# Acute Esophageal Necrosis in an Immunosuppressed Kidney Transplant Recipient: A Case Report

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## ABSTRACT

Acute esophageal necrosis (AEN) is rare and characterized endoscopically by distal esophageal ulceration, blackening, and necrosis. It typically arises in patients with multiple comorbidities who have significant systemic disease and frailty. Specific precipitating events are variable. Evidence suggests a multifactorial etiology likely involving esophageal ischemia in the setting of corrosive injury from gastric contents and impaired tissue repair mechanisms. In the transplant setting, immunosuppression likely plays a substantial role. We report a case of AEN in a 70-year-old man following a renal transplant.

ACUTE esophageal necrosis (AEN), also referred to as acute necrotizing esophagitis and black esophagus, is a rare clinical entity characteristically seen in the setting of significant underlying systemic disease and poor clinical status. It typically arises in patients with multiple comorbidities who have significant systemic disease and frailty [1]. Although it is an uncommon direct cause of death, it is a poor prognostic factor and associated with high mortality [2]. AEN was first described in the literature by Goldenberg et al [3] in 1990, and subsequently proposed as a distinct clinical syndrome by Gurvits et al [2] in 2007. It has a reported prevalence of 0.0125%–0.2% [1,2], with one large review in 2007 finding 88 cases in the literature spanning the 40 years between 1965–2006. It most commonly arises in older men with underlying chronic disease, vasculopathy, cardiovascular compromise, malnutrition, and generally poor clinical condition.

The underlying pathophysiology is thought to involve multiple factors that work to produce mucosal and submucosal necrosis. Corrosive damage from reflux of gastric contents in the setting of compromised esophageal blood flow and impaired mucosal defense mechanisms lead to mucosal ulceration, bleeding, and necrosis that are characteristic of the syndrome. Blood flow from shared vascular distributions feeding the esophagus and duodenum may already be reduced in these patients due to vasculopathy from sources such as diabetes, hypertension, or extensive smoking history. Further reduction in flow to the lamina propria and submucosa occurs secondary to more acute systemic disruption in the setting of acute blood loss, sepsis, or other mechanisms. Conditions that contribute to a reduction in the host defense and repair of the involved tissues, such as malnutrition, immunosuppression, and deconditioning, are often present and compound the underlying insults. Finally, while irritation and damage from reflux of gastric contents likely plays a role, it is almost certainly exacerbated by concomitant inflammation and edema in the duodenum producing gastric outflow obstruction. These factors in addition to prolonged recumbence in hospitalized patients with decreased esophageal peristalsis, and other iatrogenic sources reducing the lower esophageal sphincter function such as nasogastric tubes aggravate the insults to the esophagus.

Patients with AEN typically present with symptoms of acute gastrointestinal bleeding such as hematemesis or melena, as well as abdominal and epigastric pain, dysphagia, fever, and syncope. Diffuse circumferential blackening of the esophagus is seen on endoscopy, primarily in distal regions, terminating abruptly at the gastroesophageal (GE) junction. The duodenal bulb is often involved with ulcerations, erosions, inflammation, and edema. On biopsy, mucosal necrosis, and leukocytic infiltrates are seen, with severe inflammatory changes and microvascular thrombi. The approach to management of patients displaying signs and

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symptoms of AEN involves supportive care and treatment of their underlying disease and maintenance of hemodynamic stability through IV hydration, blood transfusion, antimicrobial therapy, and nutritional support. Patients should also be made NPO, and placed on IV proton pump inhibition therapy to limit further corrosive damage.

Gurvits et al [2] have outlined a staging system describing the course of AEN. Typically, patients progress from pre-necrotic, viable esophageal tissue (stage 0) to acute necrosis, with blackened/pigmentation and friable mucosa (stage 1). Tissue healing then leads to scattered thick white exudates in a background of pink mucosa (stage 2), with eventual resolution and return to normal mucosa (stage 3). Case reports and reviews in the literature suggest the esophagus becomes grossly normal within 2 to 3 weeks after the initial injury, and normal esophageal motility and resolution of reflux is expected within 5 to 7 months. The most feared morbidity arising directly from AEN is esophageal perforation. Some patients will go on to develop esophageal strictures and stenosis related to the healing process. The incidence of these complications is reported to be approximately 7% for perforation and greater than 10% for esophageal stricture that may require subsequent endoscopic balloon dilatation or esophagectomy in severe cases. Overall mortality rates have been reported as high as 32%; however, death resulting directly from AEN is closer to 6%.

