

Acute esophageal necrosis syndrome. The 2021 update from an Italian survey and personal experience



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Federico Selvaggi*[/]#, Anna Cichella*[/]#, Gitana Maria Aceto, Paolo Innocenti, Roberto Cotellese**

*Department of Medical, Oral and Biotechnological Sciences, "G. d'Annunzio" University Chieti-Pescara, Chieti, Italy

**Villa Serena Foundation for Research, Città Sant'Angelo, Pescara, Italy

Authors have contributed equally to this study.

Acute esophageal necrosis syndrome. The 2021 update from an Italian survey and personal experience

AIM: Black esophagus, or acute esophageal necrosis, is a rare entity with multifactorial aetiology. Modern theories suggest a combination of ischemia, compromised mucosa defences and corrosive agent's injury.

MATERIAL AND METHODS: We investigated black esophagus by means of a retrospective review of 26 cases in literature. A Medline overview is performed until May 2021 by considering the Italian results. The search terms were "black esophageal syndrome in Italy", "black esophagus in Italy", "black esophageal necrosis in Italy", and "Gurvits syndrome in Italy".

To complete these case reports, we illustrate our first experience of the syndrome successfully treated with esophagectomy, cervical diversion and gastrostomy.

RESULTS: Black esophagus is common in adult males (M/F: 21/5) (Range: 47-89 years; Average: 70.6 year-old). The most common symptoms are hematemesis, epigastric pain and dysphagia. Endoscopically, diffuse involvement of acute esophageal necrosis is diagnosed in 42.3% of cases. The treatment consisted on red blood cell transfusions, sucralfate administration, proton pump-inhibition, enteral nutrition and antimicrobial agents. Overall mortality was 38.4% and only one case underwent surgery for acute bleeding.

CONCLUSIONS: Black esophagus is often reversible both anatomically and functionally. Its treatment is based on supported therapies and hemodynamic resuscitation. This syndrome shows high mortality related to the coexisted medical conditions rather than acute esophageal necrosis. Only in selected cases, surgical treatment is indicated.

KEY WORDS: Acute necrotizing esophagitis, Black esophagus, Ischemia.

Introduction

Black esophagus (BE), acute necrotizing esophagitis or Gurvits syndrome, is an uncommon endoscopic finding of extensive black and circumferential discoloration of the esophageal mucosa caused by acute esophageal necrosis¹⁻⁶.

In the literature, the single BE instance was described in 1967, although the first diagnosed endoscopically description was recorded in 1990 by Goldenberg^{7,9}. BE incidence ranges from 0.0125% to 0.2 %^{1,7,10,-14}. Patients affected by BE were usually elderly and frequently are men that, at the time of the diagnosis, presented critical co-morbidities. Ischemia, lye ingestion, microbial infection with *Lactobacillus acidophilus*, Cytomegalovirus or *Candida albicans*, anticardiolipin antibody syndrome, herpes simplex esophagitis, diabetic ketoacidosis, acute gastric injury, massive acid reflux, hypertension, multiorgan dysfunction, gastric volvulus, traumatic transaction of the thoracic aorta, hypothermia and malignancy represent the most reported causes of BE^{1,3,15,16}. The associated condition of cancer with the hypercoagulable status and thrombosis, has been associated with BE development^{1,13,17,18}. In addition, risk fac-

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Correspondence to: Federico Selvaggi MD, PhD Medical Doctor in the Unit of Surgery, ASL2 Lanciano-Vasto-Chieti, Ospedale "Renzetti" Lanciano, Abruzzo, Italy, Tutor in Surgery, Università degli studi "G. d'Annunzio" Chieti-Pescara, Italy, (e-mail: fedeselvaggi@hotmail.com)

tors of BE are also alcohol or cocaine abuse and antipsychotics intoxication^{7,11,13,14,18}.

The most common presenting symptom of BE is upper gastrointestinal bleeding associated with epigastric pain, often combined with dysphagia^{1,7,14}. The exact physiopathology of BE is still unknown. Many clinicians have underlined the role of ischemic injury as a consequence of hypotension or thrombosis¹⁴. Although the ischemic injury is considered to be the most likely cause, it is not enough to explain the progression of BE, especially in irreversible clinical cases. The distal esophagus is less vascularized and more vulnerable to ischemic injury. Hypothetically, BE arises from a combination of an ischemic injury to the esophagus, impaired mucosa barrier system, and a backflow injury from gastric secretion¹⁵.

