

# Tacrolimus-Induced Acute Esophageal Necrosis

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## ABSTRACT

Acute esophageal necrosis (AEN) has been rarely described and has poorly understood pathophysiology although it is thought to be related to mucosal defense barrier disruption. We report a case of AEN in a 71-year-old patient with clinical signs of gastric outlet obstruction along with anemia and sepsis in the setting of a recent kidney transplant. After failing standard supportive measures, tacrolimus was switched to cyclosporin with overall rapid improvement of AEN and concomitant duodenal ulcerations. This case underscores a possible rare adverse effect of a commonly used immunosuppressant agent that, to our knowledge, has not been specifically reported.

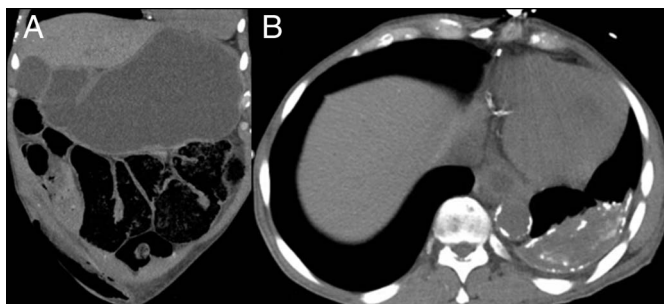
## INTRODUCTION

Acute esophageal necrosis (AEN) with duodenal ulceration is incredibly rare. Although the pathophysiology is not entirely understood, spontaneous resolution is typically seen within 1–2 weeks with supportive care.<sup>1</sup> Tacrolimus is a commonly used immunosuppressant agent in the post-transplant setting and has previously been documented to cause stomatitis. In one case report, esophageal and ileal ulceration occurred. However, tacrolimus has not previously been found to induce or contribute to AEN.<sup>2</sup>

## CASE REPORT

A 71-year-old man with coronary artery disease and type 2 diabetes complicated by end-stage renal disease presented with intractable nausea, emesis, poor oral intake, and generalized weakness 10 days postoperatively from an uncomplicated renal transplant. Immediately postoperatively, the patient was initiated on tacrolimus, mycophenolate, sulfamethoxazole/trimethoprim, acyclovir, and a 1-week course of prednisone. There was no nonsteroidal anti-inflammatory drug use. On presentation, the patient had transient volume responsive hypotension and hypothermia, which resolved in less than 24 hours. Laboratory evaluation revealed hyperglycemia (glucose 308 mg/dL), leukocytosis (white blood cell count 28.7 K/UL), hypoalbuminemia (albumin 2.2 mg/dL), a lactate of 8.8 mm/L, and a supratherapeutic tacrolimus trough of 15.8 ng/mL which had been previously therapeutic. His renal function was unchanged from 4 days earlier.

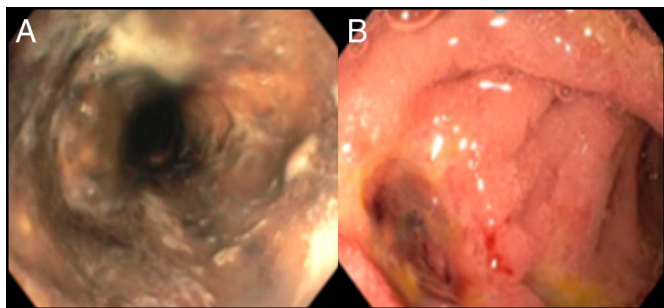
A computed tomography scan revealed a markedly distended stomach and thickened distal esophagus (Figure 1). A nasogastric tube was placed for 48 hours for gastric decompression and he was started on piperacillin-tazobactam. An infectious workup was unrevealing. Although both the trend in lactate and leukocytosis serially improved, he developed acute on chronic anemia with a hemoglobin of 6.2 mg/dL (baseline 10 mg/dL) with melena. Esophagogastroduodenoscopy (EGD) on postoperative day (POD) 13 showed pan circumferential necrosis and black pigmentation from the upper esophageal sphincter to the gastroesophageal junction with poor luminal distension, a normal stomach, and numerous clean-based duodenal ulcers extending from the bulb to the second portion (Figure 2). By comparison, an EGD from 2 months earlier showed a small duodenal adenoma but was otherwise unremarkable with gastric biopsies that were negative for *Helicobacter pylori*. He was placed on a liquid diet, high-dose oral proton pump inhibitor (PPI), and sucralfate slurry but continued to be transfusion-dependent with ongoing melena and new dysphagia. On POD 24, an EGD showed progression of proximal



