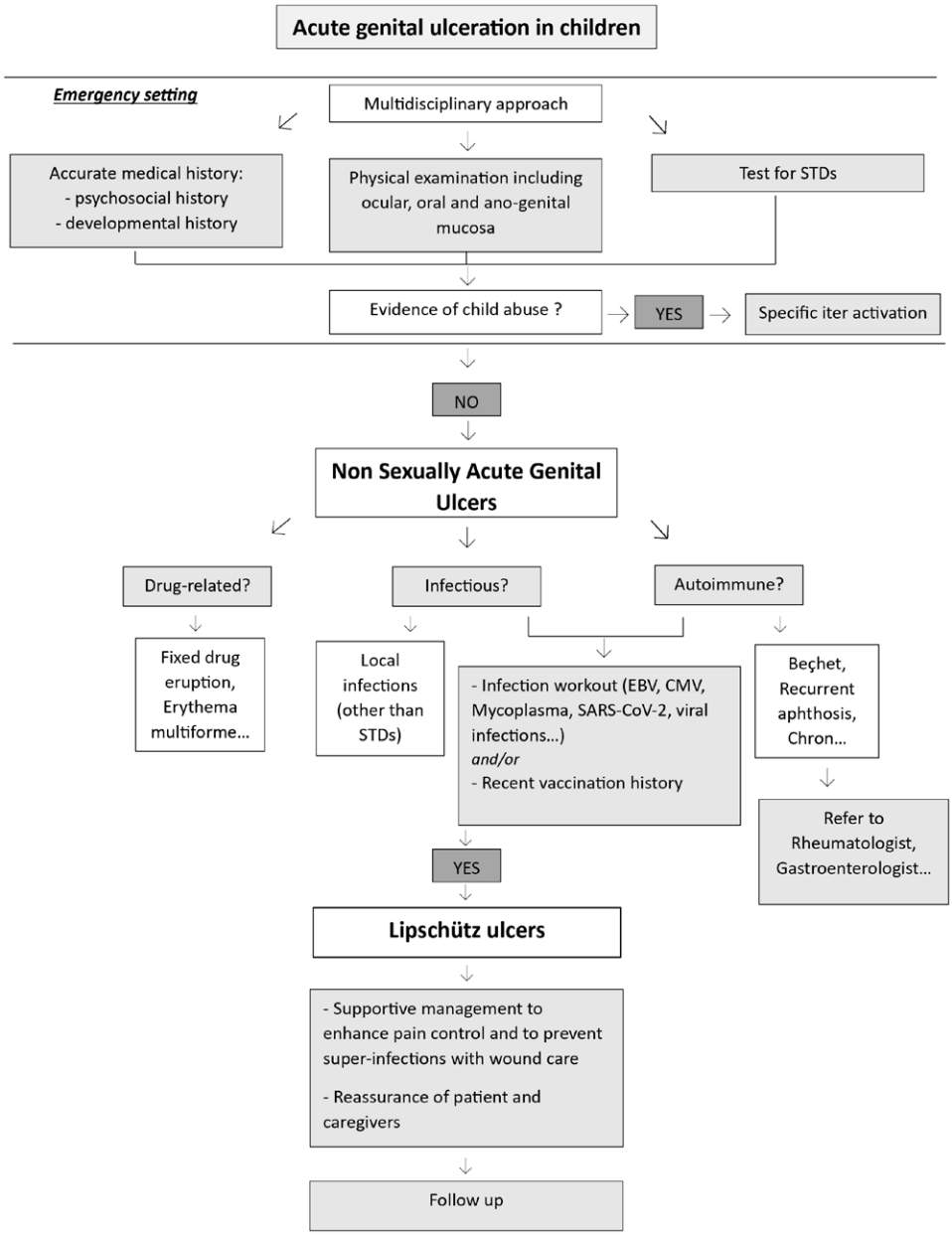

Fig. 3. Flowchart illustrating the diagnostic and therapeutic approach of acute genital ulcerations in children. CMV, cytomegalovirus; EBV, Epstein–Barr virus; STDs, sexually transmitted diseases.

