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# Acute Esophageal Necrosis as a Rare Complication of Metabolic Acidosis in a Diabetic Patient: A Case Report

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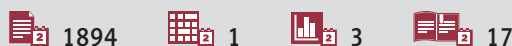
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Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Patient:** Male, 61-year-old  
**Final Diagnosis:** Challenging differential diagnosis  
**Symptoms:** Hyporexia • odynophagia • vomiting • weigh loss  
**Clinical Procedure:** Esophagogastroduodenoscopy  
**Specialty:** Infectious Diseases • General and Internal Medicine  
**Objective:** Challenging differential diagnosis**Background:** Acute esophageal necrosis, or Gurgits syndrome, is a rare clinical process often secondary to a systemic low-flow state. It can be caused by several medical conditions, and it is thought to arise from a combination of impaired mucosal barrier and chemical and ischemic insults to the esophagus. Acute esophageal necrosis usually presents with severe complications due to delayed diagnosis and only rarely has surgical indications. We present a case of Gurgits syndrome, presumably triggered by metabolic acidosis in a diabetic patient.**Case Report:** A 61-year-old man with history of hypertension and type 2 diabetes mellitus treated with metformin, canagliflozin, glimepiride, and pioglitazone came to our attention with persistent vomiting, odynophagia, chest pain after each meal, and progressive weight loss. Arterial blood analysis showed mild metabolic acidosis, while the first esophagogastroduodenoscopy performed revealed a circumferential black appearance of the esophageal mucosa, as in concentric necrosis of the distal esophagus with possible fungal superinfection. Brushing cytology confirmed the infection by *Candida* spp. and the patient was treated with intravenous fluconazole. The second esophagogastroduodenoscopy, performed after 2 weeks, showed almost complete healing of the esophageal mucosa; in this case, biopsy confirmed mucosal ischemia and necrosis, without showing deep impairment of the mucosa by fungal agents.**Conclusions:** Due to its high lethality, often caused by the underlying medical diseases, acute esophageal disease should be considered in the differential diagnosis of digestive symptoms, even without upper gastrointestinal bleeding. Prompt diagnosis and treatment of contextual collateral conditions can help clinicians to avoid the worst outcomes of the disease. Among the causative factors of metabolic acidosis leading to esophageal necrosis we recognized metformin and dapagliflozin.**Keywords:** Acute Disease • Esophageal Perforation • Esophagus  
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## Background

Acute esophageal necrosis (AEN), also known as “black esophagus”, “necrotizing esophagitis”, and Gurvits syndrome, is a rare and underdiagnosed clinical disease characterized by a striking circumferential black appearance of the esophageal mucosa and it is reported to be a very rare cause of upper gastrointestinal bleeding. It was described for the first time in 1990 by Goldenberg et al [1], but brought into the spotlight only in 2007 by Gurvits et al, who gave the name to the underlying syndrome [2].

The prevalence of AEN is up to 0.2% in autopsy series [3], while it can be even lower in endoscopy series (0.01-0.28% of cases). Its incidence seems to be higher in males (up to 4 times higher than in females) and in middle-aged subjects [4,5]. In most cases AEN affects the distal esophagus, with a prevalence of 97%, usually sparing the other two-thirds of the organ and only rarely extended proximally, stopping almost universally at the gastro-esophageal junction [6].

Since its etiopathogenesis is supposed to be multifactorial, a holistic approach to patients is needed to provide a definite diagnosis: AEN, in fact, is thought to arise from a combination of impaired mucosal barrier and chemical and ischemic insults to the esophagus [7]. Possible risk factors for the development of this syndrome are male sex, malignancies, diabetes mellitus, cardiovascular diseases, prothrombotic conditions, chronic kidney disease, malnutrition, alcohol abuse, and gastro-esophageal reflux disease [8]. Eventual complications include stenosis or stricture formation in the distal esophagus, perforation, and mediastinitis; microbial superinfections (bacterial and/or fungal) of ischemic/necrotic areas are not rare and often need broad-spectrum intravenous antibiotic or antifungal treatment [9]; general treatment include high-dose proton pump inhibitors (PPIs), fluid therapy, correction of causative conditions, and monitoring for eventual complications [10].

