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Case report

Esophageal *Cytomegalovirus* and *Herpes Simplex* virus co-infection in an immunocompromised patient: Case report and review of literature

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ABSTRACT

Herpes simplex virus and *Cytomegalovirus* co-infection has been reported to occur in a variety of sites in immunocompromised patients. To our knowledge, few cases of such co-infection have been reported to occur in the esophagus. We report a case of a 60-year-old woman who was maintained on immunosuppressive therapy for a presumed diagnosis of pemphigus vulgaris, who presented with odynophagia. Investigations revealed ulcerative esophagitis caused by both HSV and CMV. The patient was treated with valganciclovir with full recovery. We also present the results of various studies on patients with similar presentation particularly those caused by HSV and CMV co-infection.
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Introduction

Herpes simplex virus (HSV) and *Cytomegalovirus* (CMV) co-infection has been reported to occur in different organs such as the skin, genitalia, and brain. In all such cases, the patients were immunocompromised either due to Human Immunodeficiency Virus (HIV) infection, organ transplantation or long-term steroid use. HSV and CMV co-infection in the esophagus is rare. We present the case of a 60-year-old woman previously diagnosed with pemphigus vulgaris who was maintained on immunosuppressive therapy, and who later developed ulcerative esophagitis caused by HSV and CMV. We also present a literature review of the 15 reported cases of esophageal HSV and CMV co-infection.

Case presentation

A 60-year-old woman with a presumed diagnosis of pemphigus vulgaris presented with increasing odynophagia and dysphagia of 1 week duration. She was maintained on prednisone (20 mg/day) and received a recent course of cyclophosphamide. She was treated empirically with itraconazole in another hospital for a presumed fungal infection with no clinical improvement. Physical examination was unremarkable and vital signs were stable on admission. She had normal complete blood count, tested negative for HIV, and had adequate CD4 counts but had hypogammaglobulinemia. Upper gastrointestinal endoscopy revealed multiple well-delineated ulcers throughout the esophagus, more in the proximal part (Fig. 1). There was also a linear white plaque with ulceration at the gastroesophageal junction as well as salmon-colored mucosa extending proximally for about 2 cm. Multiple biopsies of the ulcers were taken. Quantitative real-time PCR was performed on a sample of the patient's serum and showed elevated CMV DNA of 2230 copies/mL.

Light microscopic examination of the esophageal biopsies revealed ulceration and acute inflammation along with characteristic viral cytopathic changes of CMV and HSV in the endothelial and squamous cells, respectively (Fig. 2). Gomori Methenamine Silver stain was negative for fungal organisms. There was no microscopic evidence of pemphigus vulgaris. Immunohistochemical staining for CMV and HSV highlighted the infected cells confirming the microscopic impression of co-infection (Fig. 2). The patient was discharged the next day on valganciclovir which lead to a subsequent improvement of her symptoms. Repeat upper gastrointestinal endoscopy and PCR for CMV DNA three weeks after hospital discharge were negative.

Discussion

The upper gastrointestinal tract particularly the esophagus is a common site of infection in immunocompromised patients [1]. Patients with HIV infection, those on chemotherapeutic agents or steroids, and transplant recipients have a high frequency of esophageal infections. However, infection by multiple viruses is very rare [2]. These patients usually present with one or more of

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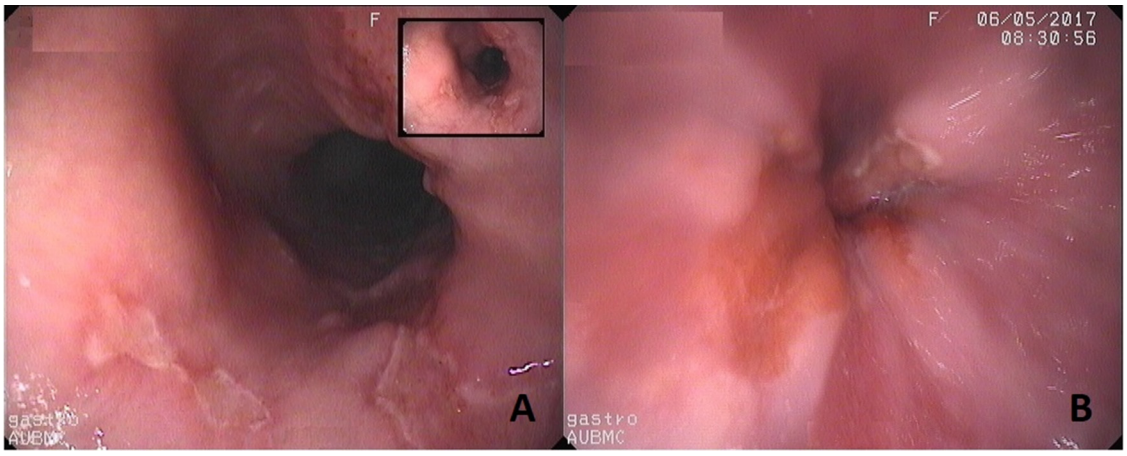

Fig. 1. Upper GI endoscopy. (**A**) Well delineated ulcers in the esophagus. (**B**) Salmon colored mucosal tongue with linear ulceration at the gastro-esophageal junction.