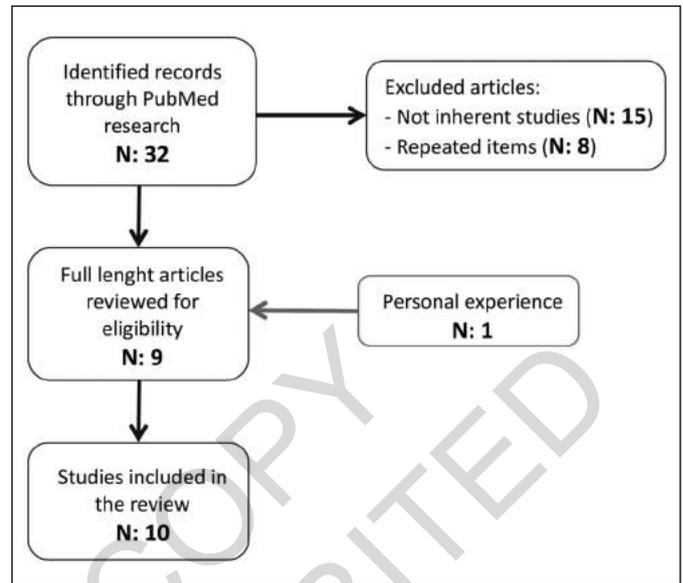
The differential diagnosis of BE includes malignant melanoma, melanosis, coal dust deposition, corrosive ingestion, acanthosis nigricans and pseudomelanosis of the esophagus^{7,15,17,18,19}. In addition to these, the intraepithelial hemorrhage of the esophagus (EIH) has to be considered in the differential diagnosis. EIH is confined mainly in the epithelium, whereas BE shows widespread mucosal sloughing and necrosis of the residual mucosa with extensive submucosa edema⁷. BE progression is classified in four distinct phases: pre-necrotic viable esophagus; the condition of diffuse, circumferential, black-appearing esophageal mucosa; the condition of residual black areas in the esophagus and thick white exudate and necrotic debris, and the condition of normal endoscopic appearance with only microscopically granulation tissue¹⁵. Worldwide, BE is associated with a reported mortality rate of 32–38%^{7,15,21,22}. Prognosis largely depends on coexisting medical conditions and age of patients. Mortality specific to the BE is much lower, and is around 6%^{15,22}. We present the current knowledge on BE syndrome based on a critical review of published Italian reports.

Evidence Acquisition

A systematic search is conducted using Medline database (through PubMed) for all reports published until May 2021 (the last search was performed on May 10th). This process yielded 32 search terms, all of which are sought in titles and/or abstracts of English written papers. Finally, two authors (A.C. and F.S.) reviewed all abstracts independently and the full text of relevant studies is considered for inclusion (Table I).

Twenty-six cases of BE are reviewed from 2001 to 2019. Criteria for BE diagnosis and inclusion were presence of circumferential black appearing esophageal mucosa that stopped abruptly in the gastro-esophageal junction. BE was more common in males (M/F: 21/5) that presented upper gastrointestinal haemorrhage (Range: 47-89 years; Average: 70.6 year-old) (Table II). Risk factors

TABLE I - Demographic characteristics, medical treatment and outcome.



included diabetes mellitus (42.3%), hypertension (42.3%), cardiomyopathy (19.2%), alcohol abuse (7.6%), chronic or acute kidney disease (23.0%), liver cirrhosis (7.6%), and atrial fibrillation (19.2%) (Table II). The BE necrosis more frequently involved the mucosal and submucosa layer of esophagus with a circumferential distribution in the distal one-third of the esophagus with or without exudate. In our analysis, BE is observed in the mild or middle-distal third portion in the majority of patients (15 cases; 57.6%). In 11 cases (42.3%), an entire discolouration of the esophagus is observed. Although proximal BE localization has been reported in international studies, any Italian experiences confirmed this selective anatomical distribution^{13,18,24}.

In BE patients, gastric or duodenal alterations, in terms of linitis plastica, hiatal hernia, gastritis, duodenitis or ulcerations, are reported³. In our analysis, duodenal ulcer or duodenitis is diagnosed in 12 cases (46.1%), and gastric involvement in terms of hyperemia or necrosis is reported in 4 cases (15.3%) (Table II).

