Case Report

Thalidomide as Adjunctive Therapy in a Case of HIV-Associated Idiopathic Esophageal Ulcer

Talidomida como terapia adjuvante em um caso de úlcera esofágica idiopática associada ao HIV

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Submitted: 23 October 2025
Accepted: 21 June 2026
Published: 24 July 2026

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DOI: 10.66004/2764-734X.e20260675-en

ABSTRACT

HIV-associated idiopathic esophageal ulcer is a rare manifestation of advanced immunosuppression with no well-established therapeutic management. We report the case of a 19-year-old female patient presenting with epigastric pain, odynophagia, and weight loss, whose endoscopy identified an extensive ulcer in the distal esophagus. The biopsy of this lesion was nonspecific, and serological testing revealed HIV infection. The blood CD4 cell count was 5 cells/μL, and antiretroviral therapy was promptly initiated. A second endoscopy revealed worsening of the inflammatory process and the esophageal ulcer; despite the lack of an etiological diagnosis, empirical treatment with ganciclovir was chosen, which was later switched to foscarnet. The absence of clinical improvement even after two weeks of treatment prompted a new examination, whose endoscopic findings showed an even more pronounced worsening of the lesion, with equally inconclusive biopsies. Thus, a diagnosis of HIV-associated idiopathic ulcer (potentially aggravated by a possible immune reconstitution inflammatory syndrome) was considered, and the introduction of thalidomide at 100 mg/day was decided. After four weeks, there was clinical resolution and complete endoscopic healing, confirming the immunomodulatory and anti-inflammatory role of thalidomide as a potential adjunctive therapy in this type of scenario without proven causality.

Headings: AIDS-Related Opportunistic Infections, Esophageal Diseases, Thalidomide, Case Report.

RESUMO

A úlcera esofágica idiopática associada ao HIV é uma manifestação rara da imunossupressão avançada, sem conduta terapêutica bem estabelecida. Relatamos o caso de uma paciente de 19 anos com dor epigástrica, odinofagia e perda ponderal, cuja endoscopia identificou úlcera extensa no esôfago distal. A biópsia desta lesão foi inespecífica e em meio a exames sorológicos constatou-se infecção pelo HIV. A contagem de células CD4 no sangue foi de 5 células/μL e logo foi iniciada terapia antirretroviral. Uma segunda endoscopia revelou piora do processo inflamatório e da úlcera esofágica e, apesar de não se ter estabelecido um diagnóstico etiológico, optou-se pelo tratamento empírico com ganciclovir substituído depois por foscarnet. A ausência de melhora clínica mesmo depois de duas semanas de tratamento motivou novo exame cujos achados endoscópicos evidenciaram piora ainda mais acentuada da lesão, com biópsias igualmente inconclusivas. Cogitou-se, assim, o diagnóstico de úlcera idiopática associada ao HIV (agravada ou não por uma possível síndrome de reconstituição imune) e decidiu-se pela introdução de 100 mg/dia de talidomida. Decorridas quatro semanas, houve resolução clínica e cicatrização endoscópica completa, ratificando o papel imunomodulador e anti-inflamatório da talidomida como uma possível terapia adjuvante neste tipo de situação sem comprovação da causalidade.

Descritores: Infecções Oportunistas Relacionadas com a AIDS, Doenças do Esôfago, Talidomida, Relato de Caso.

INTRODUCTION

Human immunodeficiency virus (HIV)-associated idiopathic esophageal ulcer is a diagnosis of exclusion described in patients with advanced immunosuppression after a negative investigation for opportunistic infections and malignancies [1,2]. Its management is not well established, and therapeutic recommendations are limited [3,4,5]. We report a case with a favorable response to thalidomide use, reinforcing its immunomodulatory and anti-inflammatory role as a possible adjunctive therapy in specific situations.

CASE REPORT

A 19-year-old woman with no known medical history or comorbidities sought medical care due to complaints of epigastric pain and retrosternal burning for approximately one month. Symptoms worsened after meals and were accompanied by postprandial nausea and vomiting, leading to anorexia and unquantified weight loss. Initially medicated only with analgesics and antiemetics, she developed clinical worsening, which prompted her to consult a gastroenterologist, who ordered an upper gastrointestinal endoscopy. This examination revealed an ulcer in the distal third of the esophagus (images not available), whose biopsies demonstrated nonspecific chronic inflammation with granulation tissue, with no evidence of infectious agents or viral inclusions. Treatment with a proton pump inhibitor was initiated, and routine laboratory tests included serologies for hepatitis B and C, syphilis, and HIV—the latter yielding a reactive result. She was then referred to a specialized care service, where the initial CD4+ T-lymphocyte count of 5 cells/μL and an HIV viral load of 1,703 copies/mL were found. Antiretroviral therapy (ART) with tenofovir, lamivudine, and dolutegravir was initiated. Due to the persistence of symptoms, however, the decision was made shortly thereafter to admit her to a tertiary hospital to expand the investigation for potential opportunistic diseases.