LU associated with COVID-19 infection and SARS-CoV-2 vaccination has been registered.[8] LU associated with COVID-19 or vaccination are considered similar to LU classically reported in literature, in terms of clinical presentation, spontaneous resolution, importance of supportive care, and ideal management; however, recurrence of the lesions upon re-exposure to COVID-19 or vaccination has been described.[8,12]

We presented 2 young females with LU diagnosis following SARS-CoV-2 infection, with a mean remission time of 3 weeks with supportive therapy: the duration of illness appears in line with other data reported in literature.[1]

A proposed diagnostic workup for the diagnosis of acute genital ulcerations envisages first a differential phase in the ER, followed by a second phase of advanced diagnostic workup, which sometimes requires hospitalization[13,17] (Fig. 3).

In particular, in the ER, for a patient with a vulvar ulcer, an accurate anamnesis must be performed, with careful psycho-social and developmental history collection and cautious recollection of sexual history, investigating not only sexually transmitted diseases (including syphilis, gonorrhea, chancroid, lymphogranuloma venereum, herpes genitalis, condylomata acuminata, chlamydia urethritis, trichomonas vaginalis, pediculosis pubis, granuloma inguinale, and HIV/AIDS) but also sexual child abuse.[18]

Then, a full physical examination must be performed, and when genital ulcers appear in children or adolescents, particular attention must be given to ocular, oral, and anogenital mucosa, in order to note any erosions and/or ulcerations. To exclude sexual child abuse-related lesions, typically attributable to a traumatic mechanism, other skin signs must be looked for, in particular bruising in characteristic body regions.[18]

Hospitalization is usually indicated both for the complexity of the differential diagnostic process,[13,17] and for the relevant emotional and psychological repercussions.[12] In this setting, more frequently observed causes of genital ulcerations in young population must be investigated, such as infectious etiology and autoimmune diseases.[1,12,13]

Based on the spontaneous resolution of LU, supportive therapy must be prescribed to manage pain and to prevent superinfections.[1,8]

The pathogenesis of LU remains under investigation, and the proposed mechanisms include type III hypersensitivity reaction, triggered by immune complex deposition, which leads to microthrombosis and necrosis in the genital area. A virus-provoked cytolysis resulting after hematological spread of virus-infected lymphocytes or autoinoculation through self-contact can also be taken into consideration.[4,13] Another possibility could imply the cytopathic effects of the virus on the epithelium, which may lead to papules, vesicles, or ulcers.[9,19] As shown in this and other case reports, LU should be, therefore, included among the cutaneous manifestations of COVID-19.[11,20]

In fact, it is nowadays widely known that SARS-CoV-2 infection can trigger a "cytokine storm," which could be defined as a loss of regulatory control of proinflammatory cytokine production, both at local and systemic levels.[21] This proinflammatory milieu could, therefore, be related not only to the typical clinical manifestations of COVID-19 but also to these cutaneous signs.[6,19]

In conclusion, SARS-CoV-2 pandemic seems to be related to acute genital ulcerations in a double way: on the one hand, COVID-19 infection and vaccination is being recognized as an emerging trigger of LU,[4–13] and on the other hand, restrictive measures implemented during lockdown have produced an increase in child abuse.[14–16]

The awareness of LU, even though it represents a rare entity, helps to avoid unnecessary investigations, and treatment, and to possibly reduce patients and family anxiety. An extended physical examination, paying attention to other types and other sites of possible skin injury is one of the most important diagnostic steps and must be included in the diagnostic algorithm.[13,17] A multidisciplinary team, consisting of pediatrician/pediatric gynecologist and dermatologist, with the support of an expert in child protective evaluations, is strongly required, similarly to the one gathered in cases of directly reported sexual abuse in ER,[22] for ideal patient management.

Conflicts of interest

None.

Funding

Supported by Fondi Ricerca Corrente, Ministero della Salute, Italy.

Study approval

N/A

Author contributions

IB and VB participated in conceptualization, investigation, and writing. MV, AQ, CG, and ET participated in investigation and final writing and editing. GLM participated in supervision, validation, and final writing and editing. VB participated in investigation, supervision, project administration, and final writing and editing.

Patient consent

Informed, written consent was obtained from patients' legal representatives for whom photographs are present in the manuscript.

