

LIPSCHÜTZ ULCERS: A LITERATURE REVIEW BASED ON 79 CASES

*Balaji Govindan^{1,2}

1. Department of STD, Government Mohan Kumaramangalam Medical College, Salem, India

2. The Tamil Nadu Dr. M.G.R. Medical University, Chennai, India

*Correspondence to ezhilbalaji@gmail.com

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ABSTRACT

Lipschütz ulcers (LU) are acute genital ulcers that occur in women. These ulcers are painful and cause enormous emotional stress to the affected person. It is also of the utmost important for the treating physician to differentiate LU from sexually transmitted ulcers like syphilis, herpes genitalis, and chancroid. The aetiology of LU is not known but recent studies have proposed that it is associated with viral infections, such as the Epstein-Barr virus (EBV) and the cytomegalovirus (CMV), as well as other bacterial infections, such as mycoplasma. Using the PubMed database, articles published between the years of 2003 and 2015 were collected. A total of 20 studies (N=79) fulfilled the inclusion criteria and were selected for analysis. All the published articles were reviewed and relevant data extracted. The age range of patients included in these studies was 17 months to 79 years old. The causative organism was unknown in 50 patients (63%), EBV in 13 patients (16%), *Mycoplasma pneumoniae* in 4 patients (5%), CMV infections in 4 patients (5%), *Mycoplasma fermentans* in 3 patients (3.7%), mumps in 1 patient (1.2%), paratyphoid fever in 1 patient (1.2%), parvovirus B19 in 1 patient (1.2%), co-infection of influenza B and adenovirus in 1 patient (1.2%), and co-infection of EBV and CMV in 1 patient (1.2%). Even though viral and bacterial infections had been linked with LU in many of the patients included in these studies, the aetiology remains unknown. Hence, more research is warranted to ascertain the aetiological factors of LU.

Keywords: Lipschütz ulcers (LU), Epstein-Barr virus (EBV), cytomegalovirus (CMV).

INTRODUCTION

In 1912, the Austrian dermatologist Benjamin Lipschütz first described acute genital ulcers in adolescent girls without any evidence of sexually transmitted infections.¹ Lipschütz ulcers (LU) is a term synonymous with a range of others, including acute genital ulcers, reactive non-sexually related acute genital ulcers, ulcus vulvae acutum, acute vulval ulcers, and primary aphthous ulcers. It is an entity that presents as acute ulcers of the labia minora or majora, introitus, fourchette, and vestibule, with systemic symptoms such as fever, tonsillitis, lymphadenopathy, and diarrhoea. LU is a diagnosis of exclusion. It mimics a wide spectrum of diseases ranging from infective causes (syphilis, herpes genitalis, and chancroid), to inflammatory conditions (Behçet's disease, Crohn's disease), and also trauma.

Hence, a careful review of a patient's history, meticulous clinical examination, and thorough investigations are necessary to diagnose LU.

Table 1: Diagnostic criteria for Lipschütz ulcers.

| Major diagnostic criteria | |
|---------------------------|---|
| 1. | Presents with a first flare of acute genital ulcer |
| 2. | Aged <20 years |
| 3. | Absence of sexual contact in the past 3 months |
| 4. | Absence of immunodeficiency |
| 5. | Acute onset of the genital ulcer and healing within 6 weeks |
| Minor diagnostic criteria | |
| 1. | Single or multiple deep, painful ulcers, with a necrotic centre |
| 2. | Bilateral 'kissing pattern' |

Table 2: Synopsis of the analysed cases.