Currently, the overall mortality was 38.4% (10 cases) in the Italian series. Three patients died for sepsis, three patients for multiorgan failure (MOF) and two cases for acute renal failure (Table III). Of the 12 cases with resolution of acute esophageal necrosis, one patients (7.2%) required after the initial BE event, endoscopic dilatation for esophageal strictures. BE related mortality usually correlates with underlying medical conditions rather than acute esophageal necrosis.

Although no standardised medical care has been defined, the majority of BE patients is treated with supported medical therapy based on red blood cell transfusions in cases of anemia, oral intake restriction, hydration, sucralfate administration, proton pump-inhibition, total enteral nutrition and antimicrobial agents. The use of

TABLE II - Demographic characteristics, comorbidities and endoscopic findings.

	Year	Authors	Location	Age	Sex	Medical History	Endoscopy	Stomach/duodenum
1	2014	Efthymakis K et al.	Chieti	75	M	Gastritis; alcoholic liver disease; chronic pancreatitis	I-II-III	ulcer of cardia
2	2011	Calabrese C et al.	Bologna	72	M	Chronic; DM; Cerebral vascular disease; Prostatic hypertrophy	II-III	not reported
3	2018	Crescenzi O et al.	Perugia	63	F	AF; Cerebrovascular dementia; Hy; Wegener granulomatosis; RF; osteomyelitis	III	not reported
4	2017	Bonaldi M et al.	Milano	72	M	Osteomyelitis jaundice for neoplasia of ampulla of Vater (Whipple resection)	III	not reported
5	2014	De Palma GD et al.	Napoli	82	M	Coronary artery disease; Hy; DM	I-II-III	not reported
6	2017	Manno V et al.	Vibo Valentia	49	M	DM; Osteomyelitis; Sepsis	I-II-III	Hyperemia of gastric mucosa
7	2011	Selvaggi F et al.	Chieti	48	M	Alcohol abuse and alcoholic chronic liver disease	II-III	not reported
8	2001	Casella G et al.	Milano	67	M	DM; AF; Hy	I-II-III	duodenal ulcers
9	2001	Casella G et al.	Milano	69	M	Bronchial asthma; Gastric peptic ulcer; AF; Fracture of femoris	II-III	duodenal ulcers
10	2016	Rigolon R et al.	Verona	50	M	DM; Hy	II-III	no
11	2008	Orlando D et al. 2019	Roma	74	M	RF; DM; Cerebral vascular and ischemic heart disease	I-II-III	duodenal ulcers
12	2009	Orlando D et al. 2019	Roma	76	M	Cerebral vascular disease	I-II-III	duodenal ulcers
13	2010	Orlando D et al. 2019	Roma	80	M	RF	I-II-III	Bulb and pyloric necrosis
14	2010	Orlando D et al. 2019	Roma	74	M	RF; Cardiomyopathy	I-II-III	not reported
15	2012	Orlando D et al. 2019	Roma	47	M	DM; AF; Psoriasis	II-III	not reported
16	2012	Orlando D et al. 2019	Roma	69	M	Hy; DM; Depressive syndrome	III	duodenal ulcers
17	2014	Orlando D et al. 2019	Roma	81	M	RF; Silicosis; Aritmia	I-II-III	duodenal ulcers
18	2016	Orlando D et al. 2019	Roma	64	M	Stage IV pancreatic cancer	II-III	Bulb ulcers
19	2016	Orlando D et al. 2019	Roma	65	F	Zollinger-Ellson syndrome in metastatic NET	I-II-III	duodenal ulcers
20	2016	Orlando D et al. 2019	Roma	85	M	Alzheimer disease; AF	III	duodenal ulcers
21	2016	Orlando D et al. 2019	Roma	84	F	Hy, Zollinger-Ellison syndrome, Chronic Ischemic heart disease	III	duodenal ulcers
22	2017	Orlando D et al. 2019	Roma	87	F	Ischemic heart disease; Hy; DM; Parkinson disease and dementia	III	duodenal ulcers
23	2018	Orlando D et al. 2019	Roma	71	M	DM	II-III	not reported
24	2018	Orlando D et al. 2019	Roma	89	M	Hy; DM; Glaucoma, Dyslipidemia	III	not reported
25	2018	Orlando D et al. 2019	Roma	66	M	Polynuropathy; Hy; DM	I-II-III	duodenal ulcers
26	2018	Orlando D et al. 2019	Roma	77	F	Cerebral vascular disease; Hy; RF	II-III	Necrosis of II portion

M, male; F, female; AF, atrial fibrillation; DM, diabetes mellitus, Hy, hypertension; RF, renal failure. BE necrosis located to distal one-third (III), distal two-third (II), proximal one-third (I).

