



Case Report

# Fever and Vulvar Ulcers in an Adolescent Girl: A Diagnosis of Lipschütz's Ulcer Associated with EBV and SARS Cov-2 Infection

Ilaria Mussinatto<sup>1\*</sup>, Chiara Benevenuta<sup>1</sup>, Anna M. Caci<sup>1</sup>, Mario M. Calvo<sup>1</sup>, Giulia Calosso<sup>1</sup>, Giulia Costagliola<sup>1</sup>, Cecilia Orsi<sup>1</sup>, Antonella Tuscano<sup>1</sup>, Davide Gallina<sup>2</sup>, Fabio S. Timeus<sup>1</sup>

<sup>1</sup>Department of Pediatrics, Chivasso Hospital, Chivasso (Torino), Italy

<sup>2</sup>Department Obstetricians and Gynecologists, Chivasso Hospital, Chivasso (Torino), Italy

\*Corresponding author: Ilaria Mussinatto, Department of Pediatrics, Chivasso Hospital, Chivasso (Torino), Italy

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## Abstract

**Introduction:** Genital ulcers are rare in pediatric age; they affect predominantly adolescents, causing concern and discomfort in the patients and their families. We report the case of a 14-years-old girl who came to our Emergency Department (ED) for vulvar ulcers and fever. **Case description:** A 14-years-old girl presented to our ED for a 5-day fever associated with a vulvar ulcer, malaise, dysuria with urinary retention. She had started oral acyclovir and amoxicillin-clavulanate two days before. Five months before she presented a similar episode. She denied any kind of sexual contact or trauma. Physical examination revealed a deep and painful ulcer of about 1.5 cm in diameter on the left minor labium, covered with fibrin, necrotic tissue, and purulent exudate. Specularly, on the inner right lip there was a small superficial ulcer of 3 mm in diameter. She had hyperemic pharynx, bilateral laterocervical and inguinal polyadenopathy. Blood tests showed increase in blood lymphomonocytes, inflammatory markers and transaminases; the pharyngeal antigenic swab for SARS-CoV2 was positive. EBV serology was compatible with acute primary infection. Serology for CMV, HSV 1-2 and Treponema, ANA, Rheumatoid factor, C3, C4, IgA, IgG, IgM, lymphocyte subpopulations, HLA-B5, B51, B27 and thyroid function tests were normal. Anti thyroid peroxidase and anti TSH receptor antibodies were positive. On the ulceral swab, PCR was positive for EBV and negative for HSV 1-2, CMV and SARS-CoV-2. Vulvar swab culture detected the presence of Escherichia coli, Enterococcus faecalis and Candida albicans. Fundus oculi and pathergy test were negative. A Lipschütz's ulcer during primary infection of EBV in concomitant SARS-CoV2 infection was suspected. The ulcers were treated with impregnated gauzes and hygiene. Antibiotic therapy was continued, and fluconazole was added, given the bacterial superinfection of the ulcer. Oral acyclovir was discontinued. Urinary catheter was kept in place until disappearance of dysuria (4 days). Multidisciplinary approach was required. Fever disappeared on the 11th day after disease onset. Vulvar ulcers completely healed in three weeks. The girl was referred to the Immuno-rheumatologically Center for follow up. **Discussion:** Genital ulcers in adolescents are most commonly referred to sexually transmitted infections, causing embarrassment and possibly compromising communication between the young patient and the doctors. However, vulvar ulcers can be caused by other conditions: our case shows that Lipschütz Ulcer, an unusual diagnosis in Pediatric ED, should not be neglected and has to be suspected in presence of a concomitant viral infection. It remains a diagnosis of exclusion: if episodes recur, careful follow-up is needed to rule out other causes, such as autoimmune or auto inflammatory diseases.

**Keywords:** Non-sexually acquired acute genital ulcer; Lipschütz's ulcer

## Introduction

Genital ulcers are rare in pediatric age; they affect predominantly adolescents, causing concern and discomfort in the patients and their families(1). We report the case of a 14-years-old girl who came to our Emergency Department (ED) for vulvar ulcers and fever.

