EDITORIAL

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# Tissue-invasive upper gastrointestinal cytomegalovirus disease in transplant and non-transplant patients

Seokin Kang

Division of Gastroenterology, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

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Cytomegalovirus (CMV) is a double-stranded DNA virus belonging to the Herpesviridae family. CMV has a high global seroprevalence, ranging from 40–90% in the general population [1,2]. CMV generally does not cause symptoms in individuals with an intact immune system as the host cell-mediated immunity effectively prevents the manifestation of noticeable CMV infections [3]. However, CMV can emerge as an opportunistic pathogen in immunocompromised patients, causing encephalitis, retinitis, hepatitis, and nephritis. Specifically, CMV infection is a key concern for transplant recipients, and it is recommended that they receive CMV prophylaxis with antiviral agents (such as ganciclovir) after transplantation [4].

Among the various organ systems, the gastrointestinal (GI) tract is frequently affected by CMV, accounting for 30% of tissue-invasive CMV diseases in immunocompromised individuals [5]. Within the GI tract, the colon is the most commonly affected site, followed by the esophagus [6]. CMV can affect any segment of the upper GI tract, from the esophagus to the duodenum. Nevertheless, its diagnosis remains challenging because no specific clinical signs or endoscopic findings definitively indicate an upper GI CMV infection.

Although several studies have examined the clinical features and endoscopic findings of tissue-invasive GI CMV disease, data for establishing definitive guidelines or management plans remain limited. The study by Kim et al. [7] provides new insights into the clinical characteristics and endoscopic features of upper GI CMV disease in immunocompromised patients, particularly the comparison of transplant and non-transplant groups. The authors analyzed 219 immunocompromised patients with tissue-invasive upper GI CMV disease (132 transplant and 87 non-transplant patients) over a median follow-up period of 51 months. The results revealed that 18.7% of the patients were asymptomatic in accordance with previous research, despite the presence of distinct mucosal lesions (such as erosion and ulceration) observed on endoscopy.

According to previous studies, CMV most frequently affects the esophagus in the upper GI organs, often presenting as deep ulcers with clear margins. In this study, non-transplant patients showed a pattern consistent with prior studies; however, transplant patients exhibited gastric involvement most frequently (90/132) and a higher rate of gastric erosion, which contrasts with earlier literature. Furthermore, the authors identified different characteristics between the two groups: transplant patients were younger at the time of upper GI CMV diagnosis (56.0 vs. 64.0, $p = 0.001$), had lower baseline Charlson Comorbidity Index scores (4.0 vs. 5.0, $p = 0.001$), and showed a higher rate of complete response (87.7% vs. 62.1%, $p < 0.001$). Several hypotheses have been proposed to explain these differences. First, routine post-transplant surveillance endoscopy may enable the early detection of CMV disease. Second, transplant patients present with milder manifestations of upper GI CMV disease, owing to CMV prophylaxis. Finally, GI CMV disease might be primarily associated with baseline comorbidities, rather than with immunosuppression alone.

Although CMV blood tests, including those for serum antibodies, antigenemia, and polymerase chain reaction (PCR) for CMV DNA can provide valuable information, they are



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not definitive diagnostic methods for GI CMV infections. In this study, the rate of CMV antigenemia/viremia was relatively low (63.2%) in patients with upper GI CMV disease (67.2% and 55.0% in transplant and non-transplant patients, respectively; $p = 0.117$). Histopathological examination is the definitive diagnostic method (positive results of immunohistochemical staining or PCR for CMV). Accordingly, it is crucial to initially suspect CMV infection and proceed with biopsy. This study underscores the importance of thoroughly observing and considering GI CMV infection and obtaining tissue samples even when endoscopic findings do not show a deep ulcer with clear margins.

A major strength of this study is its large sample size (219 patients) and long-term follow-up period (median 51 months), representing the largest dataset and longest follow-up reported for upper GI CMV disease to date. However, the single-center, retrospective design may limit the generalizability of the findings. Additionally, the absence of immunocompetent patients in this study prevented direct comparison between immunocompetent and immunocompromised patients.

Overall, upper GI CMV disease in transplant patients may differ from that in non-transplant patients, manifesting in the stomach more frequently and in various forms, including erosions and ulcers. Suspecting CMV infection and performing biopsies for histopathological examination are crucial for prompt diagnosis and treatment to prevent further complications. This remains critical even when endoscopy reveals only mild mucosal abnormalities, particularly in transplant patients. However, additional clinical research is required to fully understand the clinical and endoscopic features of tissue-invasive upper GI CMV infections.

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**Correspondence to**
Seokin Kang, M.D., Ph.D.
Division of Gastroenterology, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea
Tel: +82-31-910-7992, Fax: +82-31-910-7219
E-mail: seokinkang.md@gmail.com
https://orcid.org/0000-0003-2228-6479

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