Case report

Recurrent reactive non-sexually related acute genital ulcers: a risk factor for Behcet's disease?

Ilaria Brambilla[1], Alice Moiraghi[2], Carmen Guarracino[1], Carmelo Pistone[1], Enrico Tondina[2], Giovanna Riccipetitoni[2,3], Alessandro Raffaele[3], Silvia Cavaiuolo[3], Mirko Bertozzi[2,3], Valeria Brazzelli[4]

[1] Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [2] Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; [3] Pediatric Surgery Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [4] Dermatological Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Abstract. *Background and aim:* Lipschutz ulcers (LU) are idiopathic genital lesions characterized by the sudden appearance of painful, usually symmetric vulvar ulcers, typically occurring in sexually inactive adolescents. LU is a diagnosis of exclusion. As these lesions heal spontaneously, in the absence of tissue scarring, the therapy is mainly symptomatic and focuses on pain relief. Recurrence of LU associated with oral ulcers describes the clinical picture of complex aphthosis, which belongs to Behçet's disease (BD) pathological spectrum. Our work aims to analyze the correct diagnostic approach to recurrent aphthous, focusing on the importance of a multidisciplinary assessment and immunogenetic investigation to identify the subjects at risk of progression towards BD. *Methods:* We present the case of a 12-year-old non sexually active Italian girl who was diagnosed with LU. After 15 months, she presented recurrent reactive non sexually related acute genital ulcer associated with a history of oral aphthous. According to clinical features and anamnesis, complex aphthosis was diagnosed. For diagnostic purposes, she underwent an immunogenetic analysis that showed HLA-B51 positivity. *Results:* In the absence of clinical and laboratory criteria to define the risk of progression of complex aphtosis towards BD, we think that besides a strict follow-up, in pediatric patients with a suggestive clinical history, it is crucial to adopt a multidisciplinary approach, comprehensive of HLA investigation, in order to guarantee an early diagnosis and a prompt therapeutic intervention. *Conclusions*: In children and adolescents with genital ulcers, it is essential to consider all the possible differential diagnoses to undertake a timely and correct course of treatment. (www.actabiomedica.it)

Key words: acute genital ulcers, non-sexually transmitted genital ulcers, Lipschütz ulcers, ulcus vulvae acutum, recurrent aphtous ulcers, complex aphthosis, Behcet's disease, adolescents, children

Introduction

Lipschutz ulcers (LU), also named reactive non-sexually related acute genital ulcers (RNSRAGUs), are characterized by the sudden appearance of painful, usually symmetric vulvar "kissing ulcers" that typically occur in young, sexually inactive adolescents (mean age at diagnosis 16,6 years) (1).

Aphthous ulcers are discrete ulcers on non-keratinized mucosa with a yellow-gray fibrinous base and surrounding erythema that usually appear on the medial surface of the labia minora and are accompanied by dysuria. RNSRAGUs can be single or multiple lesions, with different morphological features: gangrenous (the most common form), chronic or relapsing, and miliar, i.e., pinhead-sized ulcers with inflammatory edges. Besides this morphological differentiation, the histological examination is non-specific and nondiagnostic (2).

The illness is characterized by acute onset of fever, chills, and malaise, followed by the appearance of aphthous ulcers that heal spontaneously in 7 to 10 days in the absence of tissue scarring; in case of major ulcers

(>1 cm), the healing process can last about 1-2 months (2). Oral aphtosis can be an associated symptom in about 70% of cases (3).

Even if the etiology of LU is still unclear, some reports have demonstrated a correlation with previous or concomitant acute infection with EBV, CMV, paratyphoid fever, influenza A, mycoplasma, and HIV (2).

The mechanisms that trigger the formation of aphthous lesions far from the site of the primary infection are poorly understood. It has been supposed that vulvar epithelium injury may be due to cytotoxic/toxin-mediated effects or an inflammatory/immune dysregulation (4). Due to the limited data available, it has been impossible to identify a single infectious agent linking all the cases; thus, 70% of vulvar ulcers are still considered idiopathic (5).

