Cytomegalovirus Esophagitis Mimicking Herpetic Esophagitis in a Newly Diagnosed HIV Patient: A Diagnostic Challenge.

Abstract

Background: Cytomegalovirus (CMV) esophagitis is a severe opportunistic infection occurring almost exclusively in profoundly immunocompromised patients with HIV disease and CD4 counts below 100 cells/μL. It represents an AIDS-defining illness and can be life-threatening if not promptly recognized and treated. Its clinical presentation overlaps significantly with herpetic esophagitis, making diagnosis challenging without endoscopic and histopathological confirmation.

Case Presentation: We report the case of a 31-year-old woman with newly diagnosed HIV infection (viral load 1,423,000 copies/mL, CD4 count 60 cells/μL) presenting with painful oral and anal ulcerations, epigastric pain, and retrosternal chest pain. Initial intravenous acyclovir therapy (10 mg/kg/8h) led to partial improvement of mucocutaneous lesions but failed to resolve digestive symptoms — a key clinical clue. Upper GI endoscopy revealed a large ulceration (2×3.5 cm) in the upper third of the esophagus. Histopathological examination of esophageal biopsies confirmed CMV esophagitis, demonstrating endothelial cells containing CMV intranuclear inclusions. Fundoscopy was negative for CMV retinitis. CMV plasma viral load could not be performed due to financial constraints. The patient was treated with intravenous ganciclovir 5 mg/kg/12h for 21 days with complete clinical resolution.

Conclusion: Failure of acyclovir to resolve esophageal symptoms in an HIV patient with severe immunosuppression should prompt immediate endoscopic investigation to exclude CMV esophagitis. Histopathological confirmation via endoscopic biopsy is the diagnostic cornerstone, particularly in resource-limited settings. Ganciclovir remains the treatment of choice with excellent clinical outcomes.

Keywords: *CMV esophagitis; cytomegalovirus; HIV/AIDS; opportunistic infection; AIDS-defining illness; ganciclovir; acyclovir; upper GI endoscopy; immunosuppression; resource-limited setting*

1. Introduction

Cytomegalovirus (CMV) is a ubiquitous double-stranded DNA herpesvirus belonging to the Herpesviridae family, infecting 40–90% of the adult population worldwide. While primary infection is typically asymptomatic or causes a self-limited mononucleosis-like syndrome in immunocompetent individuals, CMV can cause devastating end-organ disease in severely immunocompromised hosts. In the context of HIV infection, CMV reactivation from latency occurs when CD4 T-lymphocyte counts drop below 50–100 cells/μL, potentially affecting the retina, gastrointestinal tract, lungs, liver, and central nervous system.

CMV esophagitis accounts for approximately 10–30% of esophageal disease in advanced HIV infection and is classified as an AIDS-defining illness. It presents with odynophagia, dysphagia, retrosternal pain, and epigastric discomfort, symptoms that overlap

significantly with those of herpetic esophagitis (HSV) and esophageal candidiasis. This clinical overlap frequently leads to empirical treatment with acyclovir, which is ineffective against CMV since the virus lacks the thymidine kinase enzyme responsible for acyclovir phosphorylation. The persistence of esophageal symptoms despite adequate acyclovir therapy is therefore a cardinal diagnostic clue that should prompt endoscopic investigation.

Upper gastrointestinal endoscopy with biopsy remains the gold standard for diagnosis, typically revealing one or few large, deep, well-demarcated ulcerations, histopathologically characterized by the presence of CMV intranuclear inclusions in endothelial cells and fibroblasts. We report a case that exemplifies this diagnostic pathway: a newly diagnosed HIV-positive patient with profound immunosuppression in whom failure of acyclovir ultimately led to the endoscopic discovery of CMV esophagitis, confirmed by histopathology.

