

Risk factors and clinical outcomes of acute esophageal necrosis: retrospective case series of a rare disease with “black” prognosis

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Abstract

Acute esophageal necrosis is a rare syndrome classically characterized by black distal esophagus with a complex pathophysiology that usually involves a combination of esophageal ischemia, gastroesophageal reflux and impaired mucosal reparative mechanisms. We retrospectively analyzed the main risk factors, clinical characteristics and outcome in all patients diagnosed with acute esophageal necrosis between January 2015 and December 2020 at our center. Ten patients were identified in a total of 26854 upper digestive endoscopies (0.04%). Most patients were male (8/10) and the mean age of presentation was 71.1 years. The most common presenting symptoms were melena and hematemesis and half the patients required red blood cell transfusion. The most common risk factors were hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, peripheral artery disease, coronary artery disease, cerebrovascular disease, heart failure and malignancy. Compromised hemodynamic state was the most common precipitating event in four patients. Other recognized precipitating events included surgical interventions, decompensated heart failure, gastrointestinal bleeding from gastric malignancy and methotrexate. Endoscopic findings revealed diffuse and circumferential black distal esophagus with abrupt transition at gastroesophageal junction and variable proximal extension at presentation. The 1-month mortality rate was 30%, mostly from severe underlying illness. In conclusion, acute esophageal necrosis is a rare cause of upper gastrointestinal bleeding that should be suspected in older patients with multiple comorbidities. Although associated with a high mortality rate, appropriate treatment may result in favorable outcome in most patients. (*Acta gastroenterol. belg.*, 2022, 85, 97-101).

Keywords: acute esophageal necrosis, black esophagus, acute necrotizing esophagitis, gastrointestinal bleeding.

Introduction

Acute esophageal necrosis (AEN) is a rare disease classically characterized by a striking endoscopic image of diffuse and circumferential black mucosal discoloration of distal esophagus, with abrupt transition at gastroesophageal junction and variable proximal extension (1). It is more common in older males with general debilitation and multiple comorbidities that usually present with hematemesis or melena (2).

The pathophysiology usually involves a combination of esophageal ischemia, backflow injury from gastric chemical contents and impaired mucosal reparative mechanisms associated with debilitated physical states (3). Although it is a serious life-threatening condition, appropriate treatment may result in a favorable outcome in over 60% of patients (4).

A retrospective study of all cases of AEN diagnosed at Centro Hospitalar e Universitário de São João (Porto,

Portugal) between January 2015 and December 2020 was performed. The aims of this study were to explore the prevalence of AEN in patients who perform upper digestive endoscopy and describe the main risk factors, clinical characteristics, endoscopic findings and outcomes associated with AEN.

Case series

A total of 26854 upper digestive endoscopies were performed from January 2015 to December 2020, from which a total of ten patients (0.04%) were diagnosed with AEN (Table 1). Most patients were male (n=8) and the disease typically presented at advanced age, with a mean age at diagnosis of 71.1 years (range 45-85). Only two patients were younger than 65 years old at presentation.

All patients were diagnosed in the emergency setting with overt clinical manifestations. The most common clinical presentation was upper gastrointestinal bleeding in eight patients, as melena (n=5), hematemesis (n=2) or bright red blood in the nasogastric tube (n=1). Additional symptoms included abdominal pain (n=2), nausea and vomiting (n=2), dysphagia (n=1) and diarrhea (n=1). The most common physical signs at presentation were hypotension (n=5), tachycardia (n=4), fever (n=2) and cachexia (n=2).

A compromised hemodynamic state was the most common triggering event in four patients, secondary to septic shock in three (primary foci of infections including acute gastroenteritis, peritonitis and bacterial endocarditis) and to hypovolemic shock from diarrhea in the other. Surgery was another common triggering event, that occurred in two patients, including one who had undergone coronary artery bypass graft 4 days earlier and other who had undergone exploratory laparotomy with sigmoid resection for gastric volvulus followed by a second laparotomy with peritoneal lavage in one week and 2 days later developed AEN. Other recognized triggering events included: decompensated heart failure,

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Table 1. — Demographic, clinical, and endoscopic characteristics of the patients included in our series