Ruling out other causes of genital ulcers, such as sexually transmitted diseases, Crohn's disease, BD, nutritional deficits, systemic diseases, drug-induced reactions, and lesions due to trauma, is fundamental, as LU is a diagnosis of exclusion.

The diagnostic workup for a patient with a vulvar ulcer should include an accurate anamnesis, a complete physical examination with particular attention to ocular, oral and genital mucosa, viral, bacterial, and fungal cultures to exclude an infectious etiology (HSV PCR and bacterial culture from swab specimen, smear for acid-fast bacilli, rapid streptococcal throat swab or antistreptolysin O titer, serological evaluation for EBV, CMV, Mycoplasma pneumoniae, HIV and syphilis), and a blood sample to check for infectious parameters. A biopsy can help rule out other conditions, but, as we said before, the histologic examination is not pathognomonic for LU (6).

Five major criteria plus 1 or 2 minor criteria are required for diagnosis, which should be applied only after excluding infectious etiology and systemic diseases.

Table 1. Diagnostic criteria for LU

Diagnostic criteria for LU
Major criteria:
- Age < 20 years
- First outbreak presentation of acute genital ulcer
- No sexual contact in the previous three months
- Abrupt onset and complete healing in 6 weeks
- Exclusion of immunodeficiency
Minor criteria:
- discrete painful ulcer(s) with a fibrinous and/or necrotic center
- "kissing pattern", symmetric specular vulvar lesions.

The therapy of LU focuses on pain relief and is symptomatic, as they have a spontaneous regression.

Local analgesics are the first-line therapy if symptoms are mild, while topical corticosteroids can be helpful in the healing process in case of moderate lesions; if the pain is not well controlled and the ulcers are severe, NSAIDs, opioid analgesics, together with systemic antibiotics and corticosteroids can be used. Hospitalization should be considered in case of severe pain, malaise and dysuria (7). It is essential for the pediatrician to reassure parents and patients that the ulcers are not sexually transmitted, and that complete healing is the rule.

Even if LU does not recur in most patients, relapse has been reported in up to 30% of cases, after about a year (3,4). A high recurrence of RNSRAGU associated with oral aphtosis describes the clinical picture of complex aphthosis, which belongs to the BD pathological spectrum (2).

Specifically, diagnosis of complex aphthosis requires:

1. the almost constant presence of 3 or more oral ulcers, or
2. recurrent oral and genital ulcers, and
3. exclusion of BD (8).

The progression rate of RNSRAGU and, thereby, of complex aphthosis towards a full-blown BD is unknown, and, currently, insufficient data are available. From the analysis of 3 case series, 6 to 20% of women who experienced a recurrence of orogenital ulcers were ultimately diagnosed with BD (3).

BD is an inflammatory disease with multisystemic involvement, characterized by a chronic relapsing course. The most prominent clinical manifestations are recurrent oral ulcerations, genital ulceration, and ocular inflammation, but also neurological, gastrointestinal, and articular involvement are reported with considerable frequency.

An international expert consensus has recently proposed new classification criteria for children with BD: three of 6 items shown in Table 2 are required to classify a patient as having pediatric BD (9).

BD is rare in pediatric age (<16 years occurs in 4-26% of patients), and its recognition relies substantially on clinical features and expert evaluation, mak-

ing the diagnosis extremely critical. BD diagnosis is even more challenging in children due to the long time interval between disease onset and the development of a clinical picture compatible with the diagnostic criteria (1, 10).

Most children and adolescents observed at the onset of BD present with oral and/or genital ulcers, but these symptoms do not fully satisfy BD classification criteria; thus, a diagnosis of "partial" BD is usually performed.

Unfortunately, no clinical and laboratory criteria are available to define the risk of progression towards BD until now. Therefore, a detailed history, a systemic examination, and long critical monitoring during follow-up are fundamental for a prompt diagnosis (10).