nasogastric tube after the diagnosis of BE syndrome has been reported. This medical procedure is indicated in order to monitor the upper gastrointestinal bleeding but, on the other side, the passage of the nasogastric tube might expose to a higher risk of esophageal perforation. Although the passage of a Sengstaken-Blakemore tube has been reported in limited conditions, this procedure should be prohibited, as the friability of the esophagus

will lead to tragic perforation and death. Surgery is indicated in cases of perforated BE resulting in mediastinitis, abscess formation or uncontrolled esophageal bleeding^{2,29}. Wu and colleagues have reported a case of perforated BE treated with transhiatal esophagectomy and esophageal reconstruction using a gastric tube, via the retrosternal route³⁰. Groenveld and co-workers have described a case of perforated BE with leakage to the

TABLE III - Demographic characteristics, medical treatment and outcome.

	Year	Authors	Location	Age	Sex	Medical Therapy	Outcome
1	2014	Efthymakis K et al.	Chieti	75	M	Colloidal infusion; HE; PPI; Terlipressin; Ab; Antifibrinolytics; PN	25 days; Resolution after 8 months
2	2011	Calabrese C et al.	Bologna	72	M	PPI; PN	10 days; Resolution
3	2018	Crescenzi O et al.	Perugia	63	F	Invasive mechanical ventilation; PPI; PN; Ab	Resolution
4	2017	Bonaldi M et al.	Milano	72	M	HE; PN; PPI	7 days; Resolution
5	2014	De Palma GD et al.	Napoli	82	M	Not reported	The outcome of case 5: Not reported
6	2017	Manno V et al.	Vibo Valentia	49	M	Hemodialysis; Ab; Nil per os; PN; PPI; Fluconazole; Acyclovir	Resolution after 3 months
7	2011	Selvaggi F et al.	Chieti	48	M	Nil per os; PPI; HE; PN	15 days after surgery
8	2001	Casella G et al.	Milano	67	M	Oral sucralfate; ranitidine,	Exitus: 5 days later
9	2001	Casella G et al.	Milano	69	M	Intensive medical treatment	Exitus: less than 24 h
10	2016	Rigolon R et al.	Verona	50	M	PPI; Albumine infusion, Ab; Nil per os; PN	15 days; Resolution after 3 months
11	2008	Orlando D et al.2019	Roma	74	M	PPI *	Discharged
12	2009	Orlando D et al.2019	Roma	76	M	PPI *	Exitus for sepsis
13	2010	Orlando D et al.2019	Roma	80	M	PPI *	Exitus for MOF
14	2010	Orlando D et al.2019	Roma	74	M	PPI *	Lost to follow-up
15	2012	Orlando D et al.2019	Roma	47	M	PPI *	Esophageal stenosis
16	2012	Orlando D et al.2019	Roma	69	M	PPI *	Discharged
17	2014	Orlando D et al.2019	Roma	81	M	PPI *	Exitus for MOF
18	2016	Orlando D et al.2019	Roma	64	M	PPI *	Exitus for acute renal failure
19	2016	Orlando D et al.2019	Roma	65	F	PPI *	Resolution
20	2016	Orlando D et al.2019	Roma	85	M	PPI *	Exitus for sepsis
21	2016	Orlando D et al.2019	Roma	84	F	PPI *	Relapse 3 weeks later
22	2017	Orlando D et al.2019	Roma	87	F	PPI *	Exitus for acute renal failure
23	2018	Orlando D et al.2019	Roma	71	M	PPI *	Resolution
24	2018	Orlando D et al.2019	Roma	89	M	PPI *	Exitus for sepsis
25	2018	Orlando D et al.2019	Roma	66	M	PPI *	Resolution
26	2018	Orlando D et al.2019	Roma	77	F	PPI *	Exitus for MOF

M, male; F, female; HE, hemotransfusion; PPI proton pump inhibitor; Ab, antibiotics, PN, parenteral nutrition. * In these cases Nil per os and PN were prescribed in 60% of patients. Antibiotics and antimycotics were given to 73% and 25% of patients, respectively. HE was indicated for 50% of patients (Orlando C et al. 2019).

pleural space treated with video assisted thoracoscopic surgery². Gomez and colleagues have reported the case of BE with esophageal stricture treated with esophageal self-expandable metal stent finally complicated with tracheoesophageal fistula with erosion of the trachea³¹. The patient underwent a right thoracotomy with esophagectomy, repair of the tracheoesophageal fistula and creation of a subclavicular esophagostomy. Worrell in her personal experience has reported the case of perforated distal BE with pneumomediastinum and pleural effusion treated with emergent esophagectomy with cervical diversion⁸. To the best of our knowledge, any Italian experience has reported the outcome of BE patients surgically treated for complicated BE damage. Our personal contribution represents the first case of BE successfully

treated with the combination of medical and surgical care.

