Rare cause of odynophagia: Giant esophageal ulcer

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Abstract
Gastrointestinal complications are a frequent cause of morbidity after transplantation and may affect up to 40% of kidney transplant recipients. Here we report a rare case of idiopathic giant esophageal ulcer in a kidney transplant recipient. A 37-year-old female presented with a one-week history of odynophagia and weight loss. Upon admission, the patient presented cold sores, and a quantitative cytomegalovirus polymerase chain reaction was positive (10^5 copies/mL). An upper endoscopy demonstrated the presence of a giant ulcer. Serological test and tissue biopsies were unable to demonstrate an infectious origin of the ulcer. Immunosuppression was reduced and everolimus was introduced. An empirical i.v. therapy with acyclovir was started, resulting in a dramatic improvement in symptoms and complete healing of the ulcer. Only two cases of idiopathic giant esophageal ulcer in kidney transplant recipients have been reported in the literature; in both cases, steroid therapy was successful without recurrence of symptoms or endoscopic findings. However, this report suggests that correction of immune imbalance is mandatory to treat such a rare complication.

Key words: Acyclovir; Gastrointestinal complications; Kidney transplantation; Endoscopy; Steroid; Idiopathic
A 37-year-old female presented with a 1-wk history of severe odynophagia and epigastric pain, worsening after food intake. She had received a deceased donor kidney transplantation 6 mo prior, and the immunosuppressive regimen consisted of tacrolimus, mycophenolic acid and prednisone. Upon admission, the patient presented cold sores, the leucocytes were 1300/mm$^3$, and a quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) was positive ($10^3$ copies/mL). Graft functionality was slightly impaired (Serum creatinine, 2.1 mg/dL). Intravenous ganciclovir therapy (250 mg daily) was immediately started combined with oral acyclovir; mycophenolic acid was discontinued; and tacrolimus was replaced with everolimus, without any beneficial effects. The patient was unable to swallow solid food and lost 8 kg. Upper endoscopy was performed, showing a large ulcer in the distal esophagus measuring 40 mm in diameter (Figure 1). Endoscopic biopsies showed acute inflammation without any viral particles, but with positivity to Candida species (PASD stain) (Figure 2). Her symptoms failed to resolve after two weeks of total parental nutrition, high dose omeprazole (80 mg daily) and fluconazole (200 mg daily). Repeat endoscopy revealed only a slight improvement of the ulcer. Histological examination of biopsy and cytology material for fungal or viral infection was negative, and histochemical studies for CMV, herpes simplex virus (HSV) and adenoviruses were negative and CMV-DNA PCR was negative. Intravenous/empircic therapy with acyclovir (900 mg daily) was started. Her symptoms dramatically improved over 48 h and completely resolved within 10 d, with concomitant partial weight gain (4 kg), and normal leucocytes count (5240/mm$^3$). Repeat endoscopy 10 d after acyclovir treatment revealed near complete resolution of the ulcer (Figure 3). The patient continued oral valganciclovir and acyclovir therapies, without recurrence of symptoms six months after diagnosis and with excellent graft function.

**DISCUSSION**

*Candida* esophagitis is the most common esophageal disorder in renal transplant recipients, and usually occurs in leukopenic or over-immunosuppressed patients within six months after transplantation$^{[1,2]}$. In most cases, *Candida* esophagitis is associated with candidal stomatitis and epiglottitis. In general, *Candida* esophagitis presents with odynophagia, but endoscopic findings are characteristic with multiple small plaques in the upper or mid esophagus. Other causes of esophagitis include CMV or herpes simplex infection. The typical appearance of herpetic esophagitis is represented by multiple vesicular lesions with or without ulcers along the entire esophagus$^{[2]}$. However, the endoscopic manifestation of herpetic esophagitis may be similar to that of CMV esophagitis, such that diagnosis should be confirmed by cytology, histological examination and viral cultures.

Idiopathic giant ulcers are rarely observed and are
more commonly encountered in patients with HIV infection\(^4,5\). HIV has been observed in ulcer tissue, suggesting that HIV itself could be the direct cause of these lesions\(^6\). However, it can also be detected in esophageal biopsies from patients with *Candida*, *CMV* and *HSV* esophagitis\(^5\). Our report and other previous cases\(^7,8\) provide clinical evidence that idiopathic giant esophageal ulcer can occur in the absence of HIV infection, and favor a defect of immunity rather than a virus etiology in the pathogenesis of idiopathic esophageal ulceration\(^5\).

In our report, although the clinical context of the patient suggested a potential CMV-related ulcer, there was no evidence of viral cytopathology as assessed from routine histological or immunohistochemical studies. Furthermore, our patient was on high dose ganciclovir and did not demonstrate any clinical beneficial effect on odynophagia and weight loss because the patient continued to be unable to swallow solid food. Histological finding of fungal infection was most likely related to a direct contamination of the ulcer because there was no evidence of *Candida* stomatitis or characteristic endoscopic lesions in the esophagus. Moreover, the ulcer failed to improve after a high dose of fluconazole. Histopathological features cannot distinguish idiopathic ulceration from gastroesophageal reflux disease, but the patient presented no endoscopic appearance to suggest reflux disease and her symptoms and esophageal ulceration failed to improve to high dose omeprazole and total parental nutrition. Although the clinical finding of cold sores and the dramatic temporal response to high-dose acyclovir therapy may suggest a herpetic origin for the giant ulcer, we were unable to demonstrate the presence of viral particles using histological or immunohistochemical studies, and routine serological tests for HSV were negative.

There have only been two reports of idiopathic giant esophageal ulcer in kidney transplant recipients\(^6,7\), and both patients were previously subjected to over-immunosuppression to prevent acute rejection episodes. In both cases, steroid therapy was successful without recurrence of symptoms or endoscopic findings. The response to idiopathic esophageal ulcer to steroids is clearly documented in AIDS, with a clinical remission observed in more than 90% of cases\(^9\). The prednisone regimen consists of 40 mg/d, tapering 10 mg/wk for a 1-mo treatment course. The relapse rate for esophageal ulcers in AIDS treated with steroids is approximately 40%, but retreatment is usually successful.

Leucopenia has been shown to be involved in the pathogenesis of giant ulcer in a kidney transplant recipient\(^7\) as a result of overimmunosuppression. Our report provides the first clinical experience that a combination of reduction in immunosuppression and high-dose of acyclovir may result in a normalization of leucopenia and correction of immune imbalance, leading to rapid healing of the ulcer and a resolution of symptoms.

In conclusion, giant esophageal ulcers are uncommon in kidney transplant recipients and the diagnosis of causality is often delayed. Treatment is often empirical and the aggressive nature of the disease may result in erroneous treatment decision, leading to higher patient morbidity.

The correction of the immune imbalance found in these patients plays a key role in the management of giant esophageal ulcer.
Peer-review
This is an interesting case report. Farrell et al reported previously the first case of giant esophageal ulceration responsive to steroids in an immunosuppressed human immunodeficiency virus negative patient. It's well written and acceptable for publication.

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