An esophageal-mediastinal fistula in a renal transplant patient—a late complication that shall both dither the clinician and be rapidly fatal: A case report

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ABSTRACT

Although renal transplantation has said to have transformed the quality of lives of most of the end stage renal disease patients, it is attended by its own set of complications including allograft rejection, drug-related side effects, small to potentially lethal infections, and various malignancies in the long run. Esophageal ulcers are known to occur after renal transplantation due to various infections including cytomegalovirus (CMV)/Herpes and the drugs Mycophenolate mofetil (MMF) and steroids. We hereby report a rare gastrointestinal complication of esophageal-mediastinal fistula in a renal transplant patient that presented as severe mediastinitis and had a rapidly downhill course in our patient.

Keywords: Esophageal-mediastinal fistula, Mediastinitis, Renal transplant

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INTRODUCTION

Renal transplantation has transformed the lives of almost all the end stage renal disease patients with drastic positive change in their quality of life, an imminent improvement in the uremic symptomatology, a feel good appeal of not to face long and painful needles of hemodialysis anymore, etc. Nevertheless, it would be a gross lopsided tilt if the serious and detrimental effects of immunosuppression are conveniently ignored. Of all the side effects, gastrointestinal (GI) symptoms take a big scourge on the patients because of their common occurrence and the cumbersome nature. The spectrum of GI complications ranges from mild mucosal injury, mucocutaneous ulcerations, biliary tract disease to serious and life-threatening perforations, pancreatitis, and malignancy [1]. Among the hollow viscus perforations, colon, small bowel, stomach, duodenum have been reported in several studies with varying incidences [2]. Esophageal perforations leading to esophageal-mediastinal fistula and severe mediastinitis have very occasionally been reported. We hereby report one such case of a deep esophageal ulcer perforating into the mediastinum through a fistula causing severe
mediastinitis and sepsis and finally turning out to be rapidly fatal for the patient.

**CASE REPORT**

Our patient, a 27-year-old lady renal allograft recipient got admitted with several episodes of severe vomiting followed by a four day history of high grade fever, severe chest discomfort, choking sensation, odynophagia, vomiting, and retching. Approximately seven months before this presentation, she underwent renal transplantation in our institution with her sister as the donor. Her basic disease was probably chronic glomerulonephritis. Her preoperative endoscopy was normal and there was no exposure to tuberculosis. She was discharged with excellent graft function and was put on triple drug immunosuppression. Cytomegalovirus status was D-R+. No induction was given at the time of transplantation and she was given valganciclovir and septran prophylaxis appropriately. Mycophenolate mofetil was given as 1 g twice daily for one week post-transplantation and converted to 500 mg bid from then on. Tacrolimus was started at a dose of 0.15 mg/kg/day and steroid as prednisolone was slowly tapered to reach a nadir dose of 5 mg/day from the fourth month. Her clinical examination showed high temperature, an apathetic look, and mild bilateral basal crackers on the lung fields. Her gums were inflamed and the pharyngeal wall showed signs of oral thrush.

She had raised white blood cell (WBC) count and an acute allograft dysfunction with a creatinine of 2.4 mg/dL. X-ray chest findings were nonspecific. As she had typical symptoms suggestive of obstruction in the upper GI tract, we immediately proceeded with an upper GI endoscopy.

Endoscopy revealed features suggestive of lower esophageal candidiasis (Figure 1) and inflamed exudates along with a large excavating ulcer at approximately 20 cm from the incisor teeth (Figure 2). The ulcer was in the right lateral wall of the esophagus with a possible fistulous communication with the mediastinum. Biopsy was taken from the ulcer and the tissue was sent for CMV polymerase chain reaction (PCR), tuberculosis (TB) PCR, Herpes simplex, and CMV intranuclear giant cell inclusion bodies.

Meanwhile, a Ryle’s tube was inserted for feeding. Broad spectrum antibiotics were started and immunosuppressants dose was drastically reduced. Fluconazole was started orally with adjustment to tacrolimus dose. Plain computed tomography (CT) scan was also done which showed a fistulous communication between the deep-seated ulcer and the mediastinum (Figure 3).

While a simultaneous oral contrast study was to be done to demonstrate the fistulous tract as per the plan, the patient became very sick and the procedure had to be abandoned. Later, despite all the measures the patient could not be saved.

Though moniliasis was diagnosed by endoscopy, the ulcer failed to grow any Candida species on culture and

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**Figure 1:** Esophageal moniliasis seen in the endoscopy.

**Figure 2:** A large excavated and perforating ulcer seen in the right lateral wall of the esophagus (indicated by the white arrow). The normal esophageal path is shown by the red arrow.

**Figure 3:** Plain CT showing the esophageal-mediastinal fistula.
tissue for CMV PCR, TB PCR, and Herpes simplex were also negative in the biopsy specimen, the results of what were obtained at a later date. Real-time PCR for CMV quantitative DNA analysis in blood was also negative.