Black Esophageal Syndrome: Personal Experience

Our first experience concerns a case of 48-year-old man who was admitted to the emergency room of the University Hospital of Chieti for facial trauma and melena. The patient presented impaired general conditions with severe haemorrhagic shock. His medical and surgical history was uneventful with exception for smoking and alcohol abuse. Upper endoscopy showed circumferential, black appearing, distal esophageal mucosa suggestive of ischemic esophagitis. Esophageal mucosa pre-

sented necrotic areas and ulcerations with active bleeding. Biopsy was not indicated due to active bleeding and the risk of perforation. Resuscitation and correction of medical parameters were performed with complete stability of the haemodynamic status. The patient was kept nil-per-os and treated with high dose of proton pump inhibitors, hydration, red blood cell transfusion and total parenteral nutrition. During hospitalization, patient showed several episodes of melena with anemia and haemodynamic instability. Due to the uncontrolled esophageal bleeding and anemia, patient underwent emergency surgery. Esophagectomy with cervical diversion and gastrostomy were performed. Macroscopically, esophageal mucosa of the distal and middle portion was necrotic with active foci of bleeding. Subsequently, patient underwent reconstructive surgery with cervical esophago-gastroplasty with cervical anastomosis, pyloroplasty, splenectomy and cholecystectomy. At laparotomy, alcoholic steato-hepatitis was documented by biopsy. The histological exam finally confirmed the diagnosis of BE. Immunostaining for Cytomegalovirus was negative. The patient was discharged in a stable condition on postoperative day 15.

Evidence Synthesis

BE syndrome is still a rare clinical entity with multifactorial aetiology, primarily described in post-mortem status^{7,11,12}. Recent evidences suggest that BE syndrome usually shows a transient and reversible nature with complete resolutions of symptoms. The mechanisms of acute BE are not well understood, but several risk factors have been identified. The combination of all conditions that predispose to ischemia and necrosis of esophageal distal mucosa can be involved^{32,36}. Nowadays, three are the most relevant hypothesis of BE necrosis. First, the “low flow vascular state” that it is diagnosed in patients with low systemic perfusion and hemodynamic instability. According to this hypothesis, the “low-flow” state predisposes to ischemia and necrosis of mucosa and submucosa of the esophagus. Hypothermia might increase the risk of low-flow vascular state, leading to vasoconstriction with progression to tissue necrosis³². Secondly, the so called “acid bath state” has been suggested as the condition that, with the direct injury to esophageal mucosa after acidic impact of corrosive agents, might cause BE acute necrosis. Finally, the defect in the intrinsic repair mechanisms of esophageal mucosa seems to be involved in BE development and progression. Alterations in mucous and saliva production together with abnormal rhythms of esophageal motility might predispose to BE damage. All the reported hypotheses might act in combination, especially in adult and debilitated patients. Risk factors of BE are greater age, male sex, cardiovascular disease, hemodynamic compromise, hypoxemia, hypercoagulable state, gastric outlet obstruction, malnu-

trition, malignancies, diabetes mellitus, renal insufficiency, trauma, alcohol or pharmacological drugs.

Poor nutritional status leads to diminish mucosal buffering, impaired protective barriers with alterations of the intrinsic repair mechanisms. In our retrospective experience, the majority of BE patients presents malnourishment or are debilitated.

Proximal BE, without evidence of distal necrosis, has been reported and might be the result of selective embolic event following cardiac arrhythmia, cardiac catheterization or cannulation of thyrocervical trunk^{13,18,36}. In the Italian survey, any patient presents proximal BE.

The endoscopic ultrasound (EUS) using a 20 MHz probe might be indicated in BE patients to study the submucosal and muscularis layer of the esophagus²⁵. The role of EUS in the diagnosis and progression of BE syndrome is currently not defined. No data have been reported to understand the adjunctive utility of EUS in defining the gravity of BE damage. On the other hand, the passage of EUS tube might be a dangerous manoeuvre especially in not skilled hands and in cases of increased friability of the esophagus.