Patient	Gender	Age	Clinical symptoms	Underlying conditions	Triggering event	Extension	Other endoscopic lesions	Reevaluation endoscopy	Short-term outcome
#1	Male	76	Melena	DM, CVD, PAOD, CKD	Septic shock (from acute gastroenteritis)	Proximal esophagus	Duodenal	Yes	Survived Asymptomatic on discharge
#2	Male	50	Melena	DM, hypertension, CAD, PAOD, CKD, smoking	CABG	Distal esophagus	Duodenal	Yes	Survived Asymptomatic on discharge
#3	Male	73	Hematemesis	DM, hypertension, alcohol, cirrhosis	Sigmoid resection	Middle esophagus	Duodenal	Yes	Survived Asymptomatic on discharge
#4	Male	85	Nausea, vomiting	Hypertension, dyslipidemia	Intestinal occlusion, dehydration	Middle esophagus	Duodenal	Yes	Survived Asymptomatic on discharge
#5	Male	70	Hematemesis	DM, hypertension, CVD, smoking	Septic shock (from peritonitis)	Middle esophagus	No	Yes; distal stricture	Survived Uncomplicated stricture
#6	Male	79	Melena	DM, hypertension, dyslipidemia, CVD, CAD, PAOD, CHF, CKD	Septic shock (from bacterial endocarditis)	Distal esophagus	No	No	Died after 6 days from septic complications
#7	Female	68	Nausea, vomiting, dysphagia	DM, hypertension, dyslipidemia, CVD, CAD, PAOD, CHF, CKD, smoking	Methotrexate	Middle esophagus	No	Yes	Survived Asymptomatic on discharge
#8	Male	80	Melena	Hypertension, smoking, CKD, CHF, prostatic adenocarcinoma	Decompensated heart failure	Middle esophagus	Duodenal	Yes; esophageal ulceration	Survived Asymptomatic on discharge
#9	Female	71	Blood in NGT	DM, hypertension, dyslipidemia, CVD, CHF, gastric cancer	Gastrointestinal bleeding (from gastric malignancy)	Middle esophagus	No	No	Died after 21 days from stroke
#10	Male	45	Melena	Alcohol, cirrhosis, dyslipidemia	Hypovolemic shock, terlipressin	Proximal esophagus	No	No	Died a few hours after admission from cardiorespiratory arrest

DM – diabetes mellitus, CVD – cerebrovascular disease, PAOD – peripheral arterial obstructive disease, CKD chronic kidney disease, CAD – coronary artery disease, CABG – coronary artery bypass graft, CHF – congestive heart failure, NGT – nasogastric tube.

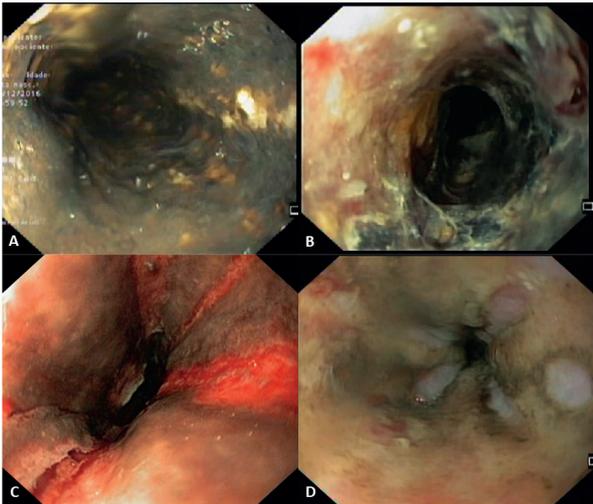


Figure 1. — Endoscopic images of acute esophageal necrosis. Acute esophageal necrosis has a characteristic endoscopic presentation of diffuse and circumferential black discoloration of distal esophagus with abrupt transition at gastroesophageal ulceration and variable proximal extension. Here are represented images from 4 patients in our series that illustrate possible presentations of this rare disorder.

upper gastrointestinal bleeding from gastric malignancy, dehydration in the setting of intestinal occlusion and methotrexate (in a patient who had recently started taking this drug for rheumatoid arthritis).

The most common chronic underlying conditions were: hypertension (n=8), diabetes mellitus (n=6), dyslipidemia (n=5), chronic kidney disease (n=5), cerebrovascular disease (n=5), smoking (n=4), heart failure (n=4), peripheral artery disease (n=4), coronary artery disease (n=3), alcohol consumption (n=2), liver cirrhosis (n=2) and malignancy (n=2). The two cases of malignancy included one gastric adenocarcinoma and one prostatic adenocarcinoma.

Laboratory studies revealed anemia in nine patients and leukocytosis in six. All patients presented elevated levels of C-reactive protein (mean level: 110.2 mg/L, range: 22.8-255.0). Lactate level was measured in six patients and four presented hyperlactatemia, with a maximum of 21.61 mg/dL. Albumin and total protein levels were measured in nine and six patients, respectively, and most (n=8) presented hypoalbuminemia and/or low total proteins level, indicating malnutrition.