## CASE REPORT

Our patient was a fairly robust 70-year-old man at the time of his transplant. He had a history of hypertensive nephrosclerosis and underwent a deceased donor renal transplant with a 27-year-old donor. Despite a prior 20 pack-year smoking history, peripheral vascular disease, and hypertension, he was relatively well-conditioned. He exercised daily including a 30-minute run on a treadmill and had good nutritional reserves with a pre-transplant albumin of 4.6. The transplant procedure was uneventful. He experienced delayed graft function during the postoperative period and required dialysis. He was re-intubated secondary to acute respiratory failure on postoperative day number 4. Since he appeared to develop acute tubular necrosis, he was placed on thymoglobulin which would allow us to stop the calcinuerin inhibitor and spare the calcineurin-induced nephrotoxicity and associated effects on renal recovery. He did recover renal function and was discharged home in stable condition with good renal function and an immunosuppressive regimen consisting of tacrolimus, mycophenolate, and prednisone.

He returned to clinic 4 days later with diarrhea, malaise, and decreased oral intake consistent with failure to thrive. He was admitted for intravenous fluid repletion, supportive care, and to evaluate the source of his failure to thrive. He was pan-cultured with no growth on blood or urine samples. He also had negative cytomegalovirus (CMV) and *Clostrium difficile* assays. His tacrolimus was held and mycophenolate reduced due to continued concern for infection. Initial imaging consisted of an ultrasound of the renal allograft and a chest radiograph that did not reveal any abnormalities. During the initial days of his admission, he had continued diarrhea and increasing leukocytosis, with development of shortness of breath and a productive cough. He was having a bowel movement on the morning of hospital day 2 and his wife noted his "eyes roll back into his head" and he became transiently unresponsive. When the staff responded, he had a systolic pressure in the 70s and he was hypoxic with oxygen saturations in the 60s. He was transferred to the surgical intensive care unit and became progressively more responsive and appropriate. He was worked up for a pulmonary embolus that was ruled out.

The next day, his hematocrit had decreased to 18 from 25.6 and the CT scan, performed the previous day, to rule out a pulmonary embolus also revealed diffusely thickened esophagus, as well as inflammatory changes in the duodenum and proximal jejunum. Given the discordance between serum CMV assays and tissue invasiveness, it was critical to rule out CMV associated duodenitis as the source of the bleeding. As such, he underwent an endoscopy with biopsy and was found to have oral candidiasis, large areas of necrotic ulceration beginning at the mid esophagus and extending to the GE junction with scattered, small, necrotic appearing ulcers in the body of the stomach, diffuse nodular gastric mucosa, and innumerable punched out ulcers with necrotic bases in the duodenum.

Since we were concerned the constellation of our findings was the result of an infectious process, the mycophenolate was also discontinued. Ganciclovir, micafungin, and ciprofloxacin were started empirically to cover potential infectious sources, and he was also placed on a pantoprazole infusion and started on total parental nutrition (TPN) and stopped all oral intake. The biopsies taken during endoscopy demonstrated ulcerations associated with neutrophilic vasculitis and microvascular thrombus within the esophagus, and focal microvascular thrombi in the antral mucosa and reactive gastropathy. He had reactive mucosa with delineated ulcerations associated with microvascular thrombi in the duodenum. Staining for herpes simplex virus, CMV, and fungal elements were negative.

He continued to have bloody output from the NG tube, and his hematocrit dropped again to a nadir of 16.3 requiring another 2 units of packed red blood cells. Repeat endoscopy was performed 3 days after the first, and again showed necrotic, black esophagus, now extending from the GE junction to the upper third of the esophagus, with slight improvement in the severity of the necrosis and ulceration (Fig 1). There were scattered superficial subepithelial ecchymosis throughout the entire stomach. An exposed vessel in the duodenal bulb sloughed off with attempted ligature, resulting in large amounts of arterial bleeding. Hemostasis was achieved with clipping, and a second exposed vessel was clipped as well. The patient required another unit of blood following the endoscopy.