| Author and year of publication | Publication type | No. of Cases | Causes |
|---|------------------------|--------------|---|
| García et al. ² 2016 | Case report | 1 | Unknown |
| Horie ³¹ 2015 | Case report | 3 | <i>Mycoplasma fermentans</i> |
| Haidari et al. ³² 2015 | Case report | 1 | Influenza B, adenovirus |
| Barrett et al. ¹⁴ 2015 | Case series | 7 | EBV |
| Vieira-Baptista et al. ⁸ 2016 | Retrospective analysis | 33 | CMV (3 patients), <i>Mycoplasma pneumoniae</i> (3 patients), EBV (2 patients), PVB19 (1 patient), unknown (24 patients) |
| Delgado-García et al. ³³ 2014 | Case report | 1 | Unknown |
| Kinyó et al. ²⁰ 2014 | Case report | 2 | Unknown |
| Ozuguz et al. ¹⁴ 2013 | Case report | 1 | EBV, CMV |
| Archel et al. ⁶ 2013 | Case report | 1 | EBV |
| Brinca et al. ¹¹ 2012 | Case report | 1 | Unknown |
| Truchuelo et al. ³⁴ 2012 | Case report | 2 | Unknown |
| Rosman et al. ³⁵ 2012 | Case series | 12 | Unknown (11 patients), <i>Mycoplasma pneumoniae</i> , (1 patient) |
| Sárdy et al. ¹³ 2011 | Case report | 1 | EBV |
| Chanal et al. ⁹ 2010 | Case report | 1 | Mumps |
| Alés-Fernández et al. ⁷ 2010 | Case report | 3 | Unknown |
| Martín et al. ¹⁰ 2008 | Case report | 1 | CMV |
| Hernández-Núñez et al. ²⁵ 2008 | Case series | 4 | Unknown |
| Bhat RM, Furtado S ¹⁶ 2007 | Case report | 1 | Unknown |
| Halvorsen et al. ¹² 2006 | Case report | 2 | EBV |
| Pelletier et al. ³⁶ 2003 | Case report | 1 | Paratyphoid |

EBV: Epstein-Barr virus; PVB19: parvovirus B19; CMV: cytomegalovirus.

After ruling out sexually transmitted infections, inflammatory conditions, and systemic illness, the diagnosis of LU is established by five major and one of two minor criteria,² as shown in [Table 1](#). Almost all of the published literature on LU is restricted to case reports and case series.³ The aetiology of this disease remained obscure until the 1960s, when the first clues revealed the involvement of viruses or bacteria. Earlier, Lipschütz assumed that LU was caused by auto-inoculation with Döderlein's bacillus,⁴ but studies have since revealed that LU is associated with viruses such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and mumps, as well as bacteria such as *salmonella*, *Mycoplasma pneumoniae*, and *Mycoplasma fermentans*. Not only do infections cause LU, it can also be caused by drugs, albeit rarely.⁵ This review of the published literature was conducted to discover the different organisms associated with LU.

METHODS

Search Strategy

A review of the literature was carried out using the PubMed database to collect all articles published about LU between the years of 2003 and 2015. 'Acute genital ulcers', 'Lipschütz ulcers', and 'non-sexually acquired genital ulcers', were the search keywords used to find the relevant articles (including case reports and series, reviews, and letters to the editor) about LU. Articles published in English which pertained to LU were included in the review.

Data Extraction

Studies were selected based on their titles and abstracts. Complete articles were retrieved for detailed analysis. Studies included were individually reviewed to identify data related to age, sexual history, clinical features, histopathology, and other

relevant investigations, as well as treatment and the associated organisms.

RESULTS

Articles published in English between 2003 and 2015 were selected for the review resulting in 20 studies involving 79 cases. A synopsis of the studies included in the review are described in [Table 2](#).

The reporting of various aspects of the cases was inconsistent in a few of the studies. For example, the demographic aspects, serology, polymerase chain reaction, blood count, and histopathological evaluation was not described in all cases.

The age of the patients was either in the second or third decade except in cases reported in the Archel et al.⁶ study (17 months), the Alés-Fernández et al.⁷ study (2 months), and in the Vieira-Baptista et al.⁸ study (79 years). None of the patients had provided their sexual history prior to the onset of genital ulcers except for the patients in the studies by Chanal et al.,⁹ Martín et al.,¹⁰ Brinca et al.,¹¹ and Halvorsen et al.¹² No patient history suggestive of trauma or child sexual abuse was identified.

Clinical Manifestations

More than 90% of the patients had multiple ulcers on the labium majora and minora. One patient had ulcers involving the perineum.¹² Tonsillitis was the most common association found in patients.^{6,10,12,13} Morbilliform rash was another associated finding, as specified by Halvorsen et al.¹² and bilateral parotitis was reported by Chanal et al.⁹ in their patient. Hepatomegaly and polyarthralgia was reported in one patient by Sárdy et al.¹³ while García et al.² outlined the presence of limb haematomas in their study.

Histopathological Evaluation

Skin biopsy is not recommended as a first-line investigation because in most of the patients it revealed non-specific mixed inflammatory infiltrate in dermis. However, a skin biopsy of the patients involved in the Sárdy et al.¹³ study revealed neutrophilic predominant infiltrate,¹³ in the Halvorsen et al.¹² study it revealed a leukocytoclastic vasculitic picture, and in the Barrett et al.¹⁴ study it revealed a lymphocytic arteritis picture.