A new upper gastrointestinal endoscopy revealed an extensive and deep ulcerated lesion in the distal esophagus, measuring approximately 6 cm, with a fibrin-covered base and elevated borders (Figure 1).

Endoscopic biopsies showed severe and erosive chronic esophagitis with rare cytopathic changes. Direct examination for acid-fast bacilli (AFB) and fungi was negative, as were the immunohistochemical techniques used to identify cytomegalovirus (CMV) and herpes simplex virus (HSV). Computed tomography scans of the chest, abdomen, and cranium showed no relevant abnormalities. Considering the high frequency of CMV esophagitis given this endoscopic appearance in a patient with advanced immunosuppression, empirical treatment with ganciclovir was chosen despite the lack of etiological confirmation. Prophylaxis for pneumocystis pneumonia with sulfamethoxazole-trimethoprim and preventive treatment for latent tuberculosis infection with isoniazid were also introduced. Antiretroviral therapy (initiated three weeks prior to hospital admission) was maintained.

After three days of treatment with ganciclovir, the patient developed bicytopenia, including significant anemia and leukopenia attributed to potential drug-induced myelotoxicity in the context of advanced immunosuppression. The decision was then made to replace ganciclovir with foscarnet combined with the use of filgrastim.

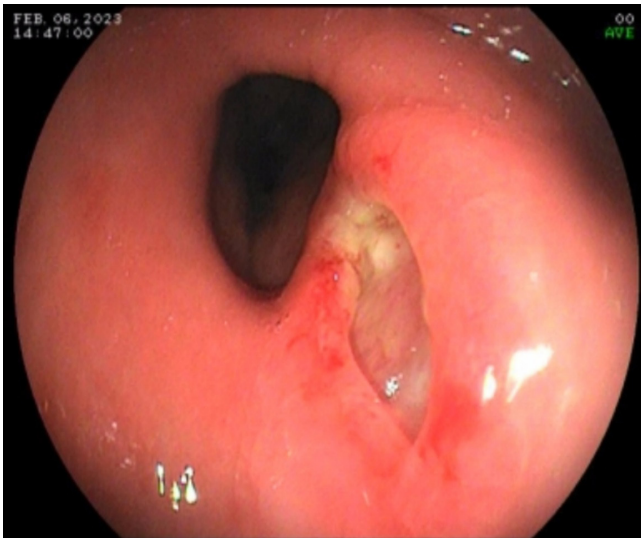

Figure 1: Image of the upper gastrointestinal endoscopy performed at the beginning of hospital admission, demonstrating an extensive ulcer in the distal third of the esophagus, characterized by a fibrinous base, well-defined limits, and slightly elevated borders, with the adjacent mucosa being mildly hyperemic.

Due to the persistence of symptoms after two weeks of specific antiviral therapy, a new endoscopy (the third performed by the patient) was carried out, demonstrating evident progression of the ulcer with pronounced mucosal edema causing partial obstruction of approximately two-thirds of the esophageal lumen (Figures 2A and 2B).