While there had been some improvement in the patient's condition, he continued to have hematochezia, and repeat endoscopy (5 days after the initial esophagogastroduodenoscopy) showed healing diffuse esophageal necrosis, normal stomach mucosa, and additional duodenal ulcers in the bulb and second portion, with 2 vessels requiring epinephrine and clipping to control bleeding. He ultimately required angiography and empiric embolization of the gastroduodenal artery due to continued gastrointestinal bleeding with melenic stool and bloody NG output. Following embolization, his hemodynamic status stabilized. Culture results including blood, sputum, stool, and urine, as well as CMV and BK virus assays were all negative to this point. He started to manifest signs of stability and recovery and given the absence of an infectious process, the immunosuppression was resumed. The ciprofloxacin was discontinued after a 14-day course, and the ganciclovir was stopped after a progressive

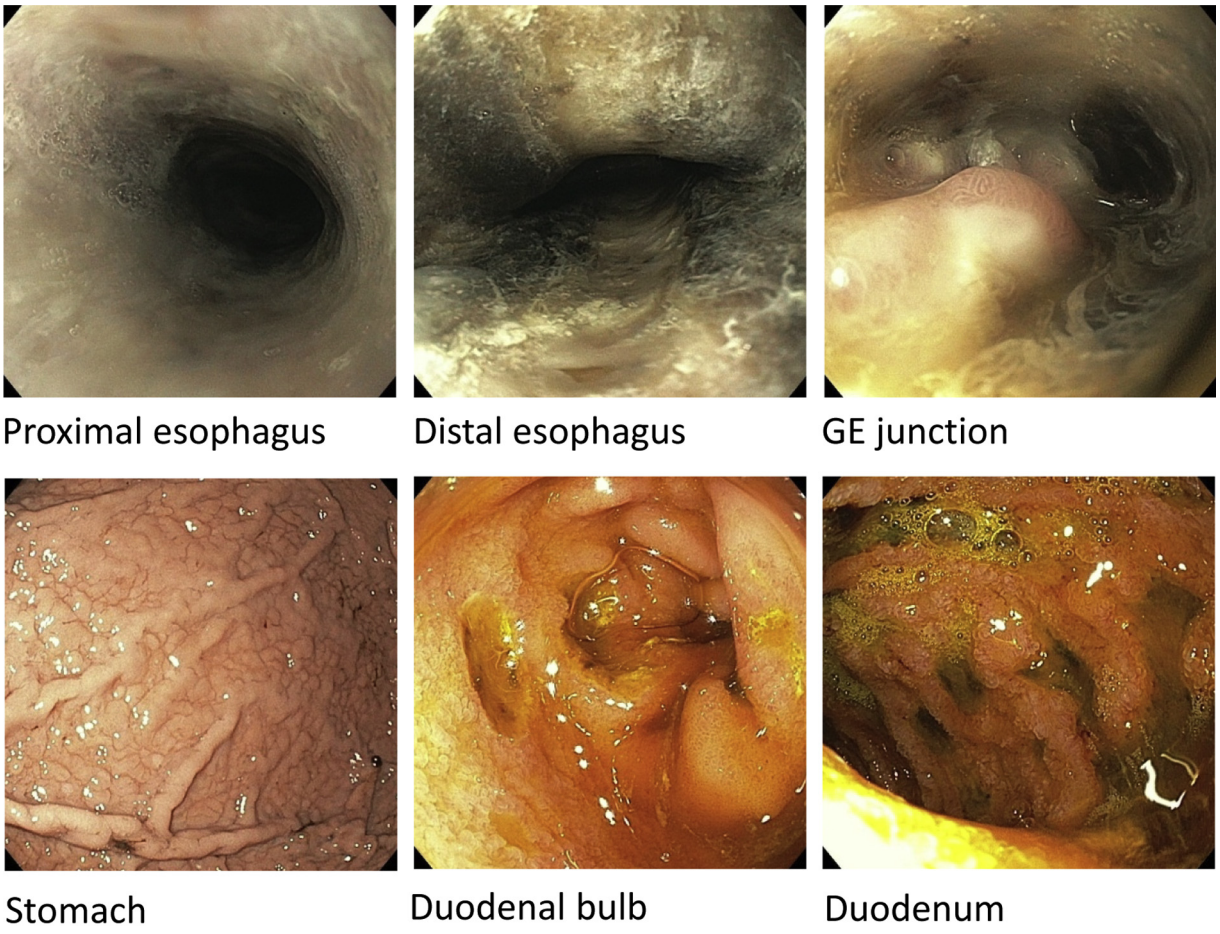


**Fig 1.** An esophagogastroduodenoscopy describing the classic findings of acute esophageal necrosis or "black esophagus." Note the diffuse, circumferential, black-appearing, esophageal mucosa spanning the entire esophagus with abrupt sparing beyond the gastroesophageal junction. Another important finding is the duodenal inflammation and edema with ulceration that often accompanies a large ischemic insult to the esophagus. The common blood supply from arterial branches off the celiac axis helps explain concomitant esophageal and duodenal pathologies.

decrease in the white blood cell count to 1.37. He did continue on micafungin, as he had been found to have significant candidiasis.

On the 20th day of his admission, he once again progressed into acute respiratory failure and was re-intubated and re-cultured. He was started on meropenem and vancomycin for presumed nosocomial pneumonia, and continued on Micafungin. At this point, it was believed it would be safe to place a nasal feeding tube to supplement his parenteral nutrition. The urine and blood cultures came back positive for coagulase negative *staphylococcus* in the urine and both *staphylococcus* and *enterococcus* in the blood, and levofloxacin was added to his antimicrobial regimen.

