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REPORTE DE CASO

Idiopathic esophageal ulcer associated with HIV: a forgotten entity in patients with acquired immunodeficiency syndrome

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Abstract

Esophageal ulceration in patients with stage 3 HIV infection may have infectious, inflammatory, neoplastic, chemical, or irritative etiologies, and their behavior has changed with the advent of highly active antiretroviral therapy. We report the case of a 33-year-old patient with a recent diagnosis of stage 3 HIV who presented with oral ulcers, progressive dysphagia, and febrile syndrome. An extensive diagnostic workup ruled out opportunistic infections, and upper gastrointestinal endoscopy revealed an ulcer involving 60% of the circumference of the mid-esophagus. Microbiological, molecular, and histopathological studies excluded the most common etiologies. After 14 days of ganciclovir therapy without clinical improvement and a repeat endoscopy again negative for cytomegalovirus, a diagnosis of HIV-associated idiopathic esophageal ulcer was established, and antiretroviral therapy along with systemic corticosteroids was initiated. Two months later, near-complete healing was observed; however, gastric lesions suggestive of unmasking Kaposi's sarcoma-associated immune reconstitution inflammatory syndrome, a clinically relevant finding given that corticosteroids increase mortality in this setting. This case highlights the diagnostic challenge posed by this entity and, additionally, raises discussion about the need to explore therapeutic approaches that minimize the risks associated with corticosteroid use, given the limited evidence currently available.

Keywords: Case report; HIV; Ulcer; Sarcoma; Kaposi; Immune Reconstitution Inflammatory Syndrome

Úlcera esofágica idiopática asociada a VIH: una entidad olvidada en pacientes con síndrome de inmunodeficiencia adquirida

Resumen

La úlcera esofágica en pacientes con VIH en estadio 3 puede tener causas infecciosas, inflamatorias, tumorales, químicas e irritativas, cuyo comportamiento ha cambiado con la terapia antirretroviral de alta eficacia. Se presenta el caso de un paciente de 33 años con diagnóstico reciente de VIH en estadio 3, quien consultó por úlceras orales, disfagia progresiva y síndrome febril. Los estudios de extensión descartaron infecciones oportunistas y la endoscopia digestiva alta mostró una úlcera que comprometía el 60% de la circunferencia del esófago medio. Los estudios microbiológicos, moleculares e histopatológicos descartaron las etiologías más frecuentes. Tras 14 días de ganciclovir sin mejoría y con una nueva endoscopia nuevamente negativa para citomegalovirus, se estableció el diagnóstico de úlcera esofágica idiopática asociada a VIH, iniciándose terapia antirretroviral y corticoide sistémico. Dos meses después se observó cicatrización casi completa, pero aparecieron lesiones gástricas sugestivas de sarcoma de Kaposi en el contexto de un síndrome de reconstitución inmune por desenmascaramiento, relevante porque los corticoesteroides aumentan la mortalidad en este escenario. Este caso destaca el reto diagnóstico de esta entidad y, adicionalmente, abre la discusión sobre la necesidad de explorar enfoques terapéuticos que minimicen los riesgos asociados al uso de corticoesteroides, dada la evidencia limitada disponible.

Palabras clave: Reporte de caso; VIH; Ulcera; Sarcoma de Kaposi; Síndrome de reconstitución inmune inflamatoria

Introduction

In patients living with HIV (PLWH) at stage 3, there are multiple etiologies of esophageal ulcers, including infectious, inflammatory, neoplastic, chemical, and irritative causes. The prevalence of these etiologies has changed since the advent of highly effective antiretroviral therapy[1,2].

Case description

We present a case of a 33-year-old male patient with a recent diagnosis of HIV infection, who presented with a CD4+ T-lymphocyte nadir of 15 cells/mm³ and a viral load of 1,274,672 copies/mL. As an identifiable risk factor, he was documented to be a man who has sex with men and had

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Recibido: 31/12/2025; Aceptado: 23/03/2026

Cómo citar este artículo: J.S. Montealegre-Díaz, *et al*. Idiopathic esophageal ulcer associated with HIV: a forgotten entity in patients with acquired immunodeficiency syndrome. Infectio 2026; 30(3): 319-322

inconsistent condom use. He consulted for one month of oral ulcers and progressive dysphagia and was therefore referred to the emergency department for further diagnostic workup.

