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Case report

Cytomegalovirus-associated esophageal stricture as a manifestation of the immune reconstitution inflammatory syndrome

BS Mansfield[a,d,*], MJ Savage-Reid[b], J Moyo[c], CN Menezes[a,d]

[a] Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa
[b] Division of Anatomical Pathology, National Health Laboratory Services, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa
[c] Department of Surgery, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa
[d] Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

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ABSTRACT

Cytomegalovirus (CMV) esophagitis is well described in immunocompromised individuals, however, esophageal stricture due to CMV is rare. CMV disease in the setting of the immune reconstitution inflammatory syndrome (IRIS) usually takes the form of an immune-recovery uveitis or retinitis. We describe a young female patient with HIV who developed an esophageal stricture due to CMV within 6 months of starting antiretroviral therapy (ART). The patient responded well to treatment which involved 14 days of intravenous ganciclovir and esophageal dilatation. This is the first description of a patient developing gastrointestinal cytomegalovirus disease as a manifestation of IRIS.

Case report

A 27-year-old female was admitted to a local hospital with community-acquired pneumonia. She tested positive for human immunodeficiency virus (HIV) and had a baseline CD4 count of 0 cells/μL. Investigations for tuberculosis were negative. At the time of her discharge, she was started on a fixed-dose combination of antiretroviral therapy (ART) which comprised tenofovir, emtricitabine and efavirenz. Four weeks after initiating ART she began experiencing dysphagia, which was initially only to solids. Empiric fluconazole therapy prescribed by her local clinic did little to alleviate her symptoms which progressively worsened over the ensuing 6 months before presenting to our institution. She described no other symptoms. She did not have diarrhea. She reported no loss of visual acuity. On examination, she was wasted. She had no palpable lymphadenopathy, nor did she have hepatomegaly or splenomegaly. Fundoscopy revealed no evidence of retinitis.

Initial haematological investigations revealed a mild normocytic anemia with a haemoglobin 10.9 g/dL. Tests for renal and liver function were normal. After 6 months of ART, the patient's CD4 count was then 106 cells/μL and she was virologically suppressed with an undetectable viral load. A barium swallow (Fig. 1A) revealed marked narrowing at the distal esophagus. A gastroscopy was performed which confirmed the presence of a distal esophageal stricture. The stricture was biopsied, and the tissue samples sent for histological examination.

Haematoxylin and eosin (H&E) sections were entirely representative of granulation tissue surfaced in areas by fibrinopurulent material, consistent with ulceration. No intact mucosa was identified. The inflamed granulation tissue comprised neovascularisation and reactive fibroblasts amidst a mixed inflammatory cell infiltrate of lymphocytes, neutrophils and eosinophils. Within the granulation tissue, isolated foci of larger, atypical cells displaying nucleomegaly were identified (Fig. 1B). Futher investigation included Ziehl-Neelsen (ZN) and Alcian blue – Periodic acid-Schiff (AB-PAS) histochemical stains, as well as CMV immunohistochemistry. CMV immunohistochemical stains highlighted the presence of multiple foci of cells showing strong, nuclear staining, confirming the presence of CMV infection (Fig. 1C). ZN and AB-PAS stains showed no acid-fast bacilli nor fungal elements, respectively.

The patient was commenced on ganciclovir 5 mg/kg intravenously twice a day for 14 days and underwent esophageal dilatation with good result. She was discharged home shortly thereafter being able to tolerate solid foods with no symptoms of dysphagia.

* Corresponding author at: Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital & The University of the Witwatersrand, Chris Hani Road, Diepkloof, Johannesburg, South Africa.
E-mail address: bmansfield@hotmail.com (B. Mansfield).