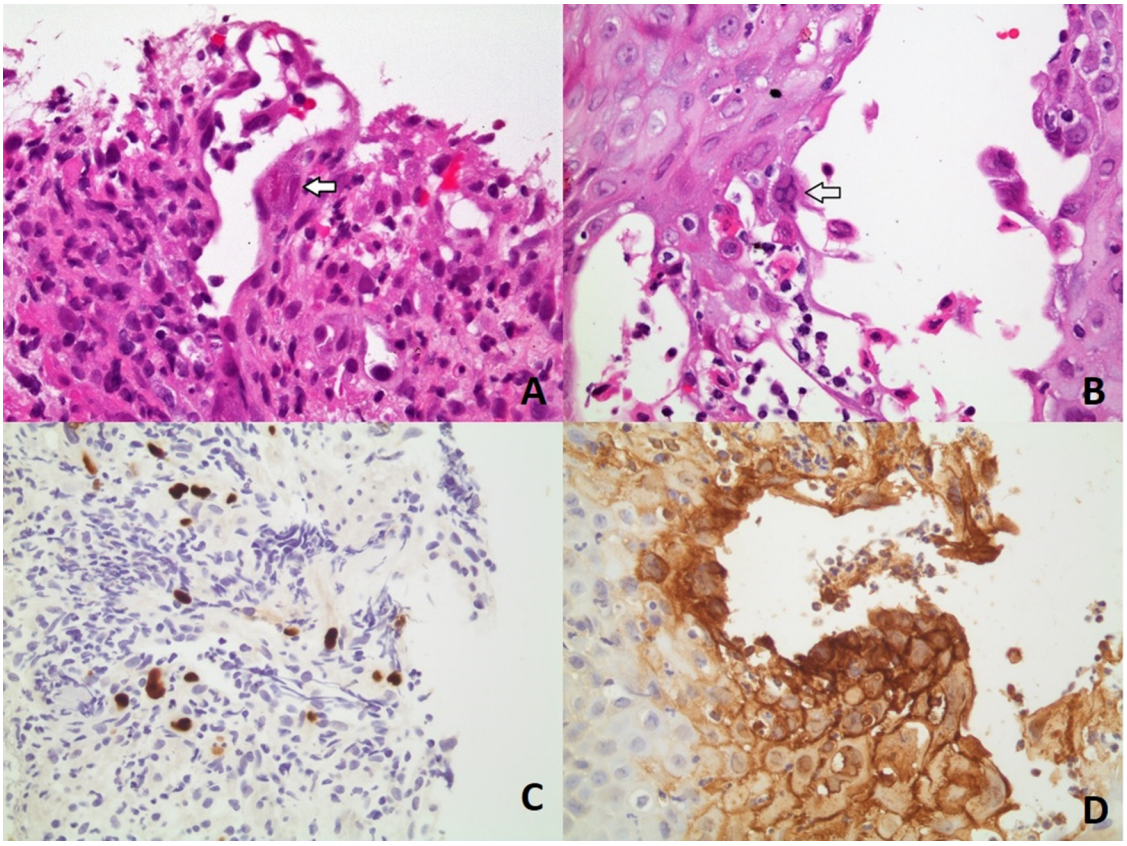

Fig. 2. (**A**) Intranuclear and cytoplasmic inclusions characteristic of CMV infection (Hematoxylin&Eosin stain; 40× magnification). (**B**) Ground glass intranuclear inclusion with multinucleation, nuclear molding, and margination of chromatin characteristic of Herpes simplex infection (Hematoxylin&Eosin stain; 40× magnification). (**C**) Positive staining for CMV (CMV immunostain; 40× magnification). (**D**) Positive staining for HSV (HSV immunostain; 40× magnification).

the following: odynophagia, dysphagia, upper gastrointestinal bleeding, nausea, or vomiting [1].