The endoscopic biopsy, although not required for BE diagnosis, might be of utility in defining the infective nature of BE and for proper management with antiviral or antimicrobial agents. Reported pathogens include *Klebsiella pneumoniae*, *Parvimonas Micra*, *Cytomegalovirus*, *Herpes simplex virus*, *Candida* and other fungal species^{1,3,15,26,27}. Although the choice of performing an endoscopic biopsy of the esophageal tissue depends by individual gastroenterologist, some authors discourage endoscopic biopsy in patients with thrombocytopenia, in immunocompetent conditions and in case of high risk of esophageal perforation^{13,16,18,38}. BE therapy is surgical and non-surgical²⁹. The majority of BE patients shows benefits with resolution of symptoms after systemic fluid resuscitation, intravenous proton pump inhibitors, total parenteral nutrition, nil-per-os state and antibiotic administration^{39,40}. To date, surgical resection should be reserved only in unresponsive and complicated patients with esophageal perforation or mediastinitis^{29,37}. Esophageal perforation is the most feared complication reported, followed by stenosis or esophageal strictures. The formation of stenotic areas or strictures, as a result of protective and reparative scar formation, was observed in the minority of cases with an incidence of 6-25%^{39,41}. The results of high-volume Endoscopy Centers confirmed the utility of repeated endoscopic sessions using balloon dilatation in the care of esophageal stricture^{1,2,3,8,31}. The main limitation of this study is its retrospective nature together with the heterogeneity of clinical data collection. In Italy, the cohort of BE patients shows limited numbers. The reported experiences are referred to data collected in different hospitals and university Centers which affect the standardization of treatments and the outcome of patients.

Conclusions

Although the pathophysiology leading to BE is still unknown, clinicians caring BE patients should focus on supportive medical therapy and correction of the underlying medical comorbidities. The contents of our retrospective analysis suggest that the majority of BE patients, that at the admission often presented hemodynamic compromise, debilitated health with multiorgan failure, shows benefits with resolution of symptoms after systemic fluid resuscitation, intravenous proton pump inhibitors, total parenteral nutrition, nil-per-os state and antibiotic or antimycotic administration. To our knowledge, the clinical case coming from our personal experience is the first patient reported in the Italian literature and treated successfully with major surgery. In any case, the indication of surgery should be reserved only for cases of esophageal perforation, resulting in mediastinitis, abscess formation or uncontrolled esophageal bleeding.

Riassunto

OBIETTIVO: Il black esofago, o necrosi esofagea acuta, rappresenta una rara entità con etiologia multifattoriale. Le teorie più moderne suggeriscono la combinazione del danno ischemico, delle alterazioni di difesa della mucosa e del danno causato da agenti corrosivi.

MATERIALE E METODI: Abbiamo studiato questa sindrome mediante revisione retrospettiva di 26 casi clinici della letteratura, analizzata fino a Maggio 2021 utilizzando la banca dati Medline. I termini di ricerca utilizzati sono stati "black esophageal syndrome in Italy", "black esophagus in Italy", "black esophageal necrosis in Italy", and "Gurvits syndrome in Italy".

A completamento di questi dati clinici, presentiamo una nostra prima esperienza relative al black esofago, trattata con successo mediante intervento chirurgico di esofagectomia, diversione cervicale e gastrostomia.

RISULTATI: Il black esofago è comune nei maschi adulti (M/F: 21/5) (Range: 47-89 anni; Average: 70.6 anni). I sintomi di presentazione più comuni sono: l'ematemesi, il dolore epigastrico e la disfagia. All'esame endoscopico, è presente nel 42.3 % dei casi una necrosi esofagea acuta diffusa. La terapia del black esofago consiste nella trasfusione di emazie concentrate, nella somministrazione di sucralfato, nell'utilizzo di inibitori della pompa protonica, nella nutrizione enterale e nella terapia antibiotica e antifungina. La mortalità complessiva è stata del 38.4% e soltanto un caso è stato sottoposto ad intervento chirurgico.

CONCLUSIONI: Il black esofago è spesso reversibile sia da un punto di vista anatomico che funzionale. Il trattamento prevede la somministrazione di terapia di supporto e procedure di rianimazione emodinamica. Questa sindrome ha una elevata mortalità che spesso è correla-

ta con le condizioni patologiche cliniche pre-esistenti piuttosto che con il danno da necrosi esofagea acuta. Soltanto in casi molto selezionati, il trattamento chirurgico è indicato.

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