Serology

Testing for HIV, syphilis, herpes simplex virus (HSV), hepatitis B, and hepatitis C was negative

in all of the patients. Specific serology in certain cases was carried out to identify EBV, CMV, mumps, mycoplasma, influenza B, parvovirus B19 (PVB19), and paratyphoid. The results revealed the association of the following organisms in the patients: EBV in 13 patients (16%), CMV in 4 (5%), *M. pneumoniae* in 4 (5%), *M. fermentans* in 3 (3.7%), mumps in 1 (1.2%), PVB19 in 1 (1.2%), paratyphoid in 1 (1.2%), co-infection of influenza B and adenovirus in 1 (1.2%), co-infection of EBV and CMV in 1 (1.2%), and the aetiology could not be confirmed in 50 patients (63%). Further studies are needed to elucidate these associations.

Treatment

Since LU are reactive ulcers, specific aetiological treatment is unnecessary. LU are self-limiting and generally recover spontaneously. Hence, patients in the studies were treated symptomatically with analgesics, topical steroids, and antibiotics. Daily treatment with topical steroids has been shown to heal the ulcer within a 2-week period. Patients in the Chanal et al.⁹ and Ozuguz et al.¹⁵ studies experienced a complete recovery without any treatment. Only patients in the Bhat and Furtado¹⁶ and Sárdy et al.¹³ studies were treated with systemic steroids. None of the patients had relapses at a 3-year follow-up, except for one patient reported by Healy and Thornhill⁵ and another by Martín et al.¹⁰

DISCUSSION

This review describes and analyses the clinical presentations and the aetiological agents associated with LU for 79 reported patients from 2003–2015.

LU, or non-sexually related acute genital ulcerative disease, occurs in women. It is characterised by a rapid onset of ulcers on the labia minora or majora, introitus, or fourchette; usually multiple, and it can be associated with fever and inguinal painful lymphadenopathy. Generally, the natural course is benign, with spontaneous regression within a few weeks. The exact incidence of LU is unknown and the average age reported in a large series of patients by Farhi et al.¹⁷ was 16.6 years.

The pathogenesis of LU still remains an enigma. It could develop from a haematogenous spread or autoinoculation, although one hypothesis suggests that it could arise from a hypersensitivity reaction to a viral or bacterial infection, leading to the deposition of immune complexes in the dermal vessels, which in turn activates the complement

system, resulting in microthrombi formation and subsequent tissue necrosis.^{18,19}

Although the cause for LU has previously remained unknown, recent studies have revealed its link to an infective aetiology; mainly viral and bacterial. This review has affirmed the following organisms associated with LU: EBV, CMV, *M. pneumoniae*, *M. fermentans*, mumps, PVB19, paratyphoid, co-infection of influenza B and adenovirus, and co-infection of EBV and CMV. The unconfirmed aetiology in 50 of the patients remains unknown.

In EBV infections, apart from the pathomechanism mentioned above, ulcers could also be due to cytolysis as seen in herpes simplex infections.²⁰ Kinyó et al.²¹ have stressed the role of local immunoglobulin (Ig)A in the development of LU in his patients who had a partial IgA deficiency. The pathogenesis of LU due to other organisms like CMV, *M. pneumoniae*, *M. fermentans*, mumps, and paratyphoid is not yet elucidated.

LU can have flu-like symptoms, such as malaise, fever, myalgia, tonsillitis, and lymphadenopathy; with single or multiple deep and painful ulcers on the vulva, and with or without oedema of the labium majora and minora.²² LU may present with different morphological patterns; pseudo-vesicles, herpetiform ulceration, or ulcers with eschar.³ Very rarely, patients have skin nodules similar to erythema nodosum, and experience morbilliform rashes in the trunk.^{17,23} Apart from its classical clinical presentation, Török et al.²⁴ described three forms of LU:

- Gangrenous
- Chronic
- Military

LU has to be differentiated from other causes of genital ulcers such as HSV infection, genital aphthosis, and Behçet's disease (Table 3).

