Presentation, causes and disease duration of Lipschütz’s acute vulvar ulcer: a systematic review

Stefano A. Vismara, MD1• Sebastiano A. G. Lava, MD2• Lisa Kottanattu, MD1• Giacomo D. Simonetti, MD1,3• Lorenzo Zgraggen, MD1• Caterina M. Clericetti, MD4• Mario G. Bianchetti, MD1,3• Gregorio P. Milani, MD1,5,6

1 Pediatric Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; 2 Cardiology Unit, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois, and University of Lausanne, Lausanne, Switzerland; 3 Università della Svizzera Italiana, Lugano, Switzerland; 4 Department of Obstetrics and Gynecology, Ospedale Regionale, Lugano, Switzerland; 5 Pediatric Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 6 Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy.

• These two authors equally contributed to the study

Correspondence: Gregorio P Milani, Pediatric unit, Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, via della Commenda 9, 20122 Milan, Italy. Phone: +390255032266, Email: milani.gregoriop@gmail.com

Email address of all authors

Stefano A. Vismara: drvismara@gmail.com
Sebastiano A. G. Lava: webmaster@sebastianolava.ch
Lisa Kottanattu: lisa.kottanattu@eoc.ch
Giacomo D. Simonetti: giacomo.simonetti@eoc.ch
Lorenzo Zgraggen: lollozgr@gmail.com
Caterina M. Clericetti: caterinaclericetti@gmail.com
Mario G. Bianchetti: mario.bianchetti@usi.ch
Gregorio P. Milani: milani.gregoriop@gmail.com

List of abbreviations: none
Abstract

In previously healthy subjects, vulvar ulcers are mostly caused by sexually transmitted microorganisms. Lipschütz’s acute vulvar ulceration, first reported in 1912, is a non-sexually acquired condition characterized by sudden onset of a few genital ulcers. We systematically review presentation, underlying causes and disease duration of Lipschütz’s ulceration. Comprehensive source of Excerpta Medica, National Library of Medicine and Web of Science databases was performed. Reports including cases of apparently previously healthy females affected by Lipschütz’s ulceration were selected a predefined database was used to extract data on demographics, history, clinical and microbiological findings, and treatment. The search disclosed 158 cases. Almost 90% of cases were ≤20 years of age and sexually inactive. Lesions were usually one to about three, painful, ≥10 mm large, well-delimited, with a fibrinous and necrotic center and a symmetric distribution. Voiding disorders and enlarged inguinal lymph nodes were observed in a large subset of cases. Canker sores were noted in 10% of patients. Lipschütz’s vulvar ulceration occurred concomitantly with an infectious disease in 139 cases. Infectious mononucleosis syndrome (N=40) was the most frequently detected well-defined infection, followed by mycoplasma species infections (N=11). The disease resolved after ≤3 weeks. CONCLUSIONS: Lipschütz’s ulceration mainly affects both sexually inactive and, less frequently, sexually active subjects ≤20 years of age, presents with ≤3 vulvar ulcers, resolves without recurrences within 3 weeks and is temporarily associated with an infection, most frequently a flu-like illness or an infectious mononucleosis syndrome.

Key words: adolescents; genital ulcers; gynecology; Lipschütz’s ulcers; non-sexually transmitted vulvar ulcers; sexually transmitted disease; voiding disturbance; urine
Introduction

In previously apparently healthy subjects, vulvar ulcers are mostly caused by sexually transmitted microorganisms such as treponema pallidum, herpes simplex virus and, more rarely, some serovars of chlamyphilia trachomatis. Occasionally, primary infection with human immunodeficiency virus also presents with vulvar ulcers. Noninfectious etiologies of vulvar ulcers include autoimmune conditions such as Behçet’s disease, Crohn's disease, cancer (such as leukemia), fixed drug reactions and trauma.\(^1,2\)

Lipschütz’s acute vulvar ulceration, first reported in Vienna by Benjamin Lipschütz (1878-1931) in 1912 as “Ulcus vulvae acutum (virginis)” or “Ulcus pseudovenereum”,\(^3\) is a non-sexually acquired condition, which is characterized by a sudden onset of a few necrotic and painful genital ulcers.\(^1,2,4\) Self-resolution without scarring and relapses is the usual course. Available reports state that Lipschütz’s acute vulvar ulceration may be triggered by Epstein-Barr virus, cytomegalovirus, mycoplasma species and toxoplasma gondii.\(^4\)

We recently managed a child with Lipschütz’s acute vulvar ulceration\(^5\) and noted that existing narrative reviews mention it only in passing.\(^1,3,4\) Furthermore, the condition has never been systematically assessed.\(^5\) Hence, we undertook an inventory of all cases Lipschütz’s ulcer in the literature. The aim of this analysis was to investigate clinical presentation, underlying causes, disease duration and efficacy of treatment with systemic corticosteroids.