By the 24th day of his admission, 3 weeks after he first showed evidence of gastrointestinal bleeding, his hematocrit had stabilized and there was apparent resolution of the AEN. His hospitalization was further complicated by tracheal aspirates, and fungitell assays were positive for systemic *Aspergillus* infection, for which he was started on an extended course of voriconazole. Due to his recurrent respiratory failure, a tracheostomy was performed, and the tracheostomy tube remained in place for a total of 23 days. He required extended parenteral nutrition which was weaned once his nutritional requirements were met with tube feeds. The vancomycin and meropenem were continued for a 30-day course, and the voriconazole was continued for a 3-month course.

Following a prolonged stay in the intensive care unit, the tracheostomy was eventually de-cannulated, and his tube feeds were weaned as his oral diet was gradually advanced. Unfortunately, he had persistent difficulty with oral intake and a barium swallow was performed revealing a normal proximal esophagus with tapering to a long segment of strictured esophagus distally that extended to the GE junction. This necessitated placement of a gastrostomy tube (G-tube), and the patient and his wife were taught to administer feeds, and all of his medications were also administered through the G-tube. During this entire time, his renal function was excellent, and he did well and was ultimately discharged home after a 76-day hospitalization. He has been followed as an outpatient and underwent esophageal stricturoplasty. Since the stricturoplasty, he started eating without limitations, and gained weight from 145 lbs–172 lbs. He has done well and returned to a fully functional state working full time,

hunting and engaging in a very full life. He remains well with excellent allograft function with a creatinine of 0.72 5 years post-transplant.

## DISCUSSION

AEN is a rare condition that has only recently been described as a clinical syndrome. It is most commonly seen in older men, with an average age of 67, and particularly in those with multiple comorbidities and underlying cardiovascular disease. Patients who develop AEN most often present with signs of gastrointestinal bleeding, such as hematemesis, melena, and anemia. Other common symptoms on presentation include abdominal pain, nausea, vomiting, and dysphagia. The diagnosis is usually established through endoscopic and histopathologic findings that are characteristic of the disease. These include circumferential ulceration, black pigmentation, and necrosis of the distal portions of the esophagus on endoscopy, typically ending abruptly at the gastroesophageal junction, as well as varying degrees of gastric and duodenal involvement including inflammation and ulceration. Histologic finding on biopsy of the involved tissue show necrosis involving the mucosa and submucosa, severe inflammatory changes with leukocyte infiltration, and microvascular thrombi.