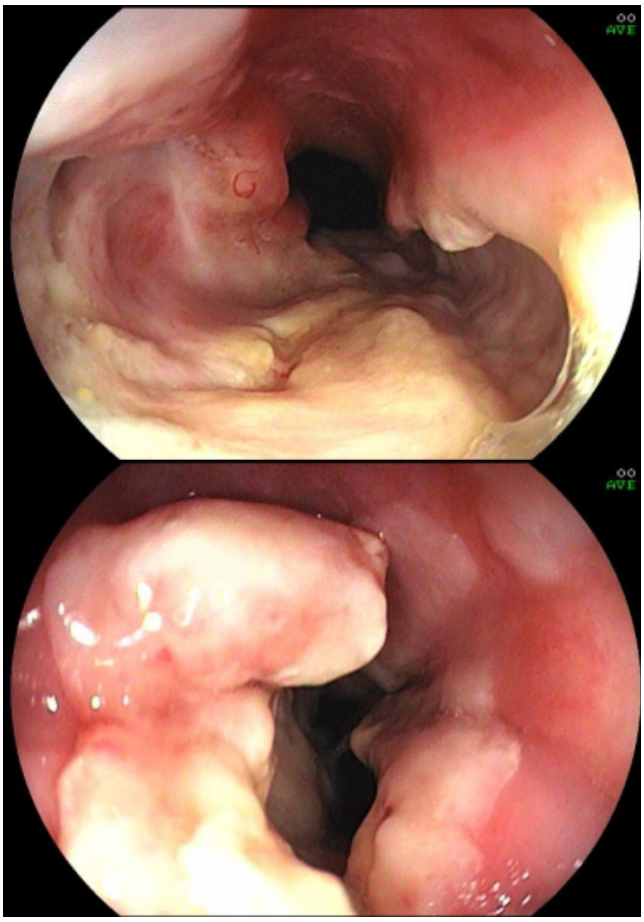

Figure 2: Images of the upper gastrointestinal endoscopy performed 15 days after the first examination, illustrating evident progression of the esophageal ulcer in both extension and depth, now with elevated and irregular margins, covered by a thick fibrinous exudate and associated with pronounced edema and hyperemia of the adjacent mucosa (2A). The inflammatory process causes a significant reduction in the lumen, affecting approximately two-thirds of the esophageal lumen (2B).

New biopsies maintained the nonspecific histological pattern, and all investigations and immunohistochemical studies remained negative for AFB, fungi, CMV, HSV, and now human herpesvirus type 8.

In view of the endoscopic worsening and the exclusion of the main infectious etiologies in this context, a diagnosis of HIV-associated idiopathic esophageal ulcer was considered, possibly aggravated by immune reconstitution inflammatory syndrome (IRIS), although no new immunovirological data were available at that time. The decision was made to discontinue foscarnet.

However, the significant dietary restriction resulting from the painful symptoms suffered by the patient prompted the introduction (one and a half months after the initiation of ART) of thalidomide at a dose of 100 mg daily, duly preceded by a specialized gynecological evaluation and the implementation of a hormonal contraceptive injection and a barrier method. Thalidomide was maintained for four weeks, during which the patient progressed with gradual improvement in pain and food intake. A new follow-up endoscopy (the fourth examination) at this time demonstrated complete healing of the esophageal ulcer (Figure 3). No type of corticosteroid was administered during the entire hospital stay.

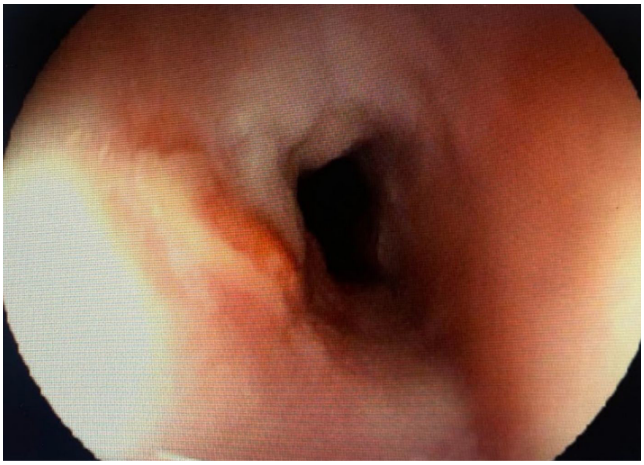

Figure 3: Endoscopic image of the examination performed after four weeks of thalidomide use (associated with antiretroviral therapy), demonstrating complete healing of the esophageal ulcer.

DISCUSSION

Esophageal ulcers in immunosuppressed individuals, such as people living with HIV/AIDS (PLHA), have distinct etiologies from those observed in immunocompetent individuals, as fungal infections, tuberculosis, and, above all, viral reactivations like CMV and HSV predominate [3]. In this context, CMV is the etiology most frequently associated with deep ulcerative lesions of the esophagus, especially in PLHA with advanced immunosuppression [2]. It is worth noting, however, that the diagnosis of AIDS in this patient was previously unknown, making the initial investigation timely to explain this rather unusual endoscopic finding in a 19-year-old young woman.

The morphological pattern of the lesions visualized endoscopically is not sufficient to differentiate the etiology of esophageal ulcers, let alone distinguish between different viral agents [2,3]. Because CMV is the most prevalent, the choice of empirical treatment with ganciclovir can be considered consistent and appropriate, although this diagnostic definition was never confirmed.