DISCUSSION

The incidence of GI complications is quite high after renal transplantation. It can be as high as 20% [3] and can be severe and life threatening in up to 10% of patients [4]. The wider spectrum of GI manifestations ranges from simple nausea, vomiting, mucosal ulcers, stomatitis, oral thrush, gastric and esophageal ulcers to life-threatening hollow viscus perforations (mainly gastric and duodenal ulcer perforations), severe pancreatitis, infectious colitis, ischemic or infectious colonic perforation, diverticulitis, post-transplant lymphoproliferative disorder (PTLD), and rarely Helicobacter pylori associated MALTomas [5].

The GI tract is the commonest organ to be involved in CMV infection and esophagitis is the second most common GI manifestation, next to colitis [6]. Cytomegalovirus ulcers are usually shallow and multiple, though occasionally they can be deep and solitary [7]. Most of such CMV ulcers are seen in the mid to distal third of the esophagus [7]. In our case, the ulcer was solitary, deep and perforating, and was almost at the end of the cervical esophagus, approximately 20 cm from the level of the incisor teeth. Ulcer biopsy did not show any typical cytopathic effects of CMV and the tissue PCR was negative. Cytomegalovirus quantitative DNA analysis in serum was also negative.

Both Herpes simplex viruses 1 and 2 have been known to cause oral and mainly esophageal ulcers. Most of such ulcers are in the mid or distal esophagus and are usually linear, multiple and accompanied by erythema. Biopsy typically reveals the typical Cowdry type A intranuclear inclusions and ground glass multinucleated giant cells [8]. In our case, the patient had a large single perforating ulcer in the upper part of the esophagus that was not associated with any typical intranuclear inclusion bodies or cytopathic changes consistent with Herpes simplex esophagitis.

Parfitt et al. [9] did a study on 75 different transplant recipients on MMF therapy. They found ulcerative esophagitis, reactive gastropathy, and graft versus host disease like picture as the main manifestations. In another similar study by Nguyen et al. [10], GI-related symptoms and abnormalities due to MMF manifested between 1 month and 10 years of various solid organ transplantations. Active esophagitis did occur in 43%, esophageal ulceration in 29%, and erosion in 14% of the patients. Serum mycophenolic acid (MPA) levels do not usually correlate well with the toxicity associated with MMF, nor is it available universally.

Invasive fungal infection particularly as a cause of esophageal perforation alone is extremely rare and most often occurs in the immediate postoperative period. Gock et al. reported a case of fatal invasive fungal candidiasis causing esophageal perforation [11]. They could grow hyphal elements of Candida species. Additionally, the patient had other features of disseminated candidiasis like severe neutropenia, pleural effusion, etc. Our patient’s ulcer did not grow any fungal elements nor were there any other systemic manifestations. Fatal systemic fungal infections most often occur in the immediate postoperative period, in the first month after renal transplantation, where the patient is at the peak of her/his immunosuppression. Our patient presented with perforation, seven months after renal transplantation when the immunosuppression doses have almost reached a nadir.

Boerhaave syndrome is the most common type of spontaneous esophageal perforation. It usually occurs out of a sudden increase in intraoesophageal pressure while the intrathoracic pressure is negative as in severe vomiting. This perforation usually involves the left posterolateral aspect of the distal intrathoracic esophagus but can occur in the cervical or intra-abdominal esophagus as well. Our patient had several episodes of severe vomiting before the onset of fever, though the esophageal perforation was located at the cervicothoracic junction approximately and was rather on the right lateral wall than on the left wall of the esophagus [12].

Mortality associated with esophageal perforation varies depending on the size of perforation and the time of diagnosis. The reported mortality from treated esophageal perforation is 10–25%, when therapy is initiated within 24 hours of perforation, but it could rise up to 40–60% when the treatment is delayed beyond 48 hours [13]. Our patient presented nearly four days after the onset of the symptoms and the perforation was quite large. We could not do much for our patient as she presented in a very sick state, nearly four days after the symptoms and there was severe mediastinitis and sepsis at the time of presentation itself.

CONCLUSION

Esophageal ulcer to the extent of going for perforation and forming esophageal-mediastinal fistula in a post-renal transplantation is rare and can be rapidly fatal in the setting of severe mediastinitis. Cytomegalovirus, Herpes simplex virus, MMF, prolonged, repeated, and severe vomiting on itself are the common causes of esophageal perforation and the resultant fistula. While infectious causes need to be treated accordingly, rapid surgical intervention for the closure of the perforation is of paramount importance. Patients while on maintenance immunosuppression should be warned about such symptoms like dysphagia, odynophagia and fever, and should approach the nephrologist much early for proper and prompt intervention.
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Author Contributions

Rajesh Jayaraman – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ganesh Aravindh – Design of the work, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Vidyasagar Subramaniam – Acquisition of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Karthikeyan CRM – Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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