A variety of organisms can cause infectious esophagitis, most commonly *Candida*, HSV and CMV. Esophagitis due to HSV infection occurs usually in immunocompromised hosts but can occur to a much lesser extent in immunocompetent patients [3]. Endoscopically, the typical findings are erosions and punched-out ulcerations with a yellow rim, most commonly occurring in the distal esophagus [4,5]. Microscopically, the infected squamous cells at the ulcer edge show multinucleation, molding of nuclei which have a ground-glass appearance along with margination of chromatin, and intranuclear eosinophilic (Cowdry A) inclusions.

CMV esophagitis occurs in immunocompromised patients such as organ transplantation recipients, those on long term steroid use, and those infected with HIV [5]. Endoscopically, CMV ulcers are larger than those caused by HSV [4]. They are linear, longitudinal, and deep and are usually located in the distal esophagus [5]. Microscopically, the viral cytopathic changes characteristic of CMV are seen at the ulcer base in infected endothelial, stromal, or glandular epithelial cells. These changes include enlargement of the

Table 1
Patients reported to have esophageal HSV and CMV co-infections in the literature.

	Number of patients	Cause of immunosuppression	Immunosuppressive therapy	Endoscopic findings	Treatment	Outcome
McDonald, G.B. et al. 1984 [7]	Three	Bone marrow transplant	ND	Diffuse ulceration	ND	ND
Bonacini, M. et al. 1991 [4]	Four	HIV	ND	Erythema, friability plaques, erosions and/or ulcers	ND	ND
Wilcox, C. et al. 1995 [1]	Four	HIV	ND	Ulcers	- Ganciclovir and acyclovir (two patients) - Foscarnet - Acyclovir	Recovery
Vodovnik, A. et al. 2000 [2]	One (81-year-old female)	Glomerulonephritis	-Steroids -Cytostatics	Erosive and ulcerative esophagitis	ND	Death of sepsis
Srilatha, P. et al. 2011 [10]	One (38-year-old male)	HIV	ND	Erythema and friability	Acyclovir	Lost to follow-up
Albuquerque, A. et al. 2012 [9]	One (46-year-old male)	Liver transplant	Steroids	Large superficial well-defined ulcers	ND	Death of sepsis and liver failure
Chung, H.H. et al. 2013 [8]	One (26-year-old male)	Renal transplant	-Tacrolimus -Prednisolone -Mycophenolic Acid	- Large ulcer with exposed blood vessels. - Significant upper GI bleeding	Ganciclovir Acyclovir	Significant upper GI bleeding followed by recovery
Current case	One (60-year-old female)	Pemphigus vulgaris?	-Steroids -Cyclophosphamide	Multiple well-delineated ulcers	Valganciclovir	Recovery

HIV; Human immunodeficiency virus, GI; Gastrointestinal, ND; not determined.

cell and nucleus and presence of large eosinophilic or basophilic intranuclear inclusion that is separated from the nuclear membrane by a halo. Cytoplasmic inclusions can also be seen.

Many studies highlighted the causes of esophageal infections and ulceration in patients with HIV. Bonacini et al. studied 110 HIV patients with esophageal symptoms and found that the most frequent causes of esophagitis in these patients were: idiopathic ulceration (35 %), *Candida* (30 %), co-infection with *Candida* and CMV (20 %), CMV alone (6.5 %), HSV alone (5.6 %), and co-infection with CMV and HSV (n = 4, 4%) [4]. Furthermore, Wilcox et al. followed 100 patients with HIV and esophageal ulcers and found that CMV infection was the most common cause (45 %) followed by idiopathic ulceration (40 %), HSV (5 %), GERD (4 %), CMV and HSV (n = 4, 4%), idiopathic ulceration/CMV (1%), and pill induced (1 %) [1]. Viral co-infection with CMV and HSV was rare in both studies accounting for 4% overall.

Alexander et al. followed 68 patients on immunosuppressive therapy for liver or kidney transplantation. Only 10 patients in this series developed esophagitis during long term follow-up. HSV (n = 4), CMV (n = 3), and *Candida* (n = 3) were the causes [6]. Similarly, McDonald et al. followed 39 patients post bone marrow transplantation of whom 21 patients developed infectious esophagitis and found that CMV (n = 7; 33 %), HSV (n = 6; 28.6 %), *Candida* (n = 4; 19 %), both CMV and HSV (n = 3, 14.3 %), both HSV and *Candida* (n = 1, 4.8 %) infections were the causes of esophagitis [7]. Viral co-infection with CMV and HSV occurred in 3 of 21 (14.3 %) patients [7]. In these two (and other) studies, CMV was the most frequent cause of esophagitis in post-transplant patients.