While a definitive etiology of AEN remains elusive, it has been suggested by several researchers that the cause is likely multifactorial, with mucosal ischemia, corrosive damage caused by refluxed gastric contents, and poor overall health status being important drivers of the disease. Risk factors that have been identified by Gurvits et al [2] based on extensive review of cases identified in the literature include older age, male sex, cardiovascular disease, hemodynamic compromise, gastric outlet obstruction, alcohol abuse, diabetes, malnutrition, renal disease, malignancy, chronic pulmonary disease, hypercoagulability, external compression of the esophagus, trauma, and surgery. Other researchers have suggested additional risk factors such as fungal and viral disease. In the setting of these risk factors, ischemia to the gastrointestinal mucosa and submucosa likely occurs due to an acute worsening in hemodynamic stability and perfusion. This is supported by the localization of the process to the less vascularized portions of the esophagus, the presence of microvascular thrombosis on histology, and the rapid resolution of AEN following a return to hemodynamic stability. In addition to ischemia, additional insults from increased reflux of gastric contents into the esophagus likely plays a causative role, with hydrogen ions, bile salts, pepsin, and trypsin damaging the mucosal surface and decreasing the protective mechanisms of the tissue. A variety of specific precipitating events have been reported in the literature, including compression of the esophagus from hematoma formation, vascular occlusion due to anti-cardiolipin antibody, erythema multi-forme, gastric outlet obstruction from duodenitis with duodenal ulceration, gastric volvulus, antibiotic use, herpes esophagitis, and trauma due to NG tube insertion.

While there have been no prospective studies assessing the effectiveness of treatment approaches for AEN, management has typically involved supportive care and correction of contributing factors and re-establishing hemodynamic stability. Nutritional support with total parenteral nutrition followed by early conversion to enteral nutrition as soon as it becomes feasible is critical. Patients are also started on concomitant intravenous acid suppression therapy to decrease acid production, and sucralfate for local mucosal protection. If an esophageal stricture occurs as a result of AEN, this may require balloon dilatation, or in severe and recalcitrant cases, esophagectomy. While mortality from AEN is uncommon, the diagnosis still portends a poor outcome, with upwards of a third of patients eventually succumbing to their underlying disease.

While the patient described in this case report had many of the risk factors associated with the development of AEN, his initial presentation suggested he was more robust. He exercised with regularity and performed all of his activities of daily living without limitations. He worked full-time and appeared to have good nutritional reserves. However, he was an older man with a history of peripheral vascular disease, hypertension, and tobacco use who had recently undergone renal transplantation for hypertensive nephrosclerosis and rapidly depleted his nutritional stores due to the metabolic demands of surgical stress. This was compounded by poor oral intake and the development of diarrhea. There is also little doubt the immunosuppressive regimen contributed to the evolution of AEN. He developed delayed graft function requiring dialysis. Since he was not perceived to be frail, he was converted to thymoglobulin induction to allow us to stop the calcineurin inhibitor maintenance immunosuppression, as calcineurin inhibitors are known to compound renal recovery due to nephrotoxic side effects. Our expectation was a full renal allograft recovery and patient recovery with this strategy. In fact, his renal function did recover and he was discharged in a stable state after an initial 13-day hospitalization.

Unfortunately, the stress of surgery, immunosuppression and his comorbidities eventually revealed a frail 70-year-old man who was pre-disposed to developing a near lethal complication of AEN. Septuagenarians—people between the ages of 70–80—who are referred for transplantation are usually the healthiest of all septuagenarians. We have come to learn that we can substantially alter their “healthy life” with an attempted invasive procedure such as a kidney transplant. Moreover, the addition of immunosuppressive medications can further complicate the recovery from surgery and transplantation.