Methods

Literature Search Strategy

A systematic review of reports including cases of apparently previously healthy females affected by Lipschütz’s vulvar ulceration was performed using the PRISMA guidelines.\(^6\) The following databases were searched: Excerpta Medica, the National Library of Medicine and
Web of Science. The terms “Lipschütz(‘s) ulcer(ation)”, “Ulcus pseudovenereum” or “ulcus vulvae (acutum)” were used. Reports published after 1965 up to June 2019 in Spanish, Portuguese, Italian, German, French, English or Dutch were eligible. The literature search and the data extraction were carried out by two investigators [S.A.V. and M.G.B.] independently. Personal files and the bibliography of each identified report were also screened. Disagreements were resolved by discussion until consensus.

Selection criteria – data extraction – completeness of reporting

Full-length articles or letters were considered. We retained the diagnosis of Lipschütz’s vulvar ulceration in previously healthy and apparently immunocompetent subjects with an isolated flare of abrupt beginning vulvar swelling and few, rather large ulcers. Sexual inactivity was not a prerequisite for the diagnosis. However, patients with a sexually transmitted infection were excluded. Cases with noninfectious causes of vulvar ulcers such as Behçet’s disease or Crohn's disease, cancer, cutaneous drug reactions or trauma were also excluded. Cases presenting with both genital and canker sores, i.e. small, painful ulcers inside the mouth, were included only after carefully excluding the diagnosis of Behçet’s disease. Finally, patients with past history of genital ulcers, immunodeficiency or affected by a chronic inflammatory condition were not considered.

Data were extracted using piloted forms and transcribed into a predefined dedicated database. The data extracted from each case meeting study criteria were demographics, history including data on sexual activity (with or without vaginal intercourse), general and local clinical findings, urinary symptoms, treatment (with emphasis on systemic corticosteroids), disease duration (defined as time to recovery of ulcers), possible association with an infectious disease and microbiological studies. Authors of original articles were sometimes contacted to provide missing data or verify the accuracy of reported information.
Completeness of included case reports was judged using the following 6 components:

1. Detailed description of physical findings;
2. Reporting of acute intercurrent illnesses temporally associated with vulvar ulceration;
3. Information on sexual activity;
4. Testing for infectious agents possibly associated with vulvar ulceration;
5. Management (with emphasis on systemic steroids);
6. Disease duration, outcome and follow up.

Each component was rated as 0, 1 or 2 and the reporting quality was graded according to the sum of each item as high (≥9) or low.

Statistical analysis

Continuous data (i.e. information that can be measured on a continuum or scale) are presented as median and interquartile range, categorical data (i.e. information that can be divided into groups) as relative frequency and percentage. The Cohen’s index was used to assess the agreement between investigators on the application of the inclusion and exclusion criteria, the Fisher’s exact test to compare categorical variables and the Kruskal-Wallis test to compare continuous variables. Statistical significance was assigned at P<0.05. Because this was a review of the literature, the project did not require approval by an institutional review board.

Results

Search Results

The literature search process is summarized in Figure 1. The chance-adjusted agreement between the two investigators on the application of inclusion and exclusion criteria was 0.90. For the final analysis, we retained 112 reports published between 1966 and 2019 in English (N = 62), Spanish (N=28), French (N=10), German (N=6), Italian (N=3) and Portuguese (N=3). They had been reported from the following continents: Spain (N=30); France, N=11; Portugal, N=8; Germany, N=5; Italy, N=4; United Kingdom,
N=3; Turkey, N=3; Switzerland, N=2; Belgium, N=1; Cyprus, N=1; Hungary, N=1; Norway, N=1; Netherlands, N=1; Russia, N=1; Slovenia, N=1; Sweden, N=1), 28 from America (United States, N=19; Chile, N=3; Brazil, N=2; Mexico, N=2; Canada, N=1; Uruguay. N=1), five from Africa (Morocco, N=4), three from Asia (Japan, N=2; India, N=1) and two from Oceania (Australia, N=1; New Zealand, N=1).

The included articles individually described 158 patients. Reporting completeness was high in 103 and low in the remaining 55 cases.

Findings

Presentation, course, management

The characteristics of the 158 patients appear in table 1. Almost 90 percent of them were ≤20 years of age and sexually inactive. Information on ethnicity was often (31%) missing. The vast majority (84%) of cases with this information was white. Lesions were usually (≥80% of cases) one to about three, painful, ≥10 mm large, well-delimited, with a fibrinous, necrotic or purulent center and often (45%) a symmetric mirrorlike vulvar distribution\(^1\).

Voiding disorders (32%) and enlarged inguinal lymph nodes were observed in a large subset (24%) of cases. Canker sores were noted in 10% of patients. The disease resolved on average after 15 days. A duration of >28 days was observed in about 10% of cases. No recurrence was reported.

Lipschütz’s vulvar ulceration occurred concomitantly with an infectious disease in (88%) of the 158 cases (table 2): a flu-like syndrome in 79 and a well-defined infection in 56 cases. Testing for acute Epstein-Barr virus infection was performed and found to be negative in 61 of the cases presenting with a flu-like syndrome. Epstein-Barr infectious mononucleosis syndrome was the most frequently detected well-defined (in many cases, the virus was also

\(^1\) The term «kissing pattern» is frequently used to denote this appearance.
found in genital lesions) underlying condition (N=38), followed by mycoplasma species (N=11) infections. No case was found to be associated with Toxoplasma gondii. Only 48 cases (12%) were not associated with any symptom of infection. Age and disease duration were not statistically different in cases associated with a flu-like syndrome, in cases associated with infectious mononucleosis syndrome, in cases associated with a mycoplasma infection and in cases not associated with further well-defined infections.