Case report

A 12-year-old girl, *virgo*, presented to our pediatric ER for the appearance of painful ulcers on the labia minora, associated with dysuria and local bleeding, with no temperature increase. In her recent history, she referred to a self-limiting episode of poorly formed stools associated with fever seven days before the evaluation; some episodes of oral aphthous in the past years were also reported. Family history was negative for autoimmune diseases, recurrent aphthosis, and BD. The menstrual cycle was regular, with menarche at 11-years-old.

On physical examination, oral mucosa was normal, except for mild hyperemia of the pharynx; cardiopulmonary evaluation did not show any abnormality, the abdomen was soft and not painful; no inguinal lymphadenomegaly was appreciated; the joint examination was normal. There were no signs and symptoms suggestive of inflammatory bowel disease, celiac disease, or BD.

On gynecological examination, the external genitalia was morphologically normal, besides the presence of two symmetrical purple-blue ulcerative lesions on the labia minora of about 4-5 mm in diameter, with the typical "kissing pattern," covered by purulent material and painful at touch (Fig. 1). There were no signs of trauma or sexual abuse.

At first, blood tests were performed that showed a mild increase of C reactive protein (4.25 mg/L), with white blood cell count 8600/μL, hemoglobin 13.9 g/dl, and platelets 470000/μl. Due to severe pain, requiring symptomatic therapy, and the need to perform further diagnostic investigation, the girl, was hospitalized. Serological analysis for herpes simplex viruses 1 and 2, CMV, HIV, parvovirus B19, Toxoplasma gondii, Mycoplasma pneumoniae, treponemal (TPHA), and the non-treponemal (VDRL) test, were performed, with a negative result. Serologies for EBV were suggestive of the previous infection. Antistreptolysin O titer was normal. Urine

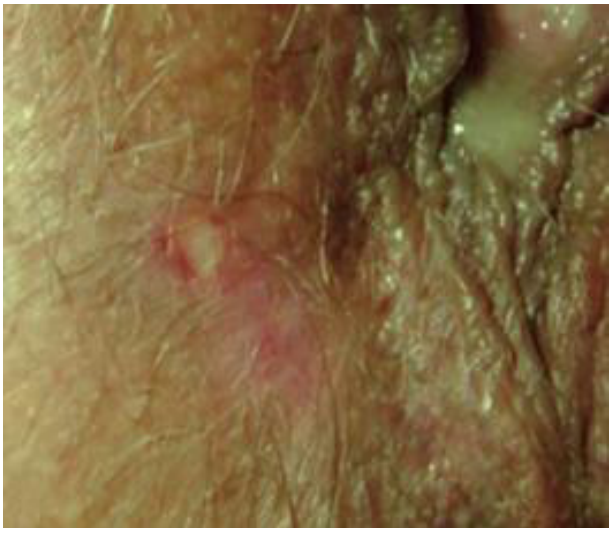

Figure 1. The typical "kissing pattern", covered by purulent material

Table 2. International classifications criteria for Pediatric Behçet's disease.

Item	Description	Value
Recurrent oral aphthous	At least three attacks/year	I
Genital ulceration and aphtosis	Typically with scar	I
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum	I
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis	I
Neurological signs	Except for isolated headaches	I
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm	I

and stool cultures were negative; cutaneous swabs on the lesions did not isolate any bacterium, virus, or fungus. Organ-specific and non-organ-specific autoantibodies were evaluated, with blood values in the range. Thyroid function was normal. No nutritional deficiency (vitamin B_{12}, folic acid, iron) has been identified. From the instrumental point of view, ultrasonographic abdomen evaluation did not reveal any sign suggestive of pelvic inflammatory disease. Due to persistent and heavy bleeding, a vaginoscopy was also performed, and no internal lesions were found. At the dermatological evaluation, the morphological characteristics of the lesions were compatible with RNSRAGU; this hypothesis was also supported by the histological examination of samples that showed superficial mucosal edema, fibrosis of the chorion capillary neo-angiogenesis, in association with focal vasculitis with perivascular lymphocytic and granulocytic infiltration. As histological features are considered non-specific for LU diagnosis, it was necessary to exclude the possibility of early onset of BD, given the anamnestic data of sporadic oral aphtosis in past years. Thus, ophthalmological and cardiological evaluations were performed to complete our diagnostic pathway, with normal findings. From the beginning of hospitalization, broad-spectrum antibiotic therapy with amoxicillin-clavulanic acid, teicoplanin, and metronidazole has been started. Topical betamethasone, gentamicin, clotrimazole, and vaseline were applied twice a day topically, with improvement and progressive healing of the ulcers. After patient discharge, a follow-up with regular gynecological and dermatological examinations was planned, with normal findings. A second hospitalization was necessary 15 months later due to the appearance of genital ulcers and dysuria, preceded by fever. Clinical examination was completely normal, besides painful ulcers on the right labia majora and vaginal ostium (Fig. 2). No oral aphthae were found at the current examination, even if they occurred in the past months.