## Case Description

A 14-years-old girl presented to our ED for a 5-day fever associated with a vulvar ulcer, malaise, dysuria with urinary retention. She had started oral acyclovir and amoxicillin-clavulanate two days before. Five months before she presented a similar episode. She denied any kind of sexual contact or trauma.

Physical examination revealed a deep and painful ulcer of about 1.5 cm in diameter on the left minor labium, covered with fibrin, necrotic tissue, and purulent exudate. Specularly, on the inner right lip there was a small superficial ulcer of 3 mm in diameter. She had hyperemic pharynx, bilateral laterocervical and inguinal polyadenopathy.

Blood tests showed increase in blood lymph monocytes, inflammatory markers and transaminases; the pharyngeal antigenic swab for SARS-CoV2 was positive. EBV serology was compatible with acute primary infection. Serology for CMV, HSV 1-2 and Treponema, ANA, Rheumatoid factor, C3, C4, IgA, IgG, IgM, lymphocyte subpopulations, HLA-B5, B51, B27 and thyroid function tests were normal. Anti thyroid peroxidase and anti TSH receptor antibodies were positive. On the ulceral swab, PCR was positive for EBV and negative for HSV 1-2, CMV and SARS-CoV-2. Vulvar swab culture detected the presence of *Escherichia coli*, *Enterococcus faecalis* and *Candida albicans*. Fundus oculi and pathergy test were negative.

A Lipschütz's ulcer during primary infection of EBV in concomitant SARS-CoV2 infection was suspected (Figure 1).

The ulcers were treated with impregnated gauzes and hygiene. Antibiotic therapy was continued, and fluconazole was added, given the bacterial superinfection of the ulcer. Oral acyclovir was discontinued. Urinary catheter was kept in place until disappearance of dysuria (4 days). Multidisciplinary approach was required.

Fever disappeared on the 11th day after disease onset. Vulvar ulcers completely healed in three weeks. The girl was referred to the Immuno-rheumatologically Center for follow up.



**Figure 1:** The Lipschütz's Ulcer.

**Epidemiology:** Non-sexually acquired acute genital ulceration, also referred to as "*Lipschütz's ulcer*" or aphthous ulcers, is a self-limited, nonsexual transmitted condition. It represents 30-36% of all the acute vulvar ulcers and it affects adolescent females and young women, with almost 90% of cases presented in <20 years and sexually inactive patients(2). The youngest patient described is a 4 months old girl(3).

**Clinical features:** Lipschütz's ulcers are characterized by the sudden onset of few (from one to three), genital deep ulcerations, temporarily associated with a flu-like illness. Lesions are always painful, large > 1 cm, well defined by a red-violaceous border, with necrotic, fibrinous or purulent centers. Ulcers typically involve the labia minora but can extend to the labia majora, perineum, vestibule, and lower vagina. A second symmetrical "kissing lesion" is characteristic. Labial edema and inguinal lymphadenopathy are common. Dysuria is almost universally reported. The ulcers typically self-resolve in < 3 weeks without scarring. Relapse is uncommon, but possible(1,4,5). Some patients have a history of oral aphthosis and/or have concomitant oral lesions.

**Etiology:** The exact pathogenesis is unclear. EBV is the most common infectious disease associated with genital ulcers and EBV DNA is frequently detected in genital lesions(2). Other viruses and bacteria are rarely detected(2), like CMV, *Mycoplasma* species(6), Influenza, Mumps, Paratyphoid fever, Streptococcal pharyngitis(7) and murine typhus(8). With the emergence of the pandemic of the new Coronavirus Sars-Cov2, related cases of Lipschütz's ulcer have also been reported. Also, some cases in response to the COVID-19 vaccine have been described(9-13).

## Diagnosis

The diagnosis is clinical after the exclusion of other common causes of genital ulcers(14). Proposed criteria for clinical diagnosis of acute genital ulceration in a young female with a recent history of mononucleosis-like illness are(15): first episode of acute genital ulceration, age <20 years, single or multiple deep, well-delimited, painful ulcers with a necrotic base on the labia minora or labia majora, bilateral “kissing” pattern, absence of any sexual contact in the previous three months, absence of immunodeficiency, acute course.