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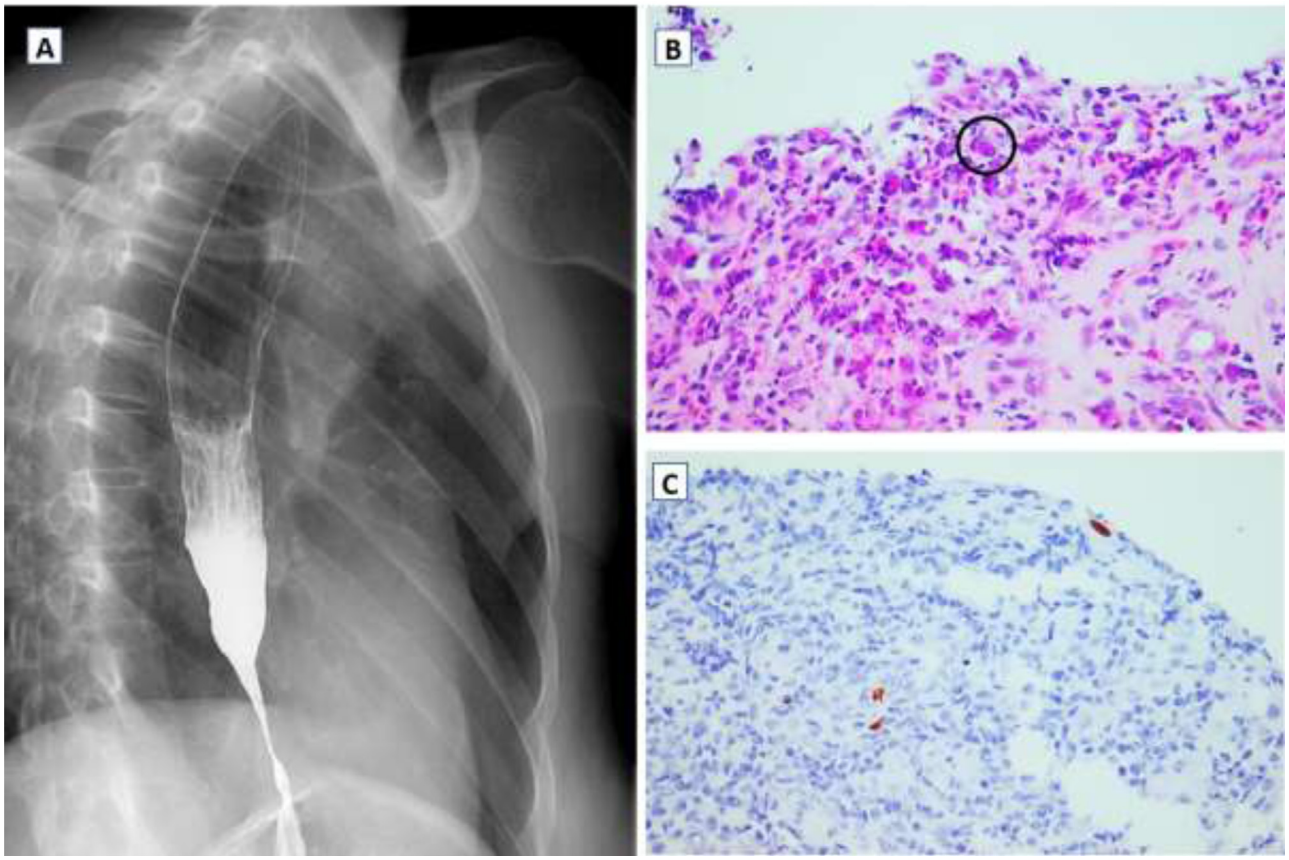

Fig. 1. (A) Barium swallow showing distal esophageal stricture (B) H&E stain at 100x magnification (C) Immunohistochemical stains at 400x magnification.

Discussion

CMV infection is common, with pooled prevalence estimates of CMV IgG seroprevalence among HIV negative adults in Africa found to be 81.8 % (55–97 %) [1]. Those with HIV had a higher seroprevalence at 94.8 % (71–100 %) [1]. HIV-infected individuals with AIDS defining criteria, by contrast, had a lower seroprevalence 81.9 % (59–100 %), which likely represents a poor humoral response to CMV infection [1]. A study in South Africa described 100 % seroprevalence among 402 HIV-infected individuals attending a primary health care clinic [2].

CMV infection causing disease in immunocompetent adults may result in an infectious mononucleosis-type illness or may be asymptomatic. Like other herpes viruses, CMV remains latent after primary infection. Re-activation typically occurs in immunocompromised individuals. CMV disease occurs in immunosuppressed individuals, particularly, HIV-infected individuals with a CD4 count less than 100 cells/μL. The prevalence of disease is declining since the advent of antiretroviral therapy (ART) [3]. However, individuals remain at risk of CMV disease while immune reconstitution occurs [3]. The presence of CMV end-organ disease is associated with reduced survival in HIV patients despite ART [4].

Ocular manifestations, in particular retinitis, are the most common among patients with advanced HIV and reportedly comprise 85 % [3]. Gastrointestinal disease is the next most common manifestation of CMV disease and accounts for around 15 % of cases [3]. Pneumonitis and encephalitis represent less than 1% of all cases of CMV disease [3]. CMV can lead to disease throughout the gastrointestinal tract [3]. CMV colitis is the commonest manifestation of CMV disease, after CMV retinitis. While CMV is among the commonest causes of HIV-related esophageal ulceration, CMV-associated esophageal strictures are rare and limited to a handful of case reports [5–7]. CMV esophagitis is clinically indistinct from that of *Candida* or Herpes simplex virus esophagitis, though co-infection is not uncommon [4]. Patients present with odynophagia or dysphagia [8]. Endoscopically, CMV esophagitis is characterised by large, shallow ulcers which are found in the mid to distal esophagus [3].

IRIS occurs in 16.1 % of HIV positive patients starting ART [9]. The risk of IRIS is dependent on the baseline CD4 count, with the highest risk occurring among patients with a CD4 count less than 50 mmol/L [9]. IRIS may refer to either the “unmasking” of a previously undiagnosed infection which now becomes evident following immune reconstitution, or it may refer to the paradoxical worsening of the symptoms of a previously diagnosed opportunistic infection, in spite of treatment [10]. IRIS associated with CMV, most commonly results in uveitis (immune-recovery uveitis) or worsening retinitis [10]. Other rare manifestations of CMV disease in the setting of IRIS include pneumonitis and colitis [11]. CMV-associated IRIS usually occurs within 8 weeks of starting ART [3]. However, cases of IRIS have been reported up to 6 months after starting ART [10].