On physical examination at admission, lesions consistent with oral candidiasis were documented, along with dysphagia to solids, a violaceous inguinal plaque measuring less than 1 cm suggestive of Kaposi sarcoma, and a febrile syndrome of 10 days' duration. Empiric treatment with fluconazole was initiated due to suspected concomitant esophageal candidiasis. Imaging studies were performed, including contrast-enhanced computed tomography of the neck, chest, abdomen, and pelvis, along with sequential endoscopic evaluations to identify opportunistic infections or other relevant systemic conditions (Table 1). Upper gastrointestinal endoscopy revealed an ulcer involving 60% of the esophageal circumference in the mid-esophagus. A tissue sample was obtained from the ulcer base and processed for polymerase chain reaction (PCR) testing for cytomegalovirus (CMV), which yielded a negative result. Due to persistent suspicion of a viral etiology, intravenous ganciclovir was initiated at a dose of 5 mg/kg every 12 hours, and immunohistochemistry was requested on the pathology specimen. Histopathology showed moderate mixed inflammation accompanied by abundant granulation tissue and ulcer base, intermingled with fragments of necrotic esophageal epithelium showing severe reactive epithelial changes, while CMV immunohistochemistry was negative. After 11 days of empirical treatment, the symptoms persisted, and new oral ulcers were documented. Repeat upper gastrointestinal endoscopy was performed, again demonstrating the ulcer, without changes in size compared with the previous endoscopic study. No new ulcers, plaques, or tumoral lesions were identified. A repeat biopsy of the ulcer was obtained, including CMV immunohistochemistry, PCR for *Mycobacterium tuberculosis*, and cultures for common bacteria, fungi, and mycobacteria, all of which were negative.

Given the lack of response to ganciclovir after 14 days and the progressive exclusion of multiple infectious and non-infectious opportunistic conditions, a diagnosis of HIV-associated idiopathic esophageal ulcer was established. In the absence of contraindications, antiretroviral therapy was initiated with tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and dolutegravir (DTG), in addition to oral prednisolone at a dose of 40 mg daily for 1 week, with a weekly taper of 10 mg/day for a total of 4 weeks. Clinical improvement began to be noted between the fourth and seventh days of therapy, with progressive tolerance of oral intake, leading to hospital discharge.

Fifty days later, the patient was readmitted for high-output diarrhea secondary to norovirus infection and anemia, with upper gastrointestinal bleeding and worsening of previously known violaceous cutaneous plaques. A new upper gastrointestinal endoscopy was performed. Although near-complete healing of the esophageal ulcer was observed, new violaceous gastric lesions suggestive of Kaposi's sarcoma were identified, which had not been observed in previous endoscopic studies. These findings were considered compatible with unmasking Kaposi sarcoma-associated immune reconstitution inflammatory syndrome (KS-IRIS).

Discussion

The causes of esophageal ulcers in the context of HIV infection are diverse and include both non-infectious and infectious processes. With the advent of antiretroviral therapy (ART), non-infectious causes have gained increasing relevance. Among these, gastroesophageal reflux disease (GERD) is the most common, while eosinophilic esophagitis, associated with food allergies, drug-induced esophagitis—particularly when medications are ingested without water or in the supine position and are more commonly associated with zidovudine—and aphthous ulcers, which are frequent in patients with stage 3 disease, are also relevant. In addition, mucositis secondary to chemotherapy or radiotherapy and ingestion of corrosive substances such as bleach represent additional non-infectious causes of esophageal ulceration[1,2].

Infectious causes, on the other hand, are particularly prevalent in immunocompromised patients, such as those with CD4 counts <200 cells/mm^3, patients receiving oncologic treatment, or transplant recipients. The most frequently involved pathogens include *Candida albicans*, herpes simplex virus (HSV), and CMV, with *Candida* spp. being the most prevalent in patients with stage 3 disease[1,2].

Less prevalent but described infectious etiologies include acute HIV infection, *M. tuberculosis*, *Pneumocystis jirovecii*, Epstein–Barr virus, and human papillomavirus. In patients with stage 3 disease, Kaposi sarcoma (KS) can involve the esophagus, accounting for up to 7% of cases presenting with esophageal symptoms, along with other neoplasms such as esophageal carcinoma and lymphoma[1,2].

In some cases, despite extensive clinical, endoscopic, and microbiological evaluations, no etiologic agent is identified, a context that warrants consideration of idiopathic esophageal ulceration (IEU). This entity affects approximately 5% of PLWH with stage 3 disease who present with esophagitis, has a nonspecific clinical presentation, and is a diagnosis of exclusion, all of which make it particularly challenging. On endoscopy, these ulcers appear as large, well-demarcated lesions, usually located in the middle or distal third of the esophagus[1,2]. Histologically, tissue necrosis with lymphocytic infiltrate was observed without evidence of infectious agents. HIV-induced apoptosis of the esophageal mucosa has been proposed as a pathogenic mechanism, although the direct role of the virus in the genesis of these ulcers remains a matter of debate[3].

The treatment of IEU has traditionally included corticosteroids and thalidomide based on limited and older evidence. Corticosteroids, such as prednisone, have demonstrated high efficacy, with symptomatic resolution in most patients and

reported cure rates ranging from 92% to 96%, depending on the duration regimen, the most commonly used being prednisolone 40 mg with a weekly taper of 10 mg to complete 4 weeks. Thalidomide has been shown to be an effective alternative, with significantly higher cure rates (73%) compared with placebo (23%) for both oropharyngeal ulcers and IEU[1,4,5].

