

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

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**List of abbreviations:** none

43 **Abstract**

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

64

65 **Key words:** adolescents; genital ulcers; gynecology; Lipschütz's ulcers; non-sexually  
66 transmitted vulvar ulcers; sexually transmitted disease; voiding disturbance; urine

67

## 68 **Introduction**

69 In previously apparently healthy subjects, vulvar ulcers are mostly caused by sexually  
70 transmitted microorganisms such as *treponema pallidum*, herpes simplex virus and, more  
71 rarely, some serovars of *chlamydomphila trachomatis*. Occasionally, primary infection with  
72 human immunodeficiency virus also presents with vulvar ulcers. Noninfectious etiologies of  
73 vulvar ulcers include autoimmune conditions such as Behçet's disease, Crohn's disease,  
74 cancer (such as leukemia), fixed drug reactions and trauma.<sup>1,2</sup>

75 Lipschütz's acute vulvar ulceration, first reported in Vienna by Benjamin Lipschütz  
76 (1878-1931) in 1912 as "Ulcus vulvae acutum (virginis)" or "Ulcus pseudovenereum",<sup>3</sup> is a  
77 non-sexually acquired condition, which is characterized by a sudden onset of a few necrotic  
78 and painful genital ulcers.<sup>1,2,4</sup> Self-resolution without scarring and relapses is the usual  
79 course. Available reports state that Lipschütz's acute vulvar ulceration may be triggered by  
80 Epstein-Barr virus, cytomegalovirus, mycoplasma species and *toxoplasma gondii*.<sup>4</sup>

81 We recently managed a child with Lipschütz's acute vulvar ulceration<sup>5</sup> and noted that  
82 existing narrative reviews mention it only in passing.<sup>1,3,4</sup> Furthermore, the condition has  
83 never been systematically assessed.<sup>5</sup> Hence, we undertook an inventory of all cases  
84 Lipschütz's ulcer in the literature. The aim of this analysis was to investigate clinical  
85 presentation, underlying causes, disease duration and efficacy of treatment with systemic  
86 corticosteroids.

87

## 88 **Methods**

### 89 **Literature Search Strategy**

90 A systematic review of reports including cases of apparently previously healthy females  
91 affected by Lipschütz's vulvar ulceration was performed using the PRISMA guidelines.<sup>6</sup> The  
92 following databases were searched: Excerpta Medica, the National Library of Medicine and

93 Web of Science. The terms “Lipschütz(‘s) ulcer(ation)”, “Ulcus pseudovenereum” or “ulcus  
94 vulvae (acutum)” were used. Reports published after 1965 up to June 2019 in Spanish,  
95 Portuguese, Italian, German, French, English or Dutch were eligible. The literature search  
96 and the data extraction were carried out by two investigators [S.A.V. and M.G.B.]  
97 independently. Personal files and the bibliography of each identified report were also  
98 screened. Disagreements were resolved by discussion until consensus.

### 99 **Selection criteria – data extraction – completeness of reporting**

100 Full-length articles or letters were considered. We retained the diagnosis of Lipschütz’s  
101 vulvar ulceration in previously healthy and apparently immunocompetent subjects with an  
102 isolated flare of abrupt beginning vulvar swelling and few, rather large ulcers.<sup>2</sup> Sexual  
103 inactivity was not a prerequisite for the diagnosis. However, patients with a sexually  
104 transmitted infection were excluded. Cases with noninfectious causes of vulvar ulcers such as  
105 Behçet’s disease or Crohn’s disease, cancer, cutaneous drug reactions or trauma were also  
106 excluded. Cases presenting with both genital and canker sores, i.e. small, painful ulcers inside  
107 the mouth, were included only after carefully excluding the diagnosis of Behçet’s disease.  
108 Finally, patients with past history of genital ulcers, immunodeficiency or affected by a  
109 chronic inflammatory condition were not considered.<sup>1,2,4</sup>

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

117 Completeness of included case reports was judged using the following 6 components<sup>7</sup> 1.  
118 detailed description of physical findings; 2. reporting of acute intercurrent illnesses  
119 temporally associated with vulvar ulceration; 3. information on sexual activity; 4. testing for  
120 infectious agents possibly associated with vulvar ulceration; 5. management (with emphasis  
121 on systemic steroids); 6. disease duration, outcome and follow up. Each component was rated  
122 as 0, 1 or 2 and the reporting quality was graded according to the sum of each item as high  
123 ( $\geq 9$ ) or low.

## 124 **Statistical analysis**

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

133

## 134 **Results**

### 135 **Search Results**

136 The literature search process is summarized in Figure 1. The chance-adjusted agreement  
137 between the two investigators on the application of inclusion and exclusion criteria was 0.90.  
138 For the final analysis, we retained 112 reports published between 1966 and 2019 in English  
139 (N = 62), Spanish (N=28), French (N=10), German (N=6), Italian (N=3) and Portuguese  
140 (N=3).<sup>5,8-118</sup> They had been reported from the following continents: ~~73~~ 74 from Europe  
141 (Spain, N=30; France, N=11, Portugal, N=8; Germany, N=5; Italy, N=4; United Kingdom,

142 N=3; Turkey, N=3; Switzerland, N=2; Belgium, N=1; Cyprus, N=1; Hungary, N=1; Norway,  
143 N=1; Netherlands, N=1; Russia, N=1; Slovenia, N=1; Sweden, N=1), 28 from America  
144 (United States, N=19; Chile, N=3; Brazil, N=2; Mexico, N=2; Canada, N=1; Uruguay, N=1),  
145 five from Africa (Morocco, N=4 5), three from Asia (Japan, N=2; India, N=1) and two from  
146 Oceania (Australia, N=1; New Zealand, N=1).

