Chronic genital herpes: case report and literature review

Herpes genital crônico: relato de caso e revisão da literatura

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ABSTRACT
Genital ulcers are clinical manifestations of diverse etiologies, which can make diagnosis difficult. This case report is about a 64-year-old woman with a history of progressive genital ulcer pain for 4 months, despite prior antiviral use. The ulcerated lesion showed perianal involvement. Histopathology revealed neovascularization, edema and inflammatory infiltrate. Despite the use of intravenous acyclovir for 14 days, the improvement was partial. Chronic herpes simplex reveals wart or ulcer of at least one month, usually in immunosuppressed patients. A resistance to antiviral agents is a complication factor, but the treatment response to common infections is usually slower.
Keywords: genital herpes; immunosuppression; antiviral agents.

RESUMO
Úlceras genitais são manifestações clínicas de etiologias diversas, o que pode dificultar o diagnóstico. Este relato de caso trata-se de mulher de 64 anos, com histórico de úlcera genital dolorosa há 4 meses, progressiva apesar do uso prévio de antiviral. Apresentava lesão ulcerada com comprometimento perianal. Histopatológico revelou neovascularização, edema e infiltrado inflamatório. Realizou tratamento com aciclovir endovenoso por 14 dias, com melhora parcial. O herpes simples crônico manifesta-se como verruga ou úlcera de pelo menos um mês, geralmente em imunossuprimidas. A resistência a agentes antivirais é uma complicação encontrada, mas a resposta ao tratamento costuma ser mais lenta do que nas infecções comuns.
Palavras-chave: herpes genital; imunossupressão; antivirais.

INTRODUCTION

Genital ulcers are clinical manifestations of several systemic pathologies and are connected to the inferior genital tract[(1)]. The ulcers can have infectious etiology or not, most of them caused by sexually transmitted infections. The most common infectious etiologic agents are the following: *Treponema pallidum* (primary and secondary syphilis), herpes simplex viruses (HSV-1 and HSV-2 — genital herpes and perioral, respectively), *Haemophilus ducreyi* (chancroid), *Chlamydia trachomatis* serotypes L1, L2 and L3 (*Lymphogranuloma Venereum*), and *Klebsiella granulomatis* (Donovanosis)[(2)]. Sometimes, primary infection with human immunodeficiency virus (HIV) or Cytomegalovirus (CMV) can be associated with genital ulceration, as well as tuberculosis and leishmaniasis[(3)]. The prevalence of the etiological agents have influence of geographical and socioeconomic factors, as well as of gender, number of sexual partners, drug use, among others. These agents can co-exist with the same lesion[(2)].

Non-infectious etiologies include drug reactions, Behçet syndrome, inflammatory intestine disease, bullous dermatosis (pemphigus, contact dermatitis, erythema multiforme), erosive configurations of Lichen *planus* and Lichen *sclerosus et atrophicus*, neoplasia and trauma[(2,3)].

Genital ulcers have clinical aspects quite varied, and symptoms can be preceded (or not) by painful or painless pustules and/or vesicles, burning, itching, drainage of mucopurulent material, bleeding, and lymphadenopathy in the area, indicating low sensitivity and specificity of the etiologic agent, even in cases considered classic. At least 25% of patients with genital ulcer have no laboratory confirmation of the etiological agent[(2)].

Etiological diversity and variety of presentation can delay the diagnosis of genital ulcers, slowing the adequate treatment. The authors report the case of a patient with chronic genital herpes refractory to conventional clinical treatment.

CASE REPORT

LMRS, a 64 year-old woman, divorced, dressmaker, with a history of recurrent genital ulcers for 2 years, referred to the service. Patient reports progressive painful and itchy vulvar lesions for 4 months despite previous use of acyclovir. She denied fever. Chronic lymphocytic leukemia was treated and it is in remission since the last session of chemotherapy, taken one year before this report. No other comorbidities and no use of medication were mentioned. Patient was a smoker until 50 years of age.

Physical examination revealed an extensive ulcerated lesion in the inner side of labia majora, bilaterally, hyperemic, with important perianal damage and intense local pain (**Figure 1**). In the oral cavity, an ulcerated lesion with vesicles on upper lip, compatible with oral herpes (**Figure 2**), was observed. Negative serology for HIV, syphilis and hepatitis B and C. Biopsy under sedation was carried out from the edge of the vulvar lesion due to intense local pain to manipulation. Histopathology reviewed by two pathologists revealed an ulcer with neovascularization, edema and mixed inflammatory infiltrate in the dermis, frequent eosinophilia, which might correspond to chronic herpes, although not discarding pharmacodermia as differential diagnosis.

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Patient was transferred to a joint evaluation of the Dermatology Service of the Walter Cantídio University Hospital, Universidade Federal do Ceará (UFC). Intravenous treatment with acyclovir for a period of 14 days was indicated, associated with prednisone and antibiotics due to secondary infection. After a period of treatment, patient evolved with partial improvement of the lesion (**Figure 3**). Patient was sent home in use of valacyclovir 500 mg twice a day until clinical improvement, returning every 15 days. Reassessment was carried out 30 days after hospitalization, with improvement of the pain and the aspect of injury, but still with residual ulceration (**Figure 4**).