However, corticosteroid use has been associated with an increased relative risk of infection in other populations, with a reported RR of 1.6 (95% CI: 1.3–1.8). This has raised concerns regarding the potential risks of these agents in immunocompromised patients. In a study conducted by Damba et al. specifically evaluating PLWH, the most frequently reported infections associated with corticosteroid use were pulmonary (50.4%), urinary tract (26%), and opportunistic infections (10.5%), with an incidence rate of 2.49 (95% CI: 1.71–3.60). Although this association did not reach statistical significance, the study represents the largest series published to date in this population and suggests a possible relationship between corticosteroid use and an increased infection risk[6].

Although there is no clear evidence of a detrimental impact of corticosteroids on CD4+ T-cell recovery in patients receiving antiretroviral therapy[7], corticosteroid use has been described as a risk factor for both Kaposi sarcoma (KS) progression and the development of Kaposi sarcoma–associated immune reconstitution inflammatory syndrome (KS-IRIS), as well as KS-related mortality. These observations likely reflect the different clinical settings in which corticosteroids are used. Proposed mechanisms include suppression of natural killer cell activity, stimulation of proliferation of KS spindle cells, and activation of human herpesvirus type 8 (HHV-8)[8]. However, not all observational data have specifically reported an increased incidence of Kaposi sarcoma–associated IRIS following corticosteroid exposure[6].

In light of these risks, the use of antiretroviral therapy alone has emerged as a safe and potentially effective therapeutic alternative for idiopathic esophageal and oropharyngeal ulcers, justified by the possible pathogenic role of HIV in their development. Its safety profile may be reasonable in patients with profound immunosuppression, avoiding the immunosuppressive effects of corticosteroids[9,10].

Although there are no controlled clinical trials that definitively establish the most effective treatment for this entity, the therapeutic approach most widely documented in the available literature was chosen. With this strategy, the patient showed near-complete improvement in the ulcerative lesion. However, as a complication, he developed immune reconstitution inflammatory syndrome (IRIS) with endoscopic appearance of previously absent gastric lesions compatible with Kaposi sarcoma, an event that may have been favored by the use of systemic corticosteroids. This underscores the importance of close follow-up in patients with advanced HIV infection, particularly when concomitant corticosteroid therapy is prescribed.

Table 1. Opportunistic infections and diagnostic studies

Opportunistic infection	Diagnostic rule-out method	Result
Esophageal candidiasis	Upper gastrointestinal endoscopy (UGE)	Not suggestive
Histoplasmosis	Urinary antigen of *Histoplasma capsulatum* (enzyme immunoassay)	Negative
Cryptococcosis	Seric antigen of *Cryptococcus neoformans* (lateral flow assay)	Negative
Mycobacterium tuberculosis	Cultures, PCR, histopathology and imaging	Negative
Nontuberculous mycobacteria	Blood cultures for mycobacteria and imaging	Negative
Pneumocystis jirovecii	Chest imaging (no suggestive findings)	Not suggestive
Virus *Herpes Simplex*	Empirical therapeutic trial with ganciclovir	Not succesfull
Cytomegalovirus	Two pathologies with negative immunohistochemistry, no improvement with empirical management	Negative

This particular case, together with recent reports of similar cases, illustrates the diagnostic and therapeutic challenge in comparable patients, given the profound underlying immunosuppression, the risks accentuated by steroid therapy, and their potential consequences. While the historical recommendation to use glucocorticoids laid the foundation for contemporary therapeutic strategies for this entity, it originated from studies conducted in an era when antiretroviral therapy was less potent, and immune reconstitution was slower. It is currently unclear whether the use of modern antiretroviral regimens, such as those based on second-generation integrase inhibitors, could modify the therapeutic approach to IEU. This highlights the need for larger-scale studies to further explore this issue, as confirmation of favorable outcomes could, in line with previously reported cases, lead to updated management recommendations.

Ethical considerations

Protection of persons and animals. The authors declare that all procedures performed in this case report were conducted in accordance with the ethical standards of the responsible institutional ethics committee and with the principles of the World Medical Association Declaration of Helsinki and its subsequent amendments. Approval for publication was obtained from the institutional ethics committee. Animal experiments: Not applicable.

Protection of Vulnerable Populations. Not applicable. This case report did not involve vulnerable populations as defined by the journal's guidelines.

Confidentiality. The authors declare that they have followed the protocols of their institution regarding access to and use of clinical records for research and publication purposes. Written informed consent was obtained from the patient for participation and publication of the clinical information included in this report.

Privacy. The authors have protected the patient's right to privacy and confidentiality. No identifying personal information is included in the manuscript or accompanying images. Written informed consent for publication, reproduction, and dissemination of the clinical information and images was obtained from the patient.

Financing. Not applicable

Conflict of interests. The authors have no conflict of interest to declare

Acknowledgments. The authors would like to thank the Infectious Diseases and Internal Medicine teams at Hospital Universitario San Ignacio for their support and contribution to the patient's care.

Statement on the use of artificial intelligence. No artificial intelligence (AI) tools were used in the generation, analysis, interpretation of data, or writing of this manuscript.

Authors´ contribution. It is stated that all authors accepted the ethical responsibilities required by the journal. All authors contributed to read and approved the version of the submitted manuscript.

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