Surgery is usually reserved to treat esophageal perforation with subsequent mediastinitis and abscess formation: standard surgical approaches can be followed by esophagectomy, decortication, lavage, and delayed reconstruction, while primary closure of the perforated tissue is not recommended [11].

The clinical presentation of AEN depends on the status of the esophageal mucosa and on the underlying medical conditions leading to mucosal ischemia and necrosis: symptoms range from functional pyrosis, vomiting, progressive dysphagia, and hematemesis. Overall mortality is usually related to the same conditions described above, ranging from 13% to 35%. Prompt diagnosis and therapy are thus necessary to avoid the worst outcomes related to the syndrome.

Until 2007, as reported by Gurvits et al, a total of 88 patients were diagnosed with AEN, while, to date (March 1, 2023), “black esophagus” is cited in less than 800 articles (less than 700 if we consider the “Acute esophageal necrosis”) in PubMed.

In this article we described the case of a diabetic patient admitted to our hospital with persistent digestive symptoms and later diagnosed with AEN, which was presumably caused by acidosis secondary to antidiabetic treatment, with superficial *Candida* spp. infection.

## Case Report

A 61-year-old man of Bulgarian origin with a medical history of hypertension and type 2 diabetes mellitus (T2DM) was admitted to our hospital with a 4-week history of persistent odynophagia, continuous vomiting, epigastric pain after each meal, and progressive weight loss of about 5 kilograms due to forced liquid diet. At hospital observation he was 175 cm tall, weighed 85 kilograms, with a body mass index (BMI) of 27.8 and showed cutaneous and mucosal moderate dehydration. His home medications included metformin, canagliflozin, glimepiride, and pioglitazone, but he was taking no medications for hypertension. He was a former smoker (20 pack years) and denied drinking alcohol, caustic ingestion, or eating spicy foods.

His vital signs were the following: Glasgow Coma Scale (GCS) 15 (E4V5M6), body temperature 36.5°C, blood pressure 165/100 mmHg, heart rate 120 beats per minute (bpm) and percutaneous oxygen saturation 98% on ambient air, without signs of dyspnoea (respiratory rate 14 per minute).

The physical examination was completely negative for remarkable pathological signs, while laboratory analysis revealed neutrophilic leukocytosis, and hyperglycemia (300 mg/dl), with mild elevation of glycated haemoglobin (HbA1c, 56.0 mmol/mol according to IFCC standardization) and mild hypertriglyceridemia (Table 1).

Arterial blood gas analysis showed metabolic acidosis and only partial respiratory compensation (pH 7.33, pO<sub>2</sub> 95 mmHg, pCO<sub>2</sub> 17 mmHg, HCO<sub>3</sub><sup>-</sup> 9 meq/L, LAC 1.4 mmol/L). The patient was diagnosed with “compensated metabolic acidosis in a diabetic patient.” The Emergency Room (ER) chest X-ray did not reveal signs of pneumonia or pleural effusion.

The patient was then admitted to the hospital and was treated with oral proton pump inhibitors (PPIs), later switched to intravenous administration, and basal bolus insulin with improved blood glycemic levels, and total parenteral nutrition (TPN). Empiric antibiotic treatment with amoxicillin/clavulanate was also instituted, as well as subcutaneous low-molecular-weight

heparin (LMWH, enoxaparin) at prophylactic dosage (4000 IU/die); oral antidiabetic drugs were obviously discontinued.