On the other hand, HIV itself can directly affect the gastrointestinal mucosa. This was confirmed by a study that detected the presence of the HIV *pol* gene in

biopsied specimens from 12 out of 16 patients with giant esophageal ulcers previously considered idiopathic [1]. This result was based on Reverse Transcription Polymerase Chain Reaction of messenger RNA extracted from tissues, a technique and genetic targets that are, however, poorly available in clinical practice—perhaps explaining why the term "idiopathic" is maintained in the nomenclature of this type of HIV-associated ulcer. In any case, this tissue injury (even if of "unknown" origin) can generate varying degrees of inflammatory response that compromises mucosal barrier integrity, promotes bacterial translocation, and perpetuates local inflammation mediated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) [6,7].

As a diagnosis of exclusion that implies mandatory investigation and ruling out of other more frequent infectious etiologies through biopsies combined with specific histological and microbiological techniques [2,3], HIV-associated esophageal ulcers are considered a less common entity in this context. In addition to being a seldom-recalled diagnostic hypothesis, the treatment of HIV-associated idiopathic ulcers is also highly challenging. ART emerges as a fundamental strategy, as viral suppression and immune recovery alone can promote resolution of inflammation and healing of the gastrointestinal mucosa [6]. However, the response to ART can be slow or incomplete in cases of extensive lesions, significantly impacting patient nutrition and quality of life [3,6]. It should also be highlighted that the progressive worsening of the lesion in the case reported here occurred shortly after the initiation of antiretroviral therapy, a fact that may correspond to the phenomenon of IRIS [3]. Although confirmation through a new CD4+ T-lymphocyte count or quantification of the HIV viral load was not possible during that period, the hypothesis is supported by the initial context of advanced immunosuppression and the recent initiation of ART based on dolutegravir, a second-generation integrase inhibitor with a high genetic barrier to resistance. Anyway, this aggravating factor does not exclude the diagnosis of HIV-associated idiopathic esophageal ulcer.

Among the immunomodulatory and anti-inflammatory therapies applicable to IRIS and nonspecific mucosal ulcers (such as recurrent aphthous stomatitis), corticosteroids have been the primary therapeutic resource used [8,9], but they were not employed in this case. Thalidomide, on the other hand, has been used in several gastrointestinal inflammatory conditions, such as Crohn's disease, refractory inflammatory bowel disease, the management of gastrointestinal bleeding associated with vascular lesions like angiodysplasias, as well as nonspecific ulcerative manifestations of the mucosa [10-13]. Its mechanism involves the inhibition of TNF-α synthesis and the modulation of pro- and anti-inflammatory cytokines [4,5,11,12]. Although somewhat dated, there is clinical evidence of thalidomide's efficacy in HIV-associated idiopathic ulcers [4,5], while more recent studies suggest a regulatory role of the drug in the interaction among the microbiota, mucosal inflammation, and the patient's immune response, expanding the understanding of the mechanisms involved in ulcerative diseases of the gastrointestinal mucosa [14,15].

Despite its efficacy, it is worth remembering that thalidomide is associated with significant adverse effects, such as peripheral neuropathy, and, above all, carries a high teratogenic risk [4,5,11]. For this reason, the patient depicted here (of childbearing age) underwent a specialized gynecological evaluation to rule out pregnancy and to implement effective contraceptive methods.

CONCLUSION

The association between ART and thalidomide in this case coincided with significant clinical improvement and complete endoscopic healing of the esophageal lesion, confirming a potential adjunctive role for thalidomide in selected cases of HIV-associated idiopathic ulcer. It should be reinforced, however, that a definitive causal relationship could not be established, a fact that further underscores the absolute requirement to rule out other etiologies in this context. The management of HIV-associated idiopathic gastrointestinal ulcers still represents a clinical challenge, and studies comparing the efficacy and safety of thalidomide with other therapeutic strategies, such as corticosteroids and/or anti-TNF-α biologic agents, are welcome and necessary.

"This case report deserved an official declaration of acknowledgement and ethical approval by its institution of origin and was peer-reviewed before publication, whilst the authors declare no fundings nor any conflicts of interest concerning this paper. It is noteworthy that case reports provide a valuable learning resource for the scientific community but should not be used in isolation to guide diagnostic or treatment choices in practical care or health policies.

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