Our literature review identified 15 patients with HSV and CMV co-infection; four case reports and 11 cases in the previously mentioned studies. (Table 1) [1,2,4,7–10]. Nine of the fifteen cases (60 %) had HIV infection as a cause of immunosuppression. Based on our limited data in this review, three of the seven patients with available outcome experienced significant complications; a major upper gastrointestinal bleeding in one patient who subsequently recovered and sepsis in two patients who subsequently died of it. However, the limited data suggest that patients who were promptly diagnosed and who received the drug of choice for Cytomegalovirus infection namely ganciclovir or the oral prodrug valganciclovir, had the most favorable clinical outcome with recovery.

Conclusion

Infectious esophagitis by multiple organisms can be a major cause of morbidity and mortality in immunocompromised patients and may be associated with serious complications such as a serious upper gastrointestinal bleeding. Upper gastrointestinal symptoms in such patients should be promptly investigated with proper techniques such as serology, molecular tests, endoscopy with biopsies and immune-stains to exclude different infections particularly co-infections as proper medications are available with good response rates in such cases. Similarly, in any patient presenting with infectious esophagitis for no obvious reason, immunocompromised state such as HIV infection should be suspected and ruled out.

Author contributions

S. Bannoura and S. Sinno performed the literature review, and drafted, edited, and finalized the manuscript. S. Bannoura captured the images. Z. Chakhachiro and F. Boulos drafted, edited, and finalized the manuscript. K. Barada captured the endoscopy images, edited, and finalized the manuscript, and is the article guarantor.

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Consent

Written informed consent was obtained from the patient for publication of this case report and is available upon request.

CRediT authorship contribution statement

Sami Bannoura: Investigation, Writing - original draft. **Kassem Barada:** Investigation, Writing - original draft. **Sara Sinno:** Investigation. **Fouad Boulos:** Supervision. **Zaher Chakhachiro:** Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors declare that there are no competing interests regarding the publication of this paper.

References

[1] Wilcox C, Schwartz DA, Clark W. Esophageal ulceration in human immunodeficiency virus infection: causes, response to therapy, and long-term outcome. Ann Intern Med 1995;123(2):143–9, doi:http://dx.doi.org/10.7326/0003-4819-123-2-199507150-00010.

[2] Vodovnik A, Cerar A. Synchronous herpes simplex virus and cytomegalovirus esophagitis. Z Gastroenterol 2000;38(06):491–4, doi:http://dx.doi.org/10.1055/s-2000-14887.

[3] Canalejo Castrillero E, Garcia Duran F, Cabello N, Garcia Martinez J. Herpes esophagitis in healthy adults and adolescents: report of 3 cases and review of the literature. Medicine 2010;89(4):204–10, doi:http://dx.doi.org/10.1097/MD.0b013e3181e949ed.

[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):1567–72, doi:http://dx.doi.org/10.1001/archinte.1991.00400080067012.

[5] Rosołowski M, Kierzkiewicz M. Etiology, diagnosis and treatment of infectious esophagitis. Prz Gastroenterol 2013;8(6):333–7, doi:http://dx.doi.org/10.5114/pg.2013.39914.

[6] Alexander JA, Brouillette DE, Chien MC, Yoo YK, Tarter RE, Gavaler JS, et al. Infectious esophagitis following liver and renal transplantation. Dig Dis Sci 1988;33(9):1121–6, doi:http://dx.doi.org/10.1007/BF01535788.

[7] McDonald GB, Sharma P, Hackman RC, Meyers JD, Thomas ED. Esophageal infections in immunosuppressed patients after marrow transplantation. Gastroenterology 1985;88(5, Part 1):1111–7, doi:http://dx.doi.org/10.1016/S0016-5085(85)80068-8.

[8] Chung HH, Jang JY, Byun JM, Park SH, Kim DH, Chang YW. Upper gastrointestinal hemorrhage from esophageal ulcer caused by co infection of Herpes Simplex virus and cytomegalovirus in immunocompromised patient. Korean J Helicobacter Up Gastrointest Res 2013;13(1):69–72, doi:http://dx.doi.org/10.7704/kjhugr.2013.13.1.69.

[9] Albuquerque A, Cardoso H, Ribeiro A, Rios E, Silva R, Magalhães J, et al. Herpes and cytomegalovirus esophagitis. Endoscopy 2012;44(S 02):E242–243, doi:http://dx.doi.org/10.1055/s-0032-1309385.

[10] Srilatha P, Suvarna N, Gupta A, Bhat G. Esophageal ulcer in a HIV-seropositive patient co-infected by herpes simplex and cytomegalovirus. Indian J Pathol Microbiol 2011;54(1):219–20, doi:http://dx.doi.org/10.4103/0377-4929.77420.