On day 2, the patient underwent esophagogastroduodenoscopy (EGD), which revealed a malacic esophagus with circumferential necrosis of the distal third of the mucosa stopping at the gastro-esophageal junction; moreover, EGD showed a bulbar Forrest III ulcer with no sign of recent local bleeding (Figure 1A-1C). Biopsies were not taken due to mucosal fragility, but cellular brushing was performed. The patient was kept on *nil per os* (NPO) and total parenteral nutrition (TPN) while thoraco-abdominal computed tomography (CT) scanning was requested.

We also investigated the main causes of esophagitis, excluding some of the most important viral causes (HBV, HCV, herpes simplex and zoster, CMV, and EBV), searching for signs of an immunocompromised state: the study of lymphocyte subpopulation and the HIV 1/2 test were both negative, as well as

the blood cultures performed before empiric antibiotic therapy. CT scans revealed thickening of the distal esophagus, but no esophageal perforation (Figure 2A-2C).

On day 5 we received the brush cytology report, which revealed fungal hyphae by *Candida* spp. and, consequently, parenteral antifungal treatment with fluconazole was started. Due to the improvement of digestive symptoms, the patient started oral feeding in addition to partial parenteral nutrition (PPN). The general conditions continued to improve with this treatment and EGD was repeated 2 weeks after admission, showing almost complete healing of the necrotic mucosal area that was biopsied (Figure 3A-3C). After completion of intravenous antifungal therapy for 24 days, the patient was finally discharged home in good condition. Previous home antidiabetic therapy was not re-initiated and only insulin therapy was recommended while waiting for careful specialist evaluation.

**Table 1.** Laboratory findings.

Blood tests					
Parameter	Normal value (range)	Patient's value	Parameter	Normal value (range)	Patient's value
WBC	4.00-11.00	26.29×10 <sup>3</sup> /μL*	Urea	17-43	66 mg/dL*
RBC	4.50-6.50	5.39×10 <sup>6</sup> /μL	Creatinin	0.50-1.20	0.90 mg/dL
Hb	13.0-18.0	17.0 g/dl	eGFR	>90	86 ml/min*
HCT	40-54	47%	Total bilirubin	<1.20	4.41 mg/dL*
MCV	76-96	87 fl	Direct bilirubin	0.00-0.30	0.65 mg/dL*
MCH	27.0-32.0	31.5 pg	Sodium	136-145	130 mmol/L*
MCHC	30.0-35.0	36.4 g/dL*	Potassium	3.5-5.3	3.5 mmol/L
PLT	150-450	367×10 <sup>3</sup> /μL	ALT	<50	17 U/L
Neutrophils	2.00-7.50	22.97×10 <sup>3</sup> /μL*	LDH	<248	102 U/L
Lymphocytes	1.50-5.00	1.50×10 <sup>3</sup> /μL	CPK	<170	17 U/L
Monocytes	0.20-1.00	1.77×10 <sup>3</sup> /μL*	Lipase	<67	8 U/L
Eosinophils	0.04-0.40	0.00×10 <sup>3</sup> /μL	TSH	0.25-4.50	0.65 μU/mL
Basophils	0.01-0.10	0.05×10 <sup>3</sup> /μL	CRP	<0.50	3.84 mg/dL*
PT (INR)	–	1.12	HS Troponin I	<20	9 ng/L
PT (Ratio)	0.80-1.20	1.12	Procalcitonin	<0.5	0.14 ng/mL
PTT (Ratio)	0.82-1.20	0.93	Proteins	6.6-8.4	7.6 g/dL
Fibrinogen	150-400	478 mg/dL*	Total cholesterol	<200	228 mg/dL
Glucose	70-110	300 mg/dL*	HDL cholesterol	>35	37 mg/dL
			Triglycerides	<150	345 mg/dL*