A complete blood count with differential to assess for lymphocytosis and presence of atypical lymphocytes and liver function tests should be performed. Serology for EBV is indicated. Serology for CMV and Mycoplasma pneumonia may be indicated in some patients. HSV is the most common cause of genital ulceration, so PCR or direct fluorescence antibody for HSV on ulcer swabs is indicated. Microbiologic or serologic tests for other sexually transmitted genital are performed based upon history and clinical suspicion. Bacterial cultures from the ulcer exudate should be obtained if clinical signs of bacterial superinfection or vulvar cellulitis. Biopsy is generally unhelpful, histologic findings are often nonspecific.

**Differential diagnosis:** The physical examination should focus on other skin, genital, oral or ocular signs, lymph nodes enlargement, hepatosplenomegaly.

**Infectious etiology:** most genital ulcers in the general population are caused by sexually transmitted infections (STIs)(16). STIs should be always considered and the girl's sexual history, risk factors and clinical presentation are to be investigated.

**Common STIs:** HSV 1-2 in the immunocompromised patient(17), Treponema pallidum (Primary syphilis).

**Uncommon STIs:** Chlamydia trachomatis serovars L1-3 (Lymphogranuloma venereum), Haemophilus ducreyi Chancroid, Klebsiella granulomatis, HIV, EBV, CMV, monkeypox.

Rarely, non-sexually transmitted infections can cause genital ulcerations, like tuberculosis(18), amebiasis, schistosomiasis, leishmaniasis(19)

**Noninfectious etiology:** Behçet's disease (diagnosis requires multisystem involvement, including eye, gut, vessels, joints, or central nervous system), complex aphthosis (recurrent oral and genital aphthae in the absence of other clinical features of Behçet syndrome. It may occur in association with systemic disease like IBD, HIV infection, and cyclic neutropenia), Crohn's disease, pyoderma gangrenosum, childhood vulvar pemphigoid, hidradenitis suppurative, trauma (by physical or chemical insult), neoplasm, fixed drug reactions.

**Therapy:** There are no specific protocols to treat Lipschütz's ulcer. Reassurance, local hygiene, wound care and pain control have cardinal roles in the management of the disease. Topical anesthetics as well as non-opioid and narcotic analgesics can be used to treat pain. Topical corticosteroids can be used(14,20). The use of systemic corticosteroid is frequently described but is not supported by evidence.

## Discussion of the Present Case:

In the present case, a pathogenetic role of other viruses, such as HSV and CMV, autoimmune diseases, immunodeficiency's were excluded. In the hypothesis of a manifestation of Behçet's disease, the expression of HLA-B51 and the presence of pathergy were evaluated, with negative results.

The role of EBV was confirmed by the PCR on the ulceral swab. The association between Lipschütz ulcer and SARS CoV-2 infection has been previously reported in the literature. In our case, the PCR for SARS CoV-2 on the ulceral swab was negative.

The presence of a secondary bacterial and fungal infection on the vulvar lesions required the use of antibiotics and fluconazole. In the anamnesis there is a previous episode of vulvar ulcers. This has led us to set up a careful immuno-rheumatological follow-up, even if for now there is no evidence of autoimmune or auto inflammatory diseases.

## Conclusions

Genital ulcers in adolescents are commonly referred to STIs, causing embarrassment and possibly compromising communication between the young patient and the doctors. However, vulvar ulcers can be caused by other conditions: our case shows that Lipschütz's ulcer, an unusual diagnosis in Pediatric ED, should not be neglected and must be suspected in presence of a concomitant viral infection. It remains a diagnosis of exclusion: if episodes recur, careful follow-up is needed to rule out other causes, such as autoimmune or auto inflammatory diseases.

**Informed Consent Statement:** written informed consent to publication has been obtained from the parents on behalf of the patient.

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