Endoscopy revealed characteristic findings of diffuse circumferential friable mucosa with black discoloration involving distal esophagus with abrupt transition at gastroesophageal junction in all patients (Figure 1). In two cases these changes were limited to distal esophagus whereas in six they extended to middle esophagus and in two to proximal esophagus. Signs of recent bleeding including red blood and blood clots in esophageal and gastric lumen were detected in two endoscopies, whereas none had any point of active bleeding. Other associated pathological lesions included duodenal erosions and/or

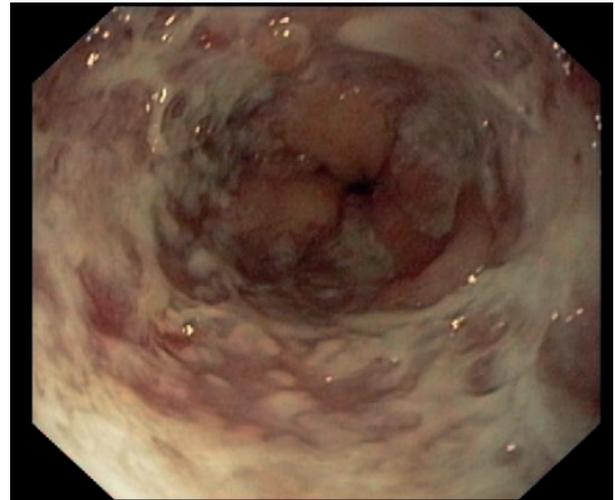


Figure 2. — Endoscopic image of the healing phase of acute esophageal necrosis, characteristically demonstrating white exudates covering pink friable mucosa in a mosaic pattern.

ulceration in five patients. No patient presented evidence of perforation.

Reevaluation endoscopy was performed in seven patients 5-71 days after initial diagnosis and all presented characteristic findings of healing with easily detachable plaques of white exudate covering friable mucosa (Figure 2). One patient had a stricture at distal esophagus that was easily traversed with the endoscope and the patient denied any symptoms of dysphagia or regurgitation; therefore, no endoscopic treatment was pursued. Mean follow-up duration was 21.0 months (range 0-76). No cases of recurrence were detected during follow-up.

Patient management focused on comorbidity control and nutritional status improvement, together with high-dose proton pump inhibitors which were administered to all patients. Most patients (9/10) presented with anemia and correction with packed red blood cell transfusion was necessary in five. Fluid therapy was started in six patients and three required vasopressor support. Antibiotics were administered to four patients, of large-spectrum in two because of septic shock.

Two patients required admission in intensive care unit and evolved favorably. Additionally, two more patients developed AEN while they were in intensive care unit: one after coronary artery bypass graft and the other for septic shock secondary to endocarditis. The mean duration of intensive care unit stay after diagnosis of AEN for these four patients was 9.25 days (range 4-18).

Mean duration of hospital stay was 19.9 days (range 0-72). Seven patients evolved favorably and were discharged with no symptoms or sequelae. In total, three patients died during the days/weeks after diagnosis, essentially from causes other than AEN related to their critical illness, which corresponds to a 1-month mortality rate of 30%.

Table 2. — Main characteristics of retrospective and prospective studies concerning prevalence of acute esophageal necrosis

<i>Authors</i>	<i>Year</i>	<i>Type of study</i>	<i>Duration (years)</i>	<i>Number of EGD examined</i>	<i>Total cases of AEN</i>	<i>Prevalence of AEN</i>
Moreto M et al (6)	1993	Retrospective	16	80.000	16	0.01%
Augusto F et al (7)	2004	Retrospective	5	10.295	29	0.28%
Julian-Gomez L et al (8)	2008	Retrospective	2	6003	7	0.11%
Ramos R et al (9)	2008	Retrospective	2	3976	11	0.28%
Singh D et al (10)	2011	Retrospective	3	9179	5	0.05%
Ben Soussan E et al (5)	2002	Prospective	1	3900	8	0.2%

EGD – esophagogastroduodenoscopy; AEN – acute esophageal necrosis.

Discussion

AEN is a rare disease that is found in a small minority of upper digestive endoscopy procedures. We found a prevalence of 0.04%, similar to other prospective (5) and retrospective (6-10) studies that reported a prevalence of 0.01-0.28% of patients undergoing upper digestive endoscopy (Table 2). The fact that our prevalence is near the lower limit reflects the fact that our center performs a large volume of elective upper digestive endoscopies which dilutes the number of cases of AEN, which are essentially diagnosed in the emergency setting.

A clear predilection for male gender and advanced age was found in our series, which is supported by a recent systematic review where AEN affected predominantly men (72%) at a mean age of 62 years (11). Upper gastrointestinal bleeding is the usual presentation form, with most patients presenting hematemesis (66%) and/or melena (33%) (4). These were also the most common symptoms in our series although melena were more common than hematemesis.