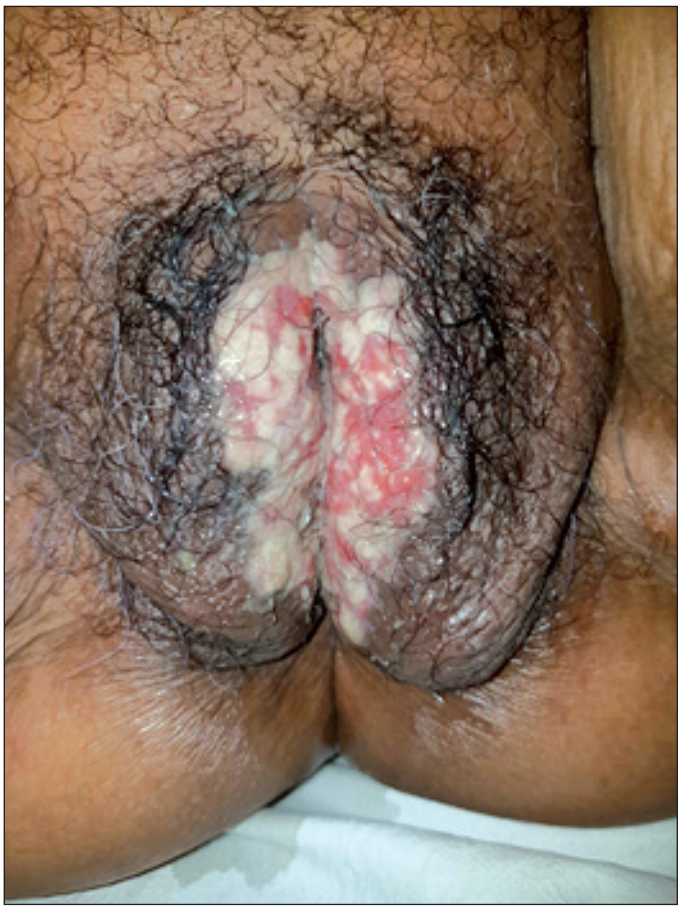

Figure 1 – Genital lesion initial appointment.

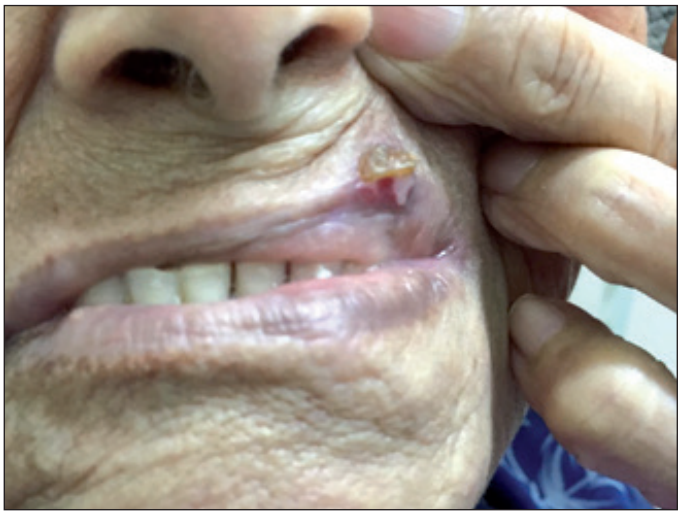

Figure 2 – Oral lesion initial appointment.

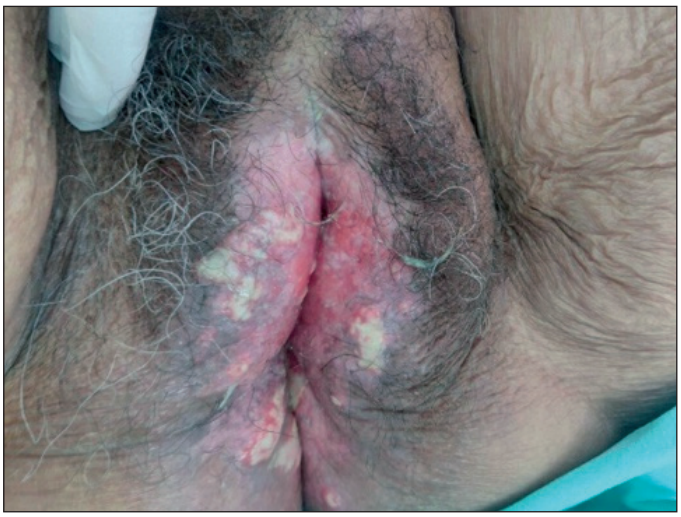

Figure 3 – Genital lesion: 10th day of antiviral treatment.