Complications of CMV ulceration of the esophagus are rare, but may include, bleeding, tracheo-esophageal fistula or esophageal stricture [6]. Among a cohort of 160 HIV positive patients with esophagitis, Wilcox (1999) described only 6 patients with CMV esophagitis complicated by esophageal stricture, one of which had an esophageal stricture at index endoscopy [6]. In a series of 21 HIV positive patients with CMV esophagitis, Olmos and colleagues (2000) described 2 patients who developed stricture following the administration of ganciclovir [12]. However, no reports of CMV-associated esophageal stricture in the setting of IRIS have been described.

The presence of high levels of CMV DNA in the plasma has a predictive effect in HIV-infected individuals who are more likely to develop CMV disease [3,13]. However, the measurement of CMV DNA and serology is not recommended as it can neither prove nor exclude the presence of CMV disease [13]. Typical symptoms of CMV gastrointestinal disease, endoscopic features and the presence of cellular inclusion bodies clinches the diagnosis of CMV disease. Due to the ubiquitous nature of CMV infection among HIV-infected individuals, a causal relationship between the presence of CMV infection and end-organ disease needs to be established [3]. This is best evaluated histopathologically or by immunohistochemistry [3]. Treatment of CMV esophagitis requires intravenous ganciclovir 5 mg/kg twice daily for 14–21 days [14]. Approximately 40 % of patients will require more than 2 weeks of treatment [14]. Maintenance therapy with valganciclovir is not recommended [14].

Conclusion

CMV is a rare cause of esophageal stricture. Nevertheless, it should be considered among the differential diagnoses of HIV-infected individuals with dysphagia. Consideration should also be given to those patients who have recently started ART and fall within the period of IRIS. Diagnosis relies on histological assessment and visualization of CMV inclusion bodies. Treatment with intravenous ganciclovir for period of 2 weeks together with esophageal dilatation proved to be successful treatment in this case.

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Ethical considerations

Written, informed consent was obtained from the patient prior to commencing any study-related activities. Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (clearance certificate no. M170759).

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

Author contribution

All authors contributed equally to the development of this manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

[1] Bates M, Brantsaeter AB. Human cytomegalovirus (CMV) in Africa: a neglected but important pathogen. J Virus Erad 2016;2:136–42.
[2] Schaftenaar E, Verjans GMGM, Getu S, McIntyre JA, Struthers HE, Osterhaus ADME, et al. High seroprevalence of human herpesviruses in HIV-infected individuals attending primary healthcare facilities in rural South Africa. PLoS One 2014;9(6):1–7.
[3] Steininger C, Puchhammer-Stöckl E, Popow-Kraupp T. Cytomegalovirus disease in the era of highly active antiretroviral therapy (HAART). J Clin Virol 2006;37(1):1–9.
[4] a Erice, Tierney C, Hirsch M, Caliendo a M, Weinberg A, Kendall MA, et al. Cytomegalovirus (CMV) and human immunodeficiency virus (HIV) burden, CMV end-organ disease, and survival in subjects with advanced HIV infection (AIDS Clinical Trials Group Protocol 360). Clin Infect Dis 2003;37(4):567–78.
[5] Goodgame RW, Ross PG, Kim HS, Hook AG, Sutton FM. Esophageal stricture after cytomegalovirus ulcer treated with ganciclovir. J Clin Gastroenterol 1991;13:678–81.
[6] Wilcox CM. Esophageal Strictures complicating ulcerative esopahgitis patients with AIDS. Am J Gastroenterol 1999;94(2).
[7] Sheth A, Boktor M, Diamond K, Lavu K, Sangster G. Complete esophageal obliteration secondary to cytomegalovirus in AIDS patient. Dis Esophagus 2010;23(6):32–4.
[8] Marques S, Carmo J, Pinto D, Bispo M, Ramos S, Chagas C. Cytomegalovirus disease of the upper gastrointestinal tract: a 10-Year retrospective study. GE Port J Gastroenterol. 2017;24(6):262–8.
[9] Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Incidence and lethality of immune reconstitution disease in HIV-infected patients starting antiretroviral therapy: systematic review and meta-analysis. Lancet Infect Dis 2010;10(4):251–61.
[10] Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS (Auckl) 2015;7:49–64.
[11] Miller R, Shaw P, Williams I. Immune reconstitution CMV pneumonitis. Sex Transm Infect 2000;76(60):60.
[12] Olmos M. Esophageal strictures complicating cytomegalovirus ulcers in patients with AIDS. Unusual Cases Tech Notes. 2000;822:.
[13] Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. J Clin Invest 1998;101(2):497–502.
[14] Blanshard C, Benhamou Y, Dohin E, Lernestedt J. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir - a randomized comparison. J Infect Dis 1995;172:622–8.