Classic AEN presents as diffuse black-appearing distal esophagus that stops abruptly at the gastroesophageal junction. Proximal extension is common and, in approximately 34% of cases, the entire esophagus may appear black (4), similar to our series where 20% of patients had pan-esophageal involvement. Generally, the classic picture of diffuse black distal esophageal mucosa is followed by a healing phase dominated by residual black areas and thick white exudates composed of necrotic debris that cover pink friable mucosa and, usually, esophageal mucosa acquires its normal endoscopic appearance in approximately 1-2 weeks (12). This classic endoscopic trajectory is illustrated in our series where these characteristic healing features were evident in all patients who performed re-evaluation endoscopy.

Although this classical endoscopic image is virtually diagnostic of AEN, one must keep in mind that endoscopy may also reveal esophageal ulceration which can make necrosis more difficult to recognize. Therefore, it is important to exclude other differential diagnoses that may produce a similar endoscopic aspect. According to

a recent retrospective study that included 100 patients with esophageal ulcers, there are many different possible etiologies, the most common gastroesophageal reflux disease, infections or drugs, with ischemia responsible for only 1% of cases of patients presenting with esophageal ulcers (13).

AEN usually results from an acute triggering event that occurs in a background of chronic predisposing conditions. These processes usually involve a combination of esophageal ischemia, gastroesophageal reflux resulting in direct mucosal damage and general debilitation states resulting in impaired defense mechanisms and regenerative ability. The precipitating event is often related to a decrease in esophageal perfusion caused by compromised hemodynamic state, being associated with shock in 33% of patients (4). The most common associated risk factors include male gender, advanced age, diabetes mellitus, hypertension, dyslipidemia, malnutrition, alcohol abuse, coronary artery disease, congestive heart failure, chronic kidney disease, liver cirrhosis and malignancy (3,4). Our study supports these pathophysiological bases as a compromised hemodynamic state was the most common precipitating event and patients had a state of general debilitation and multiple comorbidities that increased their susceptibility.

Remarkably, our series included two novel potential precipitating causes for AEN: gastrointestinal bleeding from gastric malignancy and methotrexate. The association with malignancy is well-known and supported by our study where two patients had underlying malignancy. A history of malignancy is present in 10% of patients who present with AEN (4), associated with cachexia and immune dysregulation that increase susceptibility to necrosis when exposed to a triggering event. However, we demonstrate for the first time that gastrointestinal bleeding from gastric adenocarcinoma may be itself the triggering event. Gastrointestinal bleeding has been previously reported as a cause for AEN, specifically from ruptured esophageal varices (14).

Another novel potential association is with the immunosuppressive drug methotrexate. One possible adverse effect from methotrexate is epidermal necrosis, a

rare but life-threatening cutaneous reaction that appears to be associated with old age, chronic kidney disease and high initial dosage without folate supplementation (15). Nevertheless, to the best of our knowledge, this is the first time it is associated with necrosis of esophageal mucosa. Although it is not proven yet and association in time does not prove causality, the time course was striking to suggest its involvement and further studies could address this question.

Management of AEN is mainly supportive and involves correction of coexisting clinical conditions, total parenteral nutrition, high-dose intravenous proton pump inhibitors, adequate intravenous hydration, supportive red blood cell transfusion and broad spectrum antibiotics in selected cases. Surgery is usually reserved for perforation (3). Although the frequency of surgical and endoscopic intervention has increased in recent years, outcomes have remained the same (11). Therefore, further research is needed to better define which patients are candidates for surgical and endoscopic intervention.

Possible complications include perforation and stenosis that may occur in approximately 5% and 10% of cases, respectively (4), and there is evidence that the presence of gastrointestinal symptoms at admission and need for surgical or endoscopic intervention are associated with increased odds of complications (11).

Prognosis is poor and largely dependent on the general condition of the patient, with a high mortality rate of approximately 32% (4), though the cause is most often the underlying critical illness rather than AEN itself. This is supported by our study, where the mortality rate was 30% and none of the deaths was directly related to AEN. A recent retrospective study demonstrated that white color change, septic condition, high pulse rate, low hemoglobin and low albumin are related to high mortality (16).

In conclusion, AEN is a rare cause of upper gastrointestinal bleeding that should be suspected in older patients with general debilitation and multiple medical conditions. It is usually the result of an acute triggering event with a background of multiple chronic debilitating conditions. Despite its rarity, AEN is in itself a poor prognostic factor, and increased awareness of this pathology might lead to early recognition and timely institution of proper management, thereby increasing chances of survival.

Disclosures

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