At the blood test, we found only a mild increase of C reactive protein (1.18 mg/L), white normal blood cell count (7300/μL), hemoglobin (13.9 g/dl), and platelets (277000/ul). At virologic investigations on serum, 540 copies/mL EBV DNA and 4500 copies/mL HHV7 DNA were identified; serologies for HSV-1 and -2, CMV, and Mycoplasma pneumoniae were negative. No pathogen was identified on vaginal and pharyngeal swabs. Immunoglobulin levels and screening for celiac disease were normal. No nutritional deficits have been reported. The patient underwent a further cardiological and ophthalmological evaluation that did not show any pathological sign suggestive for BD. Once again, topical antibiotics, corticosteroids, and antifungal therapy were performed with complete resolution. After hospital discharge, a rheumatological follow-up and gynecological, dermatological, cardiological, and ophthalmological evaluation were scheduled. Considering the clinical history of GU relapse and the anamnestic datum of recurrent oral ulcers, complex aphthosis was diagnosed. Moreover, we decided to perform an immunogenetic analysis that showed HLA-B51 positivity. The parents provided written informed consent.

Discussion

RNSRAGU is considered a rare pathology, but the correct incidence of this disease cannot be estimated because fear and shame linked to this condition may prevent patients from seeking medical care. Moreover, even if diagnostic criteria have been introduced, this entity still relies on a diagnosis of exclusion,

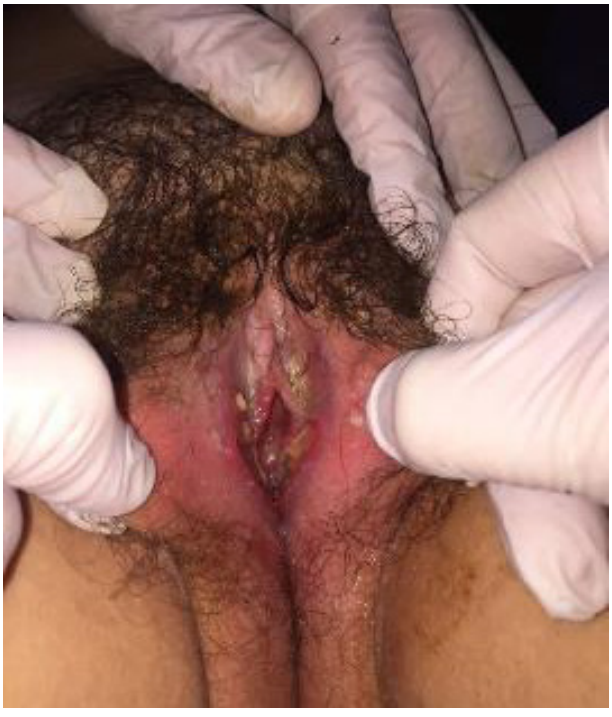

Figure 2. Small ulcers on the right labia majora and vaginal ostium

and many cases are often misdiagnosed with more frequent causes of genital ulcers (11).

BD is perhaps the most important differential diagnosis in LU. The main clinical difference is that LU usually heals without leaving marks, which does not occur in BD. Although recurrent oral ulcer is not exceptional in the general pediatric population, it is an essential clue in diagnosing BD, as is the presenting symptom in 87 to 98% of cases, and it has been found in almost all patients with BD (95%) (12).