2. Case Presentation

2.1 Patient History and Clinical Presentation

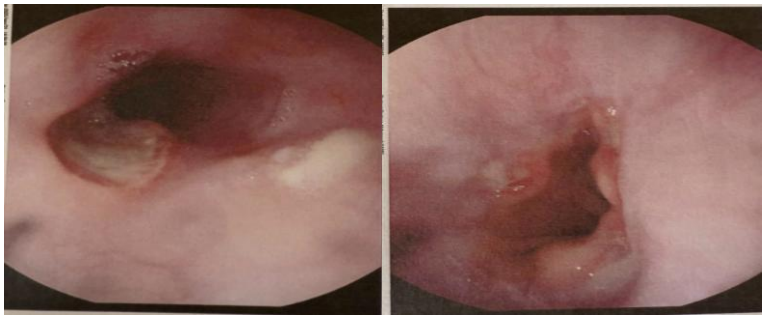
A 31-year-old Moroccan woman with no significant past medical history was referred to the Department of Infectious Diseases of CHR Hôpital Moulay Hassan Ben Mehdi, Laayoune, following a newly established diagnosis of HIV infection. Biological assessment revealed a plasma HIV viral load of 1,423,000 copies/mL and a CD4 T-lymphocyte count critically low at 60 cells/μL, indicating stage C3 AIDS. She presented with painful oral and anal ulcerations, epigastric pain, and retrosternal chest pain. A comprehensive infectious workup was performed: CMV serology showed IgG positivity with negative IgM (consistent with past infection without active primary CMV); Toxoplasma, syphilis, hepatitis B and C serologies were all negative.

2.2 Initial Treatment and the Diagnostic Clue

Based on the clinical presentation of painful mucocutaneous ulcerations, intravenous acyclovir was initiated at 10 mg/kg every 8 hours for presumed herpetic disease. This led to satisfactory improvement of the oral and anal lesions. However, the epigastric pain and retrosternal discomfort persisted without any improvement despite adequate symptomatic therapy — a critical clinical finding. The selective failure of acyclovir to resolve digestive symptoms, while improving mucocutaneous herpetic lesions, raised the strong suspicion of a concurrent CMV esophageal infection requiring specific investigation.

2.3 Endoscopic Findings

Upper gastrointestinal fibroscopy (OGD) was performed .Endoscopic examination of the esophagus revealed a large, deep, well-demarcated ulceration measuring approximately 2×3.5 cm located in the upper third of the esophagus (Figures 1–2), surrounded by erythematous mucosa with necrotic debris. The stomach (fundus, body, antrum) and duodenal bulb were macroscopically normal. Multiple biopsies were obtained from the ulcer margins and base for histopathological analysis.



Figures 1–2: Upper gastrointestinal endoscopy showing a large (2×3.5 cm) deep, well-demarcated ulceration in the upper third of the esophagus with necrotic debris and surrounding erythematous mucosa, characteristic of CMV esophagitis.

2.4 Histopathological Findings

Histopathological examination of esophageal biopsies demonstrated four biopsy fragments corresponding to a severely remodeled, ulcerated squamous esophageal mucosa covered by fibrin-leukocytic material, without architectural disorganization or atypia. The chorion was hyaline fibrotic, with a moderate mixed polymorphous inflammatory infiltrate. Endothelial cells containing characteristic CMV intranuclear inclusions were identified. No signs of malignancy were detected. Conclusion: subacute ulcerated CMV esophagitis with intranuclear inclusions compatible with CMV infection (Figures 3–5).