Older age, in association with other existing conditions, such as end stage renal disease, heart disease, diabetes, and hypertension increases the risk of complications during any given surgical procedure. These complications, in turn, increase the rate of delayed graft function in kidney transplant recipients and many other postoperative events including infectious, respiratory, and cardiovascular problems that result in a prolonged hospitalization and even death. The risks may be much greater in any 70-year-old’s case than the

marginal benefit derived from a transplant; particularly when viable options exist such as hemodialysis or peritoneal dialysis.

We know that older patients are more prone to complications after most procedures, and these complications are aggravated in patients with end stage renal disease and the need for post-transplant immunosuppressive medications. While we felt we evaluated him thoroughly, we would never have anticipated such a prompt depletion of his nutritional stores and overall reserve with rapid development of a near lethal complication. He was discharged in a stable condition and returned on postoperative day 17 with a clinical picture concerning for dehydration and potential infection. He went on to experience significant gastrointestinal bleeding requiring multiple transfusions, endoscopic clipping, and eventual IR embolization to control the bleeding. The characteristic signs of AEN, including gastrointestinal bleeding with endoscopic findings of a blackened, ulcerated, and necrotic esophagus with duodenal and moderate gastric involvement, were present (Fig 1). He also demonstrated histologic findings that are consistent with a picture of AEN, including neutrophilic vasculitis and microvascular thrombus.

Given the events occurring between his surgery and development of AEN, it is likely he experienced a low-flow state during his postoperative course resulting in hypoperfusion to the tissues of his upper gastrointestinal tract. This was likely compounded by irritation of the esophageal mucosa as a result of reflux of gastric contents related to increasing outlet obstruction secondary to duodenal inflammation and ulceration. Our patient was also in a poor nutritional state characterized by an albumin of 1.7 at readmission with associated dehydration, diarrhea, and immunosuppressed state. Providing the perfect setting for the development of AEN. Few cases have been reported in the literature of AEN developing in transplant recipients. Trappe [4] reported a case of AEN in a renal transplant patient; however, this was related to CMV esophagitis, which was never present in our patient. Grover [5] also reported a case of AEN in a patient following renal transplant with allograft loss to rejection requiring allograft nephrectomy whose course was complicated by multiple abscesses and AEN. Gomez [6] described a liver transplant patient who developed postoperative hemorrhagic shock with AEN occurring a month after this event. Not unlike our case, the common denominator in all these cases being end organ disease and immunosuppression that likely contributed to the evolution of a frail and deconditioned patient. Again, a perfect setting for AEN. The acute course with progression over a 3-week period is in keeping with the stages outlined by Gurvits [2].

Our patient was managed conservatively including correcting his hemodynamic instability, acid suppression, and total parenteral nutrition, as well as treating his comorbidities. AEN was definitively diagnosed endoscopically and histologically and resolved following IR embolization, maintenance of hemodynamic stability, and management of associated comorbidities. His course following resolution of the AEN was prolonged and complicated by multiple episodes of acute respiratory failure eventually requiring tracheostomy, systemic aspergillus infection, and prolonged enteral feeding with an feeding tube placement and TPN for nutritional needs. He ultimately developed a significant esophageal stricture which necessitated gastrostomy feeding tube placement and balloon dilatation exactly one year post-transplant. He has done well with complete resumption of all of his pre-transplant activities, to include hunting, a full-time work schedule and continues to do well 5 years from transplant with good allograft function characterized by a creatinine of 0.72.

## CONCLUSION

Acute esophageal necrosis is a rare and potentially lethal gastrointestinal syndrome and likely associated with poor perfusion of the upper gastrointestinal mucosa in the setting of other mucosal irritants and underlying clinically compromised states. It should be considered in patients with multiple comorbid conditions, particularly older men with cardiovascular disease, who present with acute upper gastrointestinal bleeding. Once confirmed via endoscopy, treatment involves maintaining hemodynamic stability, acid suppression, keeping patients NPO, managing underlying conditions, and nutritional support with TPN, and enterally as soon as it is clinically possible. The patient presented here was successfully managed with these interventions; however, he did develop an esophageal stricture requiring gastrostomy tube placement to meet outpatient nutritional support and ultimately balloon dilatation.

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