Reassurance, local hygiene, wound care, and pain control were the management in all cases. Information on disease duration was available in 23 cases (14 [13-18] years of age) treated with corticosteroids and in 98 of the remaining cases (14 [12-17] years of age): the disease duration was significantly (P<0.01) shorter in patients without (15 [10-21] days) as compared to those with (22 [18-29] days) corticosteroids. Despite various efforts, it was not possible to compare the clinical severity of Lipschütz’s vulvar ulceration in patients without and with corticosteroids due to the limited available information.

**Prevalence of Lipschütz’s vulvar ulceration among subjects with acute vulvar ulcers**

We found two retrospective case series describing each 110 and 273 unselected patients presenting with acute vulvar ulcers. The final diagnosis of Lipschütz’s vulvar ulceration was made in 33 (30%) respectively 98 (36%) of the cases.

**Discussion**

This is the first systematic review on Lipschütz’s acute vulvar ulceration. The results reveal that this condition is diagnosed clinically, occurs worldwide and mainly affects both sexually inactive and, less frequently, active subjects ≤20 years of age; it usually presents with ≤3 large (≥10 mm) vulvar ulcers that are typically painful, well-delimited, with a fibrinous, necrotic or purulent center and often a mirrorlike vulvar distribution; it tends to resolve without recurrence within 3 weeks; the majority of cases of Lipschütz’s acute vulvar
ulceration are temporarily associated with an infection, most frequently a flu-like illness or an infectious mononucleosis syndrome.

The prevalence of vulvar ulcers is unknown. The results of two case series suggest that approximately every third patient presenting with acute onset of vulvar ulcers is affected by Lipschütz’s vulvar ulceration.³⁰,¹⁰⁸

Benjamin Lipschütz first speculated that this condition is infection-associated.³ Our data show that the vast majority of cases are associated either with a flu-like or an infectious mononucleosis syndrome. More rarely, Lipschütz’s acute vulvar ulceration was associated with a mycoplasma organism. Toxoplasmosis is considered an alternative etiology of a mononucleosis-like illness but the present data point out that this infection currently plays a little, if any, role in the Lipschütz’s vulvar ulceration.

Reassurance, local hygiene, wound care, and pain control are the mainstay of management of this benign and self-remitting condition. Systemic corticosteroids are often prescribed in infectious mononucleosis. Generally accepted indications include autoimmune hemolytic anemia, meningitis, seizures, symptomatic thrombocytopenia and especially incipient upper airway obstruction.¹¹⁹ This analysis does not support the prescription of these drugs in this condition because they might even prolong the disease duration.

The mechanisms underlying Lipschütz’s vulvar ulceration are still unknown. The condition develops before the full resolution of the associated infectious disease. Furthermore, Epstein-Barr virus was very often detected in genital lesions of cases associated with infectious mononucleosis. It is therefore speculated, that Lipschütz’s ulcers directly result from the genital invasion of the responsible microorganism. Males can also be affected, although more rarely, by Lipschütz’s genital ulcers in the form of scrotal or penile ulcers.¹²⁰,¹²¹
There are limitations and strengths that should be noted when reading this communication. The major limitation results from the small number of reported cases, sometimes without or with a short follow-up. Second, the mechanisms by which some females affected by a flu-like syndrome or infectious mononucleosis develop acute genital ulcers are so far undemonstrated. Finally, since therapeutic recommendations can be uneasily inferred by pooling individual case reports, suggested therapeutic recommendations arise from low-quality evidence. The most relevant strength of the study relates to the comprehensive and exhaustive literature search, which aimed at surveying the entire literature on Lipschütz’s vulvar ulceration. It complements the results of a report published in 2016, which included 79 cases.

In conclusion, acute Lipschütz’s vulvar ulceration affects adolescent girls or young women and is characterized by one to about three large (≥10 mm), deep and painful ulcerations with a partially symmetrical appearance ("kissing pattern"). In addition to local hygiene, wound care and pain control, explanation and reassurance regarding the non-sexual transmission and the self-limited course are of paramount importance. Misdiagnosing the condition may result in unnecessary medical management and, more importantly, apprehension (table 3).

Compliance with Ethical Standards

• Disclosure of potential conflict of interest: none for all authors.

• Research involving human participants and/or animals: not applicable (review study).

• Funding: none.

Authors’ contribution

SAG Lava and GPM conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. SAV and MGB conceptualized and designed the study, collected data, carried out the initial analyses, drafted the initial manuscript and revised the manuscript.
LK, GDS, LZ and CMC contributed to study design and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Figures - Legends**

**Figure 1**

Lipschütz’s acute vulvar ulceration. Flowchart of the literature search process.