**Table 1 continued.** Laboratory findings.

Viral antibody tests			Fungal antigen tests		
Parameter	Normal value	Patient's value	Parameter	Normal value	Patient's value
HbsAg	<0.05	<0.030 IU/mL	Galactomannan Antigen	<0.16	0.02 index
HBsAb	<10	<3.00 UI/L	Beta-D-Glucan	≤7	<3 pg/mL
HbA1c	23.0-43.0	56.0 mmol/mol*			
Anti-CMV IgG	–	56 U/mL	<b>Flow cytometry</b>		
Anti-CMV IgM	–	Negative			
			Parameter	Normal value (range)	Patient's value
Anti-herpes simplex 1/2 IgG	<0.9	>30.0	Total CD3+	58-72	71%
Anti-herpes simplex 1/2 IgM	<0.9	<0.500	CD3+ CD4+	34-48	42%
Anti-herpes simplex 2 IgG	<0.9	<0.500	CD3+ CD8+	15-27	30%*
Anti-Varicella-Zoster IgG	≤134	1,776	CD4/CD8 Ratio	1.00-2.80	1.40
Anti-Varicella Zoster IgM	<0.9	0.13	Total CD3	603-2,990	1590/μL
Anti-EBV VCA IgG	<20	113	CD4	441-2,156	933/μL
Anti-EBV VCA IgM	<20	<10.0 U/mL	CD8	125-1,312	666/μL
HIV 1-2	–	Negative			

WBC – white blood cells; RBC – red blood cells; Hb – haemoglobin; HCT – haematocrit; MCV – medium corpuscular volume; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; PLT – platelets; PT(INR) – prothrombin time (international normalized ratio); aPTT – activated partial thromboplastin time; eGFR – estimated glomerular filtration rate; ALT – alanine transferase; LDH – lactate dehydrogenase; CPK – creatine phosphokinase; TSH – thyroid-stimulating hormone; CRP – C reactive protein; HBsAg – hepatitis B s antigen; HbsAb – anti-hepatitis B surface; CMV – cytomegalovirus; EBV – Epstein Barr virus; HIV – human immunodeficiency virus. Abnormal findings are reported with \*0.

The final pathology report, received after discharge, showed *Helicobacter pylori*-negative chronic gastritis, and an ulcerated and only partially necrotic esophageal mucosa penetrated by granulation tissue, with no signs of fungal infection.

## Discussion

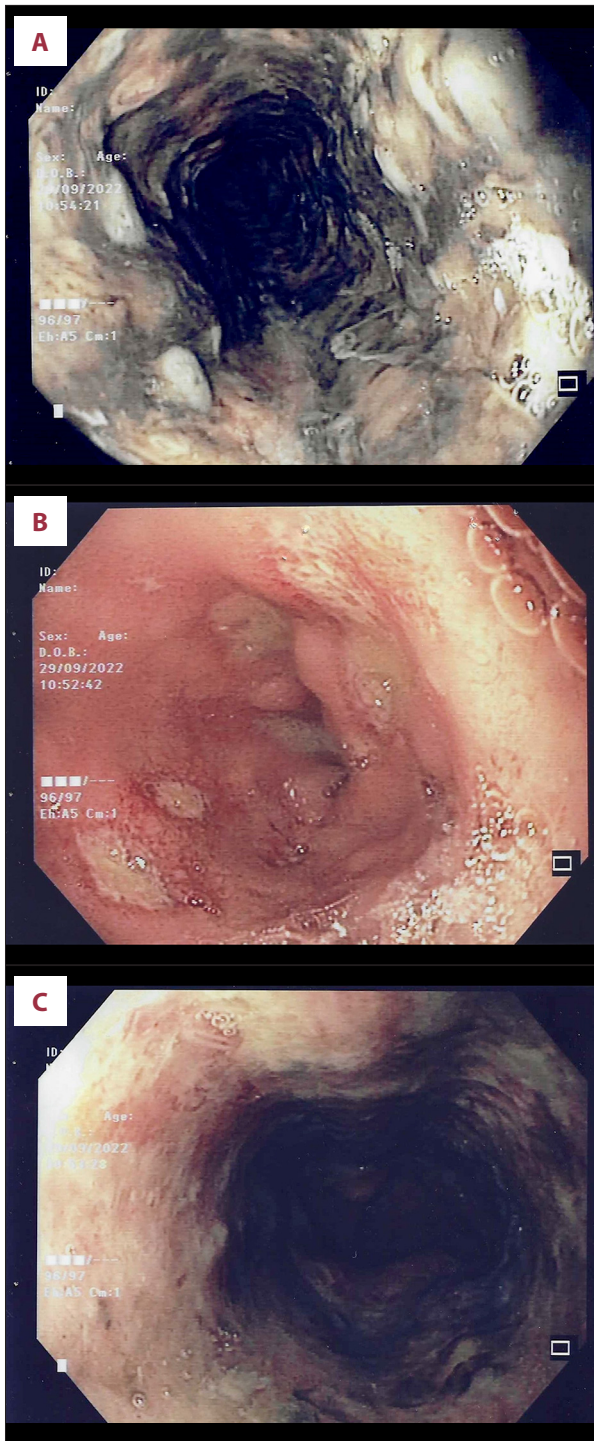
AEN is a rare condition, only occasionally reported in the literature and often leading to worse outcomes due to delayed diagnosis and complications. The multifactorial etiopathogenesis is supposed to be the basis for the development of “black esophagus” and diabetic-related acidosis can be among the most common underlying conditions [10,12].