References

1. Vismara SA, Lava SAG, Kottanattu L, et al. Lipschütz's acute vulvar ulcer: a systematic review. Eur J Pediatr 2020;179:1559–67.
2. Pereira DAG, Teixeira EPP, Lopes ACM, Sarmento RJP, Lopes APC. Lipschütz ulcer: an unusual diagnosis that should not be neglected. Rev Bras Ginecol Obstet 2021;43:414–6.
3. Schindler Leal AA, Piccinato CA, Beck APA, Gomes MTV, Podgaec S. Acute genital ulcers: keep Lipschütz ulcer in mind. Arch Gynecol Obstet 2018;298:927–31.
4. Krapf JM, Casey RK, Goldstein AT. Reactive non-sexually related acute genital ulcers associated with COVID-19. BMJ Case Rep 2021;14:e242653–3.
5. Popatia S, Chiu YE. Vulvar aphthous ulcer after COVID-19 vaccination. Pediatr Dermatol 2022;39:153–4.
6. Sartor RA, Lawson A, Moncada-Madrazo M, Altchek C, Vash-Margita A, Cron J. Vulvar aphthous ulcers in perimenarchal adolescents after COVID-19 vaccination: a multicenter case series. J Pediatr Adolesc Gynecol 2023;36:268–72.
7. Tammaro A, Kulakowska KA, Cantisani C, Parisella FR, Scarabello A, Adebanjo GAR. Female genital mucosal lesions associated with COVID-19 vaccination: a brief review of the literature. J Eur Acad Dermatol Venereol 2023;37:e143–6.
8. Vismara SA, Ridolfi A, Faré PB, et al. COVID-19, coronavirus vaccines, and possible association with Lipschütz vulvar ulcer: a systematic review [published online ahead of print, June 26, 2023]. Clin Rev Allergy Immunol 2023;65:166–71.
9. Novak N, Peng W, Naegeli MC, et al. SARS-CoV-2, COVID-19, skin and immunology – what do we know so far? Allergy Eur J Allergy Clin Immunol 2021;76:698–713.
10. Huppert J. Adolescents with vulvar ulcers: COVID-19 disease, COVID-19 vaccines, and the value of case reports. J Pediatr Adolesc Gynecol 2022;35:109–11.
11. Crofts VL, Clothier HJ, Mallard J, Buttery JP, Grover SR. Vulval (Lipschütz) ulcers in young females associated with SARS-CoV-2 infection and COVID-19 vaccination: case series. Arch Dis Child 2023;108:326–7.
12 Rudolph A, Savage DR. Vulval aphthous ulcers in adolescents following COVID-19 vaccination – analysis of an international case series. J Pediatr Adolesc Gynecol 2023;36:383–92.

13. Schmitt TM, DeVries J, Ohns MJ. Lipschutz ulcers in adolescent after Sars-CoV-2 infection. J Pediatr Heal Care 2022;37:63–6.
14. Lawson M, Piel MH, Simon M. Child maltreatment during the COVID-19 pandemic: consequences of parental job loss on psychological and physical abuse towards children. Child Abus Negl 2020;110:104709.
15. Rapp A, Fall G, Radomsky AC, Santarossa S. Child maltreatment during the COVID-19 pandemic: a systematic rapid review. Pediatr Clin North Am 2021;68:991–1009.
16. Russell KW, Acker SN, Ignacio RC, et al. Child physical abuse and COVID-19: trends from nine pediatric trauma centers. J Pediatr Surg 2022;57:297–301.
17. Rosman I, Berk D, Bayliss S, White A, Merritt D. Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol 2012;29:147–53.
18. Harth W, Linse R. Dermatological symptoms and sexual abuse: a review and case reports. J Eur Acad Dermatol Venereol 2000;14: 489–94.
19. Alberelli MC, Panariello A, Olivi M, Borghi A, Zedde P, Corazza M. Ulcus vulvae acutum and SARS-CoV-2: an aetiological role? J Eur Acad Dermatol Venereol 2021;35:e647–9.
20. Mastoraki E, Niforatou-Daskalaki S, Bunker CB, Kravvas G. A case of COVID-19-related vulval ulceration coupled with genital viral shedding. J Eur Acad Dermatology Venereol 2023;37:e1187–8.
21. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'cytokine storm' in COVID-19. J Infect 2020; 80:607–13.
22. Decree of the President of the Council of Ministers. National Guidelines for Health Agencies and Hospitals on the Subject of Rescue and Social-Health Assistance for Women Victims of Violence. 2017. Available from: https://www.gazzettaufficiale.it/eli/id/2018/01/30/18A00520/SG