In our case, the patient showed positivity for the HLA-B51 haplotype, a known risk factor for the development of BD. It has been demonstrated that the prevalence of HLA-B51 in BD patients ranges between 50 and 72% and that the carriage of HLA-B51 confers an odds ratio of 5.9 for developing BD (12). However, HLA typing is currently not part of the International Criteria for Behçet's disease, as it has been demonstrated that most HLA-B51 carriers do not develop the disease.

Nonetheless, we believe that, in the presence of a clinical condition, this datum should be taken into account in the evaluation of the risk of progression towards BD. Indeed, it has been observed that HLA-B51 positivity is more prevalent in BD than in RNSRAGU or complex aphthosis (8).

Conclusion

RNSRAGU is a relatively rare pathology with a benign course and spontaneous resolution that can recur in up to 30% of cases after about a year. More significant recurrence and the association with oral ulcers are diagnostic criteria of complex aphthosis, a clinical condition that belongs to the spectrum of BD. We think that strictly following up in a multidisciplinary team and investigating genetic predisposition factors is fundamental to detect BD at its onset, especially in the absence of apparent clinical and laboratory criteria that can help physicians define the risk of progression towards full-blown BD.

Conflict of Interest: Each author declares that they do not have commercial associations that might pose a conflict of interest in connection with the submitted article

References

1. Farhi D, Wendling J, Molinari E, et al. Non-sexually related acute genital ulcers in 13 pubertal girls: a clinical and microbiological study. Arch Dermatol. 2009;145(01):38–45.
2. Lai, K., Lambert, E. & Mercurio, M. G. Aphthous Vulvar Ulcers in Adolescent Girls: Case Report and Review of the Literature. J. Cutan. Med. Surg. 2010;14, 33–7
3. Huppert JS. Lipschutz ulcers: evaluation and management of acute genital ulcers in women. Dermatol Ther. 2010;23(5):533-40.
4. Lehman JS, Bruce AJ, Wetter DA, et al. Reactive nonsexually related acute genital ulcers: review of cases evaluated at Mayo Clinic. J Am Acad Dermatol. 2010;63(1):44-51.
5. Arellano J, Fuentes E, Moreno P, et al. Ulcer of Lipschütz, a diagnosis to consider in the pediatric population. Arch Argent Pediatr. 2019;117(3):e305-e8.
6. Eizaguirre FJ, Lucea L, Artola E, et al. Acute genital ulcer unrelated to a sexually transmitted disease. An Pediatr (Barc). 2012;76(3):170-2.
7. Rosman IS, Berk DR, Bayliss SJ, et al. Acute genital ulcers in nonsexually active young girls: case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol. 2012;29(2):147-53.
8. Keogan MT. Clinical Immunology Review Series: an approach to the patient with recurrent orogenital ulceration, including Behçet's syndrome. Clin Exp Immunol. 2009;156(1):1-11.
9. Koné-Paut I, Shahram F, Darce-Bello M, et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016;75(6):958-64.
10. Costagliola G, Cappelli S, Consolini R. Behçet's Disease in Children: Diagnostic and Management Challenges. Ther Clin Risk Manag. 2020;16:495-507.
11. Pereira DAG, Teixeira EPP, Lopes ACM, et al. Lipschütz Ulcer: An Unusual Diagnosis that Should Not be Neglected. Rev Bras Ginecol Obstet. 2021;43(5):414-6.
12. Maldini C, Lavalley MP, Cheminant M, et al. Relationships of HLA-B51 or B5 genotype with Behcet's disease clinical characteristics: systematic review and meta-analyses of observational studies. Rheumatology (Oxford). 2012;51(5):887-900.

Received: 29 March 2022
Accepted: 5 April 2022
Correspondence:
Ilaria Brambilla, MD, PhD
Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo
Piazzale Golgi n°19
Pavia, 27100 Italy
Phone: 0382502732
E-mail: i.brambilla@smatteo.pv.it