Diabetes mellitus, together with malignancies, chronic kidney disease, poor nutritional status, cardiovascular illnesses, and general deconditioning, can predispose to altered and

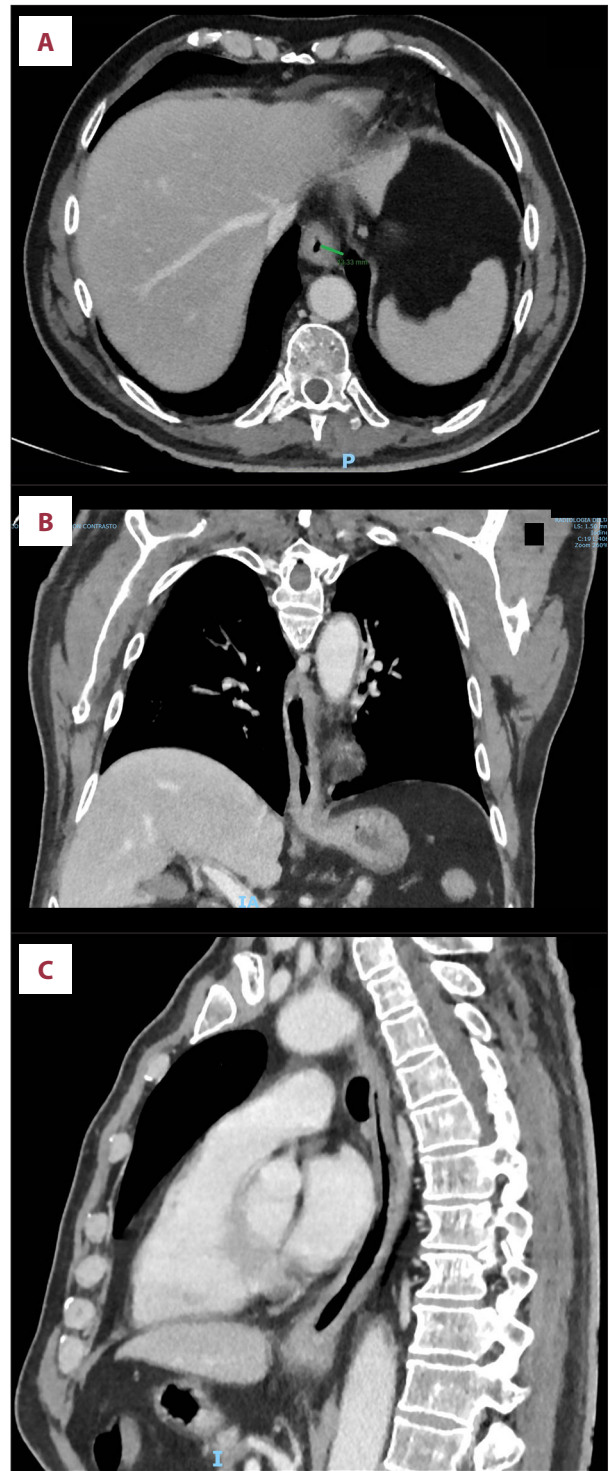
compromised mucosal barriers, which could potentiate eventual chemical or ischemic injury to the esophagus [13,14].