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

## 149 **Findings**

### 150 **Presentation, course, management**

151 The characteristics of the 158 patients appear in table 1. Almost 90 percent of them were  
152  $\leq 20$  years of age and sexually inactive. Information on ethnicity was often (31%) missing.  
153 The vast majority (84%) of cases with this information was white. Lesions were usually  
154 ( $\geq 80\%$  of cases) one to about three, painful,  $\geq 10$  mm large, well-delimited, with a fibrinous,  
155 necrotic or purulent center and often (45%) a symmetric mirrorlike vulvar distribution<sup>1</sup>.  
156 Voiding disorders (32%) and enlarged inguinal lymph nodes were observed in a large subset  
157 (24%) of cases. Canker sores were noted in 10% of patients. The disease resolved on average  
158 after 15 days. A duration of  $>28$  days was observed in about 10% of cases. No recurrence  
159 was reported.

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

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<sup>1</sup> The term «kissing pattern» is frequently used to denote this appearance.

165 found in genital lesions) underlying condition (N=38), followed by mycoplasma species  
166 (N=11) infections. No case was found to be associated with *Toxoplasma gondii*. Only 48 19  
167 cases (12%) were not associated with any symptom of infection. Age and disease duration  
168 were not statistically different in cases associated with a flu-like syndrome, in cases  
169 associated with infectious mononucleosis syndrome, in cases associated with a mycoplasma  
170 infection and in cases not associated with further well-defined infections.

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

### 178 **Prevalence of Lipschütz's vulvar ulceration among subjects with acute vulvar ulcers**

179 We found two retrospective case series describing each 110 and 273 unselected patients  
180 presenting with acute vulvar ulcers.<sup>90,108</sup> The final diagnosis of Lipschütz's vulvar ulceration  
181 was made in 33 (30%) respectively 98 (36%) of the cases.<sup>90,108</sup>

182

## 183 **Discussion**

184 This is the first systematic review on Lipschütz's acute vulvar ulceration. The results  
185 reveal that this condition is diagnosed clinically, occurs worldwide and mainly affects both  
186 sexually inactive and, less frequently, active subjects  $\leq 20$  years of age; it usually presents  
187 with  $\leq 3$  large ( $\geq 10$  mm) vulvar ulcers that are typically painful, well-delimited, with a  
188 fibrinous, necrotic or purulent center and often a mirrorlike vulvar distribution; it tends to  
189 resolve without recurrence within 3 weeks; the majority of cases of Lipschütz's acute vulvar

190 ulceration are temporarily associated with an infection, most frequently a flu like illness or an  
191 infectious mononucleosis syndrome.

192 The prevalence of vulvar ulcers is unknown. The results of two case series suggest that  
193 approximately every third patient presenting with acute onset of vulvar ulcers is affected by  
194 Lipschütz's vulvar ulceration.<sup>90,108</sup>

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

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

207 The mechanisms underlying Lipschütz's vulvar ulceration are still unknown. The  
208 condition develops before the full resolution of the associated infectious disease.  
209 Furthermore, Epstein-Barr virus was very often detected in genital lesions of cases associated  
210 with infectious mononucleosis. It is therefore speculated, that Lipschütz's ulcers directly  
211 result from the genital invasion of the responsible microorganism. Males can also be affected,  
212 although more rarely, by Lipschütz's genital ulcers in the form of scrotal or penile  
213 ulcers.<sup>120,121</sup>



214 There are limitations and strengths that should be noted when reading this communication.  
215 The major limitation results from the small number of reported cases, sometimes without or  
216 with a short follow-up. Second, the mechanisms by which some females affected by a flu-like  
217 syndrome or infectious mononucleosis develop acute genital ulcers are so far  
218 undemonstrated. Finally, since therapeutic recommendations can be uneasily inferred by  
219 pooling individual case reports, suggested therapeutic recommendations arise from low-  
220 quality evidence. The most relevant strength of the study relates to the comprehensive and  
221 exhaustive literature search, which aimed at surveying the entire literature on Lipschütz's  
222 vulvar ulceration. It complements the results of a report published in 2016, which included 79  
223 cases.<sup>122</sup>

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

231

### 232 **Compliance with Ethical Standards**

- 233 • **Disclosure of potential conflict of interest:** none for all authors.
- 234 • **Research involving human participants and/or animals:** not applicable (review study).
- 235 • **Funding:** none.

236

### 237 **Authors' contribution**

238 SAG Lava and GPM conceptualized and designed the study, drafted the initial manuscript,  
239 and reviewed and revised the manuscript.

240 SAV and MGB conceptualized and designed the study, collected data, carried out the initial  
241 analyses, drafted the initial manuscript and revised the manuscript.

242 LK, GDS, LZ and CMC contributed to study design and supervised data collection, and  
243 critically reviewed the manuscript for important intellectual content.  
244 All authors approved the final manuscript as submitted and agree to be accountable for all  
245 aspects of the work.

246

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## 566 **Figures - Legends**

### 567 **Figure 1**

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