One has to be non-judgmental in their approach to patient care with acute genital ulcers. The clinical work-up starts with a sensitive sexual history, directed towards sexual activity and potential sexual abuse. Emphasis has to be given to the examination of ocular, neurologic, gastrointestinal, and genitourinary systems to rule out systemic disease such as Behçet's disease, cyclical neutropenia, and Crohn's disease. A complete oral and skin examination is always mandatory. Due to patient discomfort, speculum examination is not routinely performed.²⁵ Biopsy in most of the LU

patients included in the review showed non-specific mixed inflammatory infiltrate in dermis, except for patients in the Barret et al.¹⁴ and Halvorsen et al.¹² studies which revealed lymphocytic arteritis and a leukocytoclastic vasculitis picture, respectively. Hence, histopathology has limited diagnostic value in patients with LU.²⁶ The following laboratory investigations have been suggested for the evaluation of acute genital ulcers:

- A complete blood count to rule out anaemia, thrombocytopenia, and neutropenia
- The serum levels of iron, folate, and vitamin B12 measured
- A Gram stain to exclude chancroid;
- Polymerase chain reaction or culture to identify HSV
- Specific serology directed towards EBV, CMV, syphilis, and HIV
- Culture for *Lymphogranuloma venereum*
- A skin biopsy from the ulcer edge is advised for ulcers lasting for more than 3 or 4 weeks.³

Thus, diagnosis of LU is made only after excluding the other causes of vulvar ulcers: venereal and non-venereal infections, inflammatory diseases like Behçet's disease, and trauma.

The main aims of treatment are pain relief and ulcer healing. LU is a self-limiting condition, however treatment with a brief course of systemic corticosteroids (0.5 mg/kg of prednisolone for 1-2 weeks) may help to heal the ulcers.^{27,28} Generally it is thought that antiviral drugs have no role in the management of LU.²⁹ However, Bhat and Furtado¹⁶ reported a rapid improvement in symptoms following treatment with Azithromycin 500 mg and intramuscular betamethasone 8 mg both once daily for 3 days, metronidazole 400 mg three times daily for 5 days, followed by dapsone 8 mg once daily.

Table 3: Other causes to be ruled out before diagnosing Lipshütz ulcers.

| | |
|-------------------------------------|---|
| Sexually transmitted infections | Herpes simplex virus, syphilis, <i>Lymphogranuloma venereum</i> , Chancroid, HIV |
| Non-sexually transmitted infections | Epstein-Barr virus, cytomegalovirus, influenza B, paratyphoid |
| Systemic illness | Behçet's disease, Crohn's disease, cyclic neutropenia, iron, folate, vitamin B12 deficiency |
| Drugs | Non-steroidal anti-inflammatory |

Patients with LU require weekly follow-up until the ulcers have healed. The mean time for ulcer healing is reported as being between 16 and 21 days.³⁻⁵ Once the ulcer has healed, yearly follow-up is needed to rule out progression to systemic diseases like inflammatory bowel disease or Behçet's disease. In two case series by Farhi et al.¹⁷ and Huppert et al.,²³ 6% of the patients were eventually diagnosed with Behçet's disease. Recently, Carmine et al.³⁰ reported the recurrence of LU, twice within a 6-month period, in a 23-year-old woman.

A limitation of this study is its inclusion of published articles exclusively from the PubMed database, leading to a small sample size; therefore, a few other organisms associated with LU could have been missed. Other limitations include the fact that the majority of relevant PubMed studies that were searched for were carried out between the years of 2003 and 2015 which is why this date range was chosen for this review. This shorter date range could have resulted in a narrower breadth of experience. Also, as many of the reviewed papers did not record whether a scar was left from LU, conclusions cannot be drawn on the long-term

cosmetic effects of the condition such as scarring. Lastly, there is no recurrence of LU in the majority of studies as they assessed their patient on only one occasion and did not revisit at a later date. Therefore, assumptions cannot be made about the recurrence of LU using this information.

CONCLUSION

LU, in spite of their characteristic symptoms, are often misdiagnosed. The diagnosis is made by exclusion after ruling out sexually transmitted infections, autoimmune diseases, trauma, and other causes of genital ulcerations. LU is painful and troublesome to the affected patient and mystifying to the physician who treats them. It is vital for practicing dermatologists, paediatricians, general practitioners, and gynaecologists to be aware of this rare and challenging entity. Patients and their family members should be certain that:

- LU are not sexually transmitted
- Ulcers are self-limiting and heal spontaneously

More studies are required to determine the organisms associated with LU and the relevant guidelines to confirm a diagnosis.

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