A low-flow state, common in case of sepsis, congestive heart failure, systemic inflammation, or lactic- and keto-acidosis, can lead to mucosal ischemia and necrosis (focal or extended), which is favoured by the particular segmentation of the arterial network of the esophagus. While the upper third is vascularized by the descending branches from the inferior thyroid arteries and numerous additional small arteries, the middle esophagus receives its blood supply from the bronchial arteries, right third or fourth intercostal arteries, and numerous small esophageal arteries from the descending aorta. Finally, the distal third of the esophagus has less blood supply, provided by small branches from the left gastric artery or left inferior phrenic artery, with several possible anatomic variations: consequently, ischemic injuries typically affect this part of the organ.

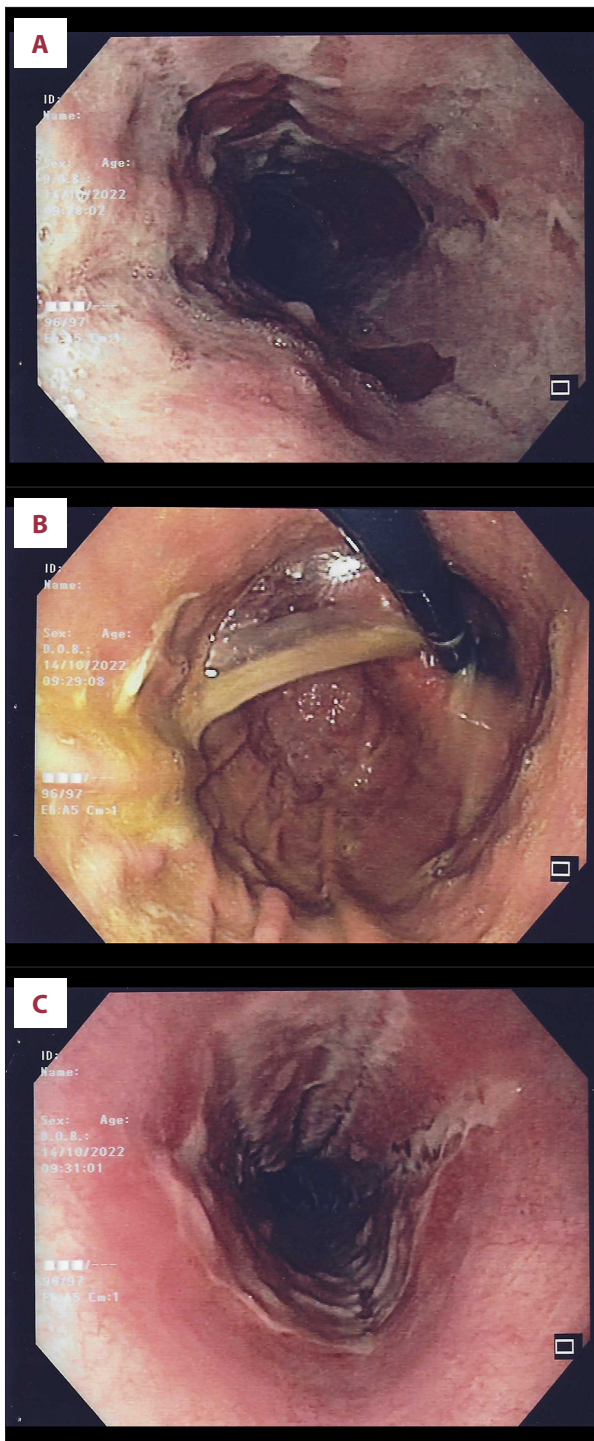




**Figure 1.** First esophagogastroduodenoscopy with circumferential necrotic mucosa: detail of the distal third of the esophagus (A); detail of the proximal gastric mucosa (B); detail of the middle third of esophageal mucosa.