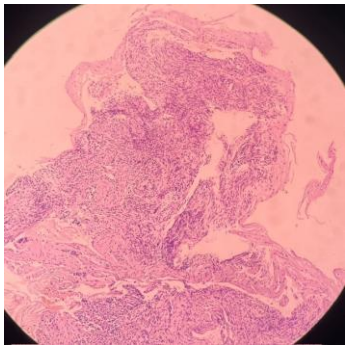
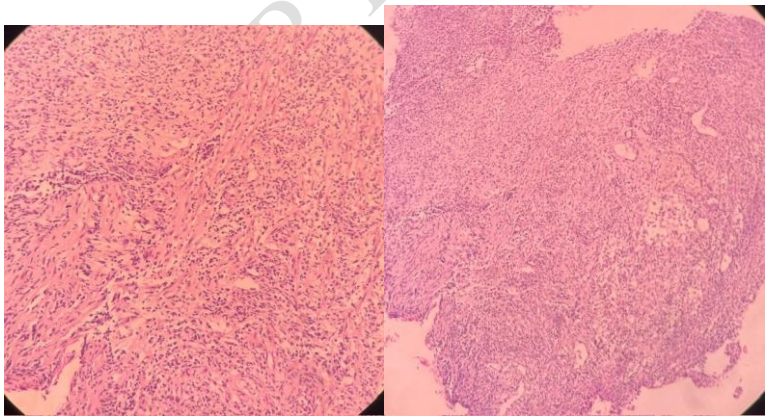


Figure 3: Low-power histopathological view (H&E) showing severely remodeled esophageal squamous mucosa with dense mixed inflammatory infiltrate and areas of ulceration



Figures 4–5: Medium and high-power views (H&E) demonstrating hyaline fibrotic chorion with moderate mixed inflammatory infiltrate. Endothelial cells containing CMV intranuclear inclusions are identified, confirming the diagnosis of CMV esophagitis. No malignancy detected.

2.5 Additional Investigations

Fundus oculi examination was performed to screen for CMV retinitis and revealed no necrotico-hemorrhagic retinal ulceration suggestive of CMV chorioretinitis. Quantitative CMV plasma viral load could not be performed due to financial constraints, illustrating the diagnostic challenges in resource-limited settings where histopathological confirmation becomes the cornerstone of diagnosis.

2.6 Treatment and Outcome

Intravenous ganciclovir was initiated at 5 mg/kg every 12 hours (induction therapy) for 21 days. The patient demonstrated excellent clinical response, with progressive resolution of retrosternal pain and epigastric discomfort, and complete restoration of oral intake by the end of the treatment course. Antiretroviral therapy (ART) initiation was planned following stabilization of CMV disease, in accordance with current guidelines recommending a delay of 2–4 weeks to minimize the risk of immune reconstitution inflammatory syndrome (IRIS).

3. Discussion

This case encapsulates the most instructive diagnostic sequence in CMV esophagitis: the failure of acyclovir to resolve esophageal symptoms despite adequate dosing and improvement of concurrent herpetic mucocutaneous disease. This selective therapeutic failure is pathophysiologically explained by the fact that CMV, unlike HSV, does not encode a thymidine kinase enzyme — the molecular target through which acyclovir achieves its antiviral activity. CMV relies instead on the viral UL97 kinase for initial drug phosphorylation, making it intrinsically resistant to acyclovir. Clinicians should therefore interpret persistence of esophageal symptoms under acyclovir as a strong signal for CMV co-infection, particularly in patients with CD4 counts below 100 cells/μL.

Our patient presented with a CD4 count of 60 cells/μL, placing her in the highest risk category for CMV end-organ disease. The concurrent CMV IgG seropositivity with negative IgM confirmed past CMV infection with reactivation, consistent with the immunopathogenesis of CMV disease in AIDS: viral reactivation from latency rather than primary infection. The inability to quantify CMV plasma viral load due to financial constraints — a common reality in North African clinical settings — underscores the critical importance of endoscopy with biopsy as a substitute diagnostic tool.

Endoscopically, CMV esophagitis characteristically presents as one or few large (≥1 cm), deep, well-demarcated ulcerations in the mid or distal esophagus, in contrast to the multiple small punched-out vesicular ulcerations of HSV esophagitis. The 2×3.5 cm ulceration observed in the upper third of our patient's esophagus is consistent with this endoscopic signature. Biopsy of the ulcer base — rather than the edges — is recommended since CMV primarily infects endothelial cells and fibroblasts in the submucosal layer, not the surface squamous epithelium.