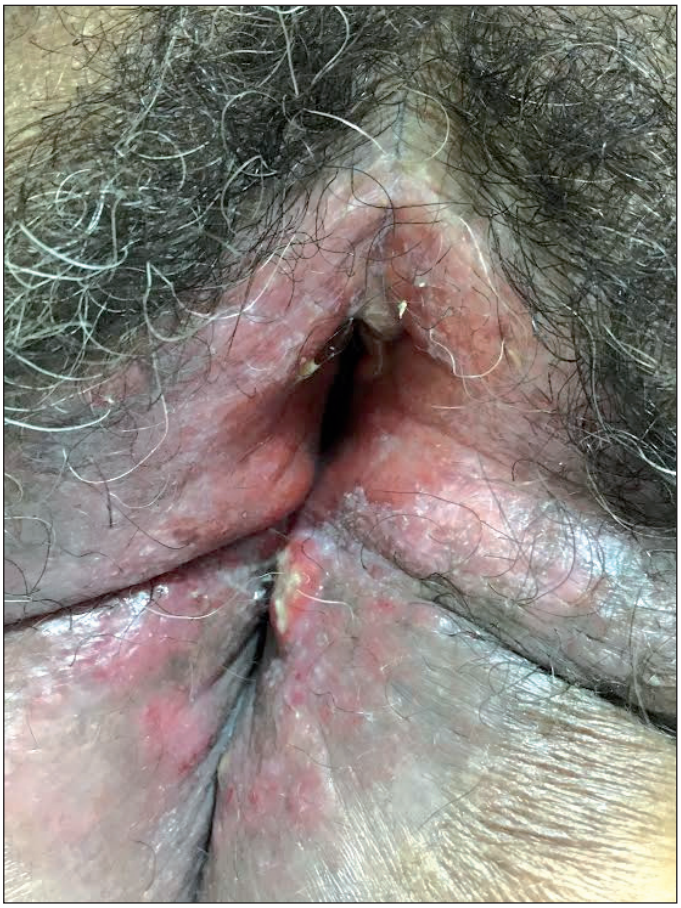

Figure 4 – Genital lesions: 30th day of antiviral treatment.

DISCUSSION

The HSV is considered the most common cause of genital ulcer[4,5]. It is a DNA virus of the *Hespesviridae* family and *Alpha-Herpesvirinae* subfamily, whose types HSV-1 and HSV-2 can cause lesions to any part of the body, with a predominance of type 2 in genital lesions, and type 1 in perioral ones[3].

The chronic herpes simplex is a symptom of HSV-2 infection in immunosuppressed patients, being defined as atypical mucocutaneous wart-like and/or ulcerative infection which can affect large areas of the perianal region and/or the genital region, persisting for a period of at least one month[6-8].

The infection with HIV is an important risk factor for the chronic herpes simplex, as it can also occur in immunocompromised patients due to other conditions, including organs transplant, hypogammaglobulinaemia, chronic lymphocytic leukemia, liver cirrhosis resulting from chronic infection by hepatitis C virus, and myeloprolipherative disorders[8,9].

Its prevalence is unknown, with most cases reported in patients infected with HIV, supposedly as an adverse effect of immunosuppression. Chronic herpes infections are apparently rare in immunocompetent patients[8].

The clinical symptoms are highly polymorphic; however, two features prevail: erosive and/or ulcerative lesions, and vegetative or hyperkeratotic lesions, and both events may occur simultaneously. The ulcerative configuration is usually the most common, characterized as single or multiple ulcerations of varied sizes and extremely painful. The hyperkeratotic configuration is uncommon, showing exhophilic and painful tumors of well-defined limits, simulating squamous cell carcinoma or other viral infections[7,9,10].

The diagnosis is based on the correlation between clinical and histological data obtained from biopsy including ulcerated edge or hyperkeratotic lesion, supported by the HSV lesion presence through immunohistochemical methods or polymerase chain reaction (PCR) and by exclusion of other infectious causes. Histologically, there is a variable hyperplasia of the epidermis with multinucleated epithelial cells and dense mixed inflammatory infiltrate composed of lymphocytes, plasmocytes and eosinophiles[7,9,10].

Infections are treated with antiviral therapy, including acyclovir, famciclovir, penciclovir and vanciclovir; however, the resistance to these agents is a complication observed[7,10]. In immunocompetent patients, acyclovir-resistant HSV is rare, with reported prevalence of 0.3%. In immunocompromised patients, this prevalence varies between 4 and 7%[11-13]. In these resistance cases, other therapeutic options include foscarnet, interferon beta, cidofovir, trifluorothymidine, and vidarabine, although with variable efficacy results[7,9,10].

The response to treatment is slower than common HSV infections, so that the treatment failure due to antiviral resistance at the outset shall not be taken into account. In addition, the susceptibility to antivirals is a dynamic process varying with time, allowing the reintroduction of antiviral drugs that have failed previously[7].

The reported case refers to a patient with chronic oral lesion associated with the anogenital lesion suggestive of herpes, with a history of chronic lymphocytic leukemia treated previously. The histopathology of the lesion showing mixed inflammatory process consistent with the diagnostic hypothesis of chronic herpes, despite being a rare variant, is a possibility that must always be considered in patients with anogenital long-term lesions, especially when associated with immunosuppression symptoms.

Conflict of interests

The authors declare no conflict of interests.

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