**Figure 2.** CT scan, transversal section of thorax, showing concentric thickening of the esophageal wall (A). The green line indicates the maximal thickening (13 mm); coronal section of thorax, showing craniocaudal extension of the esophageal wall (B); sagittal section of thorax, showing craniocaudal reduction of the esophageal lumen (C).



**Figure 3.** Second esophagogastroduodenoscopy with almost complete healing of necrotic esophageal mucosa: detail of the distal third of the esophagus (A); detail of the proximal gastric mucosa (B); detail of the middle third of esophageal mucosa (C).

The first arterial blood sample in our patient showed mild metabolic acidosis, but the prolonged vomiting in the previous days had probably buffered the blood pH, which could have been even lower during the first phases of metabolic acidosis. Some of the patient's own medications (eg, metformin and canagliflozin) may also have contributed to development of metabolic acidosis, as already described for biguanides and SGLT-2 inhibitors in a small percentage of cases [15,16].

As already stated above, microbial infections commonly complicate AEN, requiring in most cases specific and long-lasting treatment [17] – this happened to our patient, since *Candida* spp. was identified in brushing samples during the first EGD performed.

Although biopsy is not always needed to confirm the diagnosis of AEN, it is strongly recommended: necrotic debris, absence of squamous epithelium, and necrosis of mucosa are often present. We were able to collect biopsy samples only during the second EGD due to mucosal fragility at the first endoscopy: histological analysis showed the presence of ulcerated and partially necrotic mucosa, with tracks of granulation tissue, as signs of repair attempts by the esophageal mucosa itself. Hence, all symptoms and findings seem to be compatible with the diagnosis of AEN we made and, after 6 months of remote follow-up, the patient did not show further digestive symptoms and reported complete healing of the acute disease.

It is our opinion that the patient's home therapy could be the key for understanding the origin of metabolic acidosis and that one drug or both metformin and canagliflozin could have strongly contributed to it, leading to focal esophageal ischemia and necrosis and, contextually, to the digestive symptoms.

In healthy patients without immune compromise, it is very hard to find circumferential necrosis due to fungal infections, since in immunocompromised subjects such infections usually affect the entire mucosa. In our case, the only finding in mucosal tissue was partial necrosis and no signs of fungal infiltration were encountered, showing how the fungal infection was primarily the consequence and not the cause of AEN.

As in almost all cases of AEN, factors clearly leading to the disease are rarely found, and also in our case, it was hard to determine which factors formerly acted as the “primum movens” in the development of esophageal necrosis.

Although AEN is gaining attention among the medical community, it is still an underdiagnosed illness, and it is rarely recognized, with high mortality rates due to delayed diagnosis and therapy. For this reason, we are convinced that each case report is a chance for clinicians to learn about such a disease and could be the basis for further and larger studies on the topic.



## Conclusions

We presented a case of AEN presumably triggered by metabolic acidosis and complicated with fungal infection in a diabetic patient.

AEN is an uncommon, potentially lethal, medical condition, and should be included in the differential diagnosis of upper gastrointestinal bleeding or digestive symptoms in diabetic patients. The endoscopic approach, with or without biopsy, can be necessary to avoid the worst outcomes of the illness. In this case, we hypothesized that the causative agents leading to esophageal necrosis were (one or both) the antidiabetic drugs metformin and canagliflozin.

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