Histopathologically, the diagnosis was secured by the identification of CMV intranuclear inclusions in endothelial cells, against a background of mixed inflammatory infiltrate and hyaline fibrosis, without malignancy. The classic "owl-eye" appearance of CMV-infected cells — characterized by an enlarged cell with a prominent intranuclear inclusion surrounded by a clear halo — is pathognomonic and was confirmed . Immunohistochemistry for CMV antigens, when available, can further enhance diagnostic sensitivity.

Intravenous ganciclovir 5 mg/kg every 12 hours for 21 days is the established first-line induction therapy for CMV esophagitis and produced excellent results in our patient.

Alternative agents include intravenous foscarnet for ganciclovir-resistant cases or oral valganciclovir when GI absorption is preserved. The timing of ART initiation in patients with active CMV disease requires careful consideration: current guidelines recommend delaying ART by 3 weeks after starting CMV therapy to reduce IRIS risk, particularly given that CMV IRIS can paradoxically worsen retinal or systemic disease.

4. Conclusion

In HIV-positive patients with advanced immunosuppression presenting with painful dysphagia and retrosternal discomfort, failure of acyclovir to resolve esophageal symptoms is a sentinel diagnostic clue that should immediately prompt upper GI endoscopy with biopsy. CMV esophagitis, though less common than herpetic or candidal esophagitis, carries significant morbidity and requires specific ganciclovir therapy. In resource-limited settings where CMV viral load testing is unavailable, histopathological identification of CMV intranuclear inclusions in esophageal biopsies remains the gold standard for diagnosis. Early recognition, multidisciplinary collaboration, and prompt treatment are the keys to a favorable outcome.

Patient Consent Statement

Written informed consent was obtained from the patient for the publication of this case report and the accompanying endoscopic and histopathological images. Patient anonymity has been fully preserved.

Competing Interests

The authors declare no competing interests.

References

1. World Health Organization. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. Geneva: WHO; 2022.

2. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections.

3. Wilcox CM, Diehl DL, Cello JP, Margaretten W, Jacobson MA. Cytomegalovirus esophagitis in patients with AIDS: a clinical, endoscopic and pathologic correlation. Ann Intern Med. 1990;113(8):589–593.

4. Bonacini M, Young T, Laine L. The causes of esophageal symptoms in human immunodeficiency virus infection: a prospective study of 110 patients. Arch Intern Med. 1991;151(8):1567–1572.

5. Wilcox CM, Rodgers W, Lazenby A. Prospective comparison of brush cytology, viral culture, and histology for the diagnosis of ulcerative esophagitis in AIDS. Clin Gastroenterol Hepatol. 1994;20(3):318–323.

6. Bini EJ, Micale PL, Weinshel EH. Natural history of HIV-associated esophageal disease in the era of protease inhibitor therapy. Dig Dis Sci. 2000;45(7):1301–1307.

7. Poles MA, Dieterich DT. Cytomegalovirus infection in HIV-infected patients in the era of highly active antiretroviral therapy. J Acquir Immune Defic Syndr. 2000;23(4):369–372.

8. Dieterich DT, Poles MA, Dicker M, et al. Foscarnet treatment of cytomegalovirus gastrointestinal infections in acquired immunodeficiency syndrome patients who have failed ganciclovir induction. Am J Gastroenterol. 1993;88(4):542–548.

9. Jacobson MA, Mills J. Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS): clinical findings, diagnosis, and treatment. Ann Intern Med. 1988;108(4):585–594.

10. Blanshard C, Benhamou Y, Dohin E, et al. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir: a randomized comparison. J Infect Dis. 1995;172(3):622–628.

11. Connolly GM, Hawkins D, Harcourt-Webster JN, Parsons PA, Husain OA, Gazzard BG. Oesophageal symptoms, their causes, treatment, and prognosis in patients with the acquired immunodeficiency syndrome. Gut. 1989;30(8):1033–1039.

12. Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin Infect Dis. 2006;42(11):1592–1595.