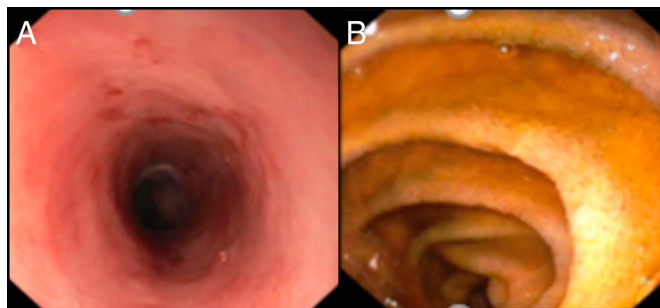
**Figure 1.** Computed tomography without contrast showing (A) gastric distention and (B) thickened distal esophagus.

luminal narrowing requiring an ultrathin endoscope to traverse the esophagus and no improvement in duodenal ulceration or esophageal necrosis. Esophageal biopsies showed granulation tissue and necrotic debris consistent with ulceration; immunostains were negative for a viral etiology. Fasting serum gastrin level was 151 pg/mL on PPI. The lack of endoscopic healing with an otherwise improved clinical picture prompted a search for an alternative cause.

A single case reported a distal esophageal and ileal ulcer in a postheart transplant patient who failed to improve with standard medical therapy, however, rapidly and completely healed on switching from tacrolimus to cyclosporin. On POD 25, the patient was transitioned from tacrolimus to cyclosporin, kept nil per os, and started on total parental nutrition. One week later, his hemoglobin stabilized. Repeat EGD on POD 32 showed marked improvement in esophageal necrosis with residual edema and friability along with nearly completely healed duodenal ulcers (Figure 3). Improvement was most pronounced in the middle and distal third of the esophagus. There was persistent luminal narrowing in the proximal esophagus. The patient was advanced to a full liquid diet and maintained on PPI. He underwent a surgical gastrostomy tube and was transitioned off total parental nutrition. Six weeks later, serial EGDs were performed for a 4-mm diameter stricture measuring 6 cm in length using Savary dilation starting at 18Fr and ultimately increased to 36Fr by the third dilation EGD.



**Figure 2.** Esophagogastroduodenoscopy showing (A) the esophagus with ulceration and necrosis throughout and (B) duodenum with numerous clean-based ulcers.



**Figure 3.** Follow-up images 1 week after discontinuing tacrolimus of (A) the esophagus and (B) duodenum.

## DISCUSSION

This case describes a rare adverse effect of a commonly used immunosuppressant, tacrolimus, and highlights the importance of pharmacovigilance in post-transplant patients. Although rare gastrointestinal side effects have been reported with calcineurin inhibitors, to our knowledge, this is the first reported case of tacrolimus-induced AEN. The pathogenesis of AEN in this patient was likely multifactorial. The patient shared many of the known risk factors for AEN, including advanced age, male gender, vascular disease, renal insufficiency, diabetes, and malnourishment.<sup>3</sup> Renal transplant literature has also described the risk of peptic ulcer disease postoperatively.<sup>4</sup> Although the pathophysiology is not entirely elucidated, the underlying mechanism is likely related to impaired mucosal defense barriers, hypoperfusion, and gastric content reflux. It is not uncommon to have gastric sparing or duodenal ulceration in AEN, as seen in this patient, although duodenal involvement does portend a poorer prognosis specifically related to the risk of stricture, which can be 25%. A case report has documented AEN in an ill postrenal transplant patient although the resolution was seen with supportive care.<sup>5</sup> Unlike expected endoscopic improvement in AEN in 1–2 weeks, our patient failed to respond to standard medical therapy. However, after discontinuation of tacrolimus, there was a rapid improvement in both esophageal and duodenal pathology, suggesting at minimum an adverse drug reaction as a contributor to the evolution and persistence of AEN. Although this patient did manifest as a typical presentation of a rare syndrome, what is notable is the unique impact of tacrolimus on AEN.

## DISCLOSURES

Author contributions: K. Wanta wrote the manuscript and is the article guarantor. AT Abegunde edited the manuscript.

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Informed consent was obtained for this case report.

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