



## Acute Necrotizing Esophagitis (Black Esophagus): A Rare Entity in Long-Term Renal Transplantation

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### Abstract

Acute Necrotizing Esophagitis (AEN) is rare and characterized by necrosis mucosa and submucosa in the distal esophagus at the gastroesophageal junction observed by endoscopy (EDG). It typically arises in patients with multiple comorbidities who have the significant systemic disease and immunocompromised. Specific precipitating events are associated with multiple factors as acute blood loss, sepsis, and immunosuppression. We report a 66-year-old woman with a deceased donor renal allograft 8 years early, which developed AEN in the septic shock setting by acute lithiasis cholecystitis. Infection by Cytomegalovirus (CMV), *Helicobacter pylori* (HP) was discarded. She was on immunosuppression regimen triple therapy. Comorbidities were: diabetic Mellitus type 2, cardiopathy, obesity, renal allograft recipient 8 years ago, and sepsis of urinary origin by *Escherichia coli* 15 days earlier. EDG showed devitalized and yellowish fibrous mucosa with areas of black dotted with ischemic appearance. Line Z was swollen. Therapy on Intensive Care Unit (ICU) support was a fluid infusion, catecholamine perfusion, antibiotics, and proton pump inhibitors. Recovery was complete. Neither stenosis nor perforation was evidenced in the long term. EDG at discharge showed a complete esophagus recovery. We describe the first case of AEN as a complication in long-term kidney transplant in which immunosuppression likely plays a substantial role. Proper recognition and early management will result in an improved clinical outcome.

### Keywords

Acute necrotizing esophagitis; Renal transplantation; Immuno suppression diabetes mellitus

### Introduction

Acute upper gastrointestinal hemorrhage is an emergency medical condition with up to 3-fold increase in-hospital mortality and substantial use of clinical resources in Chronic Kidney Disease (CKD) patients [1]. Conditions involved are impairment renal function,

diabetes mellitus, coronary artery disease, hypoalbuminemia, increased albumin/creatinine ratio, cirrhosis and use of non-steroidal anti-inflammatory drugs [2]. The incidence of AEN in CKD and renal transplant recipient is unknown.

AEN is characterized by distal necrosis mucosa and submucosa at the level of the esophagogastric junction observed on EGD [3]. Prevalence of AEN based on retrospective EDG ranges from 0.001% to 0.2% [4].

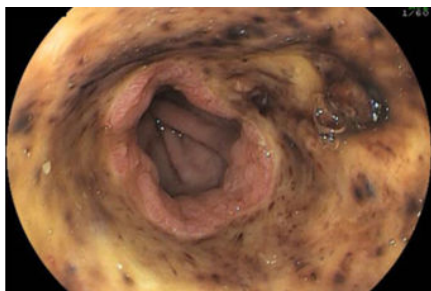
Advanced age with serious comorbid factors, malnutrition, and immunocompromised status play an important role in pathogenesis in terms of their commitment to the defense system of the esophageal mucosa and its healing capacity [5,6]. To date, 88 reports over 40 years have been reported and only two with infection origin have been published in kidney transplant recipients [7,8]. Two conditions may predispose to AEN in immunocompromised patients: the hypovascular area in the esophagus and more exposed to gastric reflux are relevant conditions; and the infections, that represent a major cause of morbidity and mortality. Clinically, the AEN express symptoms of upper gastrointestinal bleeding, abdominal and epigastric pain, dysphagia, fever, and syncope.

Gurvits et al, 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 I) [7]. Tissue healing then leads to scattered thick white exudates in a background of pink mucosa (stage II), with eventual resolution and return to normal mucosa (stage III). Overall mortality rates have been reported as high as 32%; however, death resulting directly from AEN is closer to 6% [6-8].

To best our knowledge this is the first report of AEN in a woman with long-term kidney transplant recipient with complete recovery.

