Case report

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

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\textbf{Article info}

\textbf{Abstract}

\textsuperscript{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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\textbf{Introduction}

\textsuperscript{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.

\textbf{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.

\textbf{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
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

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).
| Author                        | Patients | Cause of immunosuppression | Immunosuppressive therapy | Endoscopic findings | Number of patients | Cause of endoscopic findings | Outcome |
|------------------------------|----------|-----------------------------|----------------------------|---------------------|--------------------|-----------------------------|---------|
| S. Bannoura et al. 2013 [8]  | One      | Renal transplant - Tacrolimus | Steroids                   | Erosive and ulcerative esophagitis | One (26-year-old male) | Large superficial well-defined ulcers | Death of esophagus and liver failure |
| Albuquerque, A. et al. 2012  | One      | - Cyclophosphamide          | Steroids                   | Erosive and ulcerative esophagitis | One (46-year-old male) | Large superficial well-defined ulcers | Significant upper GI bleeding followed by recovery |
| Wilcox, C. et al. 1995 [1]   | Four     | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | Four (two patients)   | - Large ulcer with exposed blood vessels - Significant upper GI bleeding | Recovery |
| Bonacini, M. et al. 1991 [4] | Four     | ND                          | - Ganciclovir and acyclovir (two patients) | Erythema and friability | Four (81-year-old female) | Erythema and friability | Recovery |
| Vodovnik, A. et al. 2000 [7] | Three    | - Steroids                  | - Steroids                 | Erosive and ulcerative esophagitis | Three (38-year-old male) | Erythema and friability | Recovery |
| Srilatha, P. et al. 2011 [10]| One      | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | One (60-year-old female) | Erythema and friability | Recovery |
| Chung, H.H. et al. 2013 [8]  | One      | - Valganciclovir            | - Acyclovir                | Erosive and ulcerative esophagitis | One (60-year-old female) | Large superficial well-defined ulcers | Recovery |
| Bonatini, M. et al. 1991 [4] | Four     | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | Four (81-year-old female) | Death of esophagus and liver failure | Recovery |
| Wilcox, C. et al. 1995 [1]   | Four     | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | Four (two patients)   | Erythema, friability plaques, erosions and/or ulcers | Death of esophagus and liver failure |
| Wilcox, C. et al. 1995 [1]   | Four     | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | Four (two patients)   | Erythema, friability plaques, erosions and/or ulcers | Death of esophagus and liver failure |
| Wilcox, C. et al. 1995 [1]   | Four     | ND                          | - Acyclovir                | Erosive and ulcerative esophagitis | Four (two patients)   | Erythema, friability plaques, erosions and/or ulcers | Death of esophagus and liver failure |

**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. Chakhachi 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.

**Funding**

None to report.
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.

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