### Case Report

A 66-year-old female with a past medical history of diabetes mellitus type 2 on hemodialysis by 2 years, cardiopathy, obesity, renal allograft recipient 8 years ago, sepsis of urinary origin by *E. coli* 15 days earlier was admitted in the emergency department by profound hemodynamic situation secondary to a septic shock of abdominal origin. Her physical examination: afebrile, respiratory rate 25, hypotension 65/30 mmHg, heart rate 80, pallor, sweaty, nausea, cool peripheries, 1 litter of coffee-ground emesis and abdominal pain, requiring urgent hemodynamic support. Imagen studies including CT (abdomen) revealed acute lithiasis cholecystitis and a discreet diffuse parietal thickening with mucosa increased at esophagic level mainly in the distal segment, as well as a small hiatus hernia. Chest X-Ray: Cardiomegaly. Basal left lung patchy infiltrates and lingula. Cholecystectomy was performed confirming the diagnosis. Admitted in ICU for ongoing supportive management. Performed EGD evidenced in the medium and distal esophagus, devitalized and yellowish fibrous mucosa with areas of black dotted with ischemic appearance, line Z was swollen (Figure 1). It was also revealed mild gastritis and superficial ulcers in the second duodenal portion. Biopsies were taken showing necrotic and inflammatory material with cytomegalovirus and *Helicobacter pylori* negative.



**Figure 1:** Initial EGD showing areas of black necrotic appearance with ischemic appearance, line Z was swollen.

Immunosuppression regimen was triple therapy. Analysis at admission: hemoglobin 9.1 gr/dl, cell hypochromic 7.1%, Platelets  $137 \times 103/\text{mm}^3$ , Protombin time 68%, Fibrinogen 1038 mg/dl, Creatinine was 2.71 mg/dL, glomerular filtration rate (CKD-EPI equation) 18 ml/min/1.73 m<sup>2</sup>, plasma Sodium 134; plasma Potassium 5.5 mmol/L. Urine analysis: leukocyte, blood was negative. Albumin/creatinine ratio (mg/gr creatinine): 2525.49. Urinary sodium 121; urinary potassium 10.1 mmol/L. urine culture negative. Blood glucose 200-250 mg/dL, C reactive protein ultrasensitive 29.1 mg/dL, Procalcitonin 12.97 ng/dL, Amylase: 202 UI/L. Leukocytes  $21.77 \times 103/\text{mm}^3$  with differential: Neutrophils 89%; Lymphocytes 6%; Eosinophils 0%, Band forms 1%. Arterial blood gases: pH 7.49, base excess 7.4 mmol/l, lactate 1.33 mmol/l, partial pressure of oxygen 67.6 mmHg, partial pressure carbon dioxide 41 mmHg. She has elevated ischemic myocardial markers: myoglobin 115 ng/dL and troponin T ultrasensitive 71 pg/mL. CMV-Polymerase Chain Reaction (PCR), Polyomavirus were negative.

On ICU management were intravenous fluid, proton pump inhibitors, imipenem, linezolid, anidulafungin, and metronidazole. Initially, Vangancyclovir was added. Mycophenolate mofetil was discontinued and tacrolimus dose reduced. Blood and urine cultures were negative. Total parenteral nutrition was initiated.

After ICU discharge, imipenem and proton-pump inhibitors were kept. Glycemic control and blood pressure treatment were used. Laboratory parameters on 7<sup>th</sup> day of admission: glomerular filtration rate (CKD-EPI equation) 38 ml/min/1.73 m<sup>2</sup>, serum albumin 3.2 g/dL, urinary albumin-to-creatinine ratio 2.111 mg/gr creatinine, leukocytes  $5 \cdot 103/\text{mm}^3$ , haemoglobin 11.2 g/dL. C reactive protein normalized to <0.3 mg/dl.

EGD was performed at the 16<sup>th</sup> day after admission showing, not necrotic area, although mucosa was erythematous with mucous exudates and erosions (Figure 2). In the distal esophagus, discreet stenosis seemed to commence. Mild erythematous-erosive duodenitis was shown without any ulcer evidence. Histology studies performed revealing "neco-inflammatory material corresponding to an ulcerous area. Immunohistochemistry studies remained negative for cytomegalovirus and *Helicobacter pylori*.



**Figure 2:** EGD partial healing of necrotic-appearing mucosal changes.

She was recovered and discharged after 22 days of hospitalization. EGD performed two weeks later showed a healing esophageal mucosa, erythematous and several areas covered by fibrin. No stenosis. Complete healing of the esophageal mucosa was observed (Figure 3).



**Figure 3:** Complete healing of necrotic-appearing mucosal changes.

## Discussion

AEN, described by Goldenberg in 1990, although previously diagnosed at autopsies were known [5] but is a rare entity underdiagnosed because recently has been described as a clinical syndrome. Recently, increased worldwide the awareness of AEN, has been included in the differential diagnosis of upper gastrointestinal bleeding. AEN is considered the fourth leading cause with an incidence of 6% of cases [6]. It is most commonly seen in older men with an average age of 67 and associated with multiple comorbidities and underlying cardiovascular disease [7].

Renal transplantation has been much more successful following the development of new immunosuppression regimens; post-transplant infections maintain an important influence on outcome [8]. Two major insults are involved: ischemic with hemodynamic compromise and association to elderly patients with severe comorbid conditions as diabetes mellitus, septic shock, atherosclerosis, cardiovascular and renal disease [3,5,9-11]. Vascular calcification is a frequent pathology associated with chronic kidney disease, in patients on dialysis. It may predispose in some patients to injured tissue and hemodynamically instability. Recently, a case of AEN complicating calcific uremic arteriopathy in a hemodialysis patient has been reported [12]. Vascular calcification as a chronic entity associated with renal disease is a major risk factor. Immunosuppressed state in solid organs transplantation likely plays a substantial role in the development of AEN, especially by infectious origin. Up to now, this is only reported at an early stage of kidney transplantation [8,9].

The clinical picture, as in our case, is a patient severely ill, with multiple comorbidities who manifest signs of upper gastrointestinal bleeding with coffee-ground emesis, hematemesis, and melena to no symptoms [9]. In the setting of the risk factors, ischemia to the gastrointestinal mucosa and submucosa likely occurs due to an acute worsening in hemodynamic stability and perfusion. This is the reason to support the localization of the process in 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. Histology of AEN is a circumferential, black-appearing, diffusely necrotic esophageal mucosa, preferentially affecting the distal esophagus, of variable length, ends abruptly at the Z line. Mucosal injury at proximal tract is common and the entire esophagus can have the appearance blackish. Differential diagnosis should include chronic esophageal melanosis, pseudomelanosis resulting from lysosomal degradation, acanthosis nigricans, primary and metastatic melanoma, and ingestion of carbon, caustics or corrosive agents as lye ingestion [10].

Diagnosis is by EGD, showing an almost universal predilection to the distal esophagus in 97% of the cases due to its relative hypervascularity compared to the proximal esophagus [3]. Endoscopic biopsy of the esophageal tissue helps in the initial diagnosis of infection by fungus, CMV or *Helicobacter pylori*, the severity of the illness and it is not associated with additional complications or perforation. The fungal hyphae that appeared in the second biopsy in our case is a finding associated with long term immunocompromised state. Although the biopsy is not mandatory for the diagnosis of AEN, tissue histology should be considered to exclude/confirm AEN of infection etiology as in our case, where the patient was immunocompromised [3].

Currently, there is no specific treatment for suspected or established AEN, but manage of underlying medical condition with concomitant supportive care as hemodynamic resuscitation, glycemic control, Total Parenteral Nutrition (TPN), acid suppression with high dose intravenous proton pump inhibitors should be initiated, in order to re-establishing hemodynamic stability [3].

The literature and reviews suggest the esophagus becomes grossly normal within 2 to 3 weeks after the initial insult, and normal esophageal motility and resolution of reflux is expected within 5 to 7 months [2]. Our case complies with this evolution.

Esophageal perforation accounts in less 7% of the cases and constitutes a life-threatening condition that should be suspected in the setting of acute severe illness that requires surgical intervention [4].

Mortality specific of AEN accounts for about 6% and overall mortality ranges between 15%-36% related to the associated conditions [6-8]. Mortality in kidney transplant patients is unknown.

Another important sequela of AEN is the stenosis, which in some series is referred to like 25% of the cases requiring endoscopic or surgical treatment and perforation [10,11,13,14].

Our patient after a year of AEN is alive without any complications derived from previous AEN episode.

## Conclusion

In conclusion, AEN is a rare entity in renal recipients. A few cases are reported in the literature. Our case is the first report described over

3175 renal transplants performed in the last 20 years. In non-transplant is reported around 6% of the upper gastrointestinal bleeding population. Patients with high comorbidity as non-solid organs transplanted are predisposed to develop AEN, probably, in a higher frequency than reported.

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