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Original contribution

Acute (gangrenous) esophageal necrosis (black esophagus). A rare form of injury with specific histologic features and diverse clinical associations with a common pathogenesis☆,☆☆,★

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Summary Acute esophageal necrosis (AEN) also known as black esophagus is a rare form of injury to the esophageal mucosa that complicates a variety of clinical conditions. It is characterized by circumferential black discoloration of the mucosa. There is little information relating to the histopathologic features and pathogenesis of this condition. In this study we describe the histopathologic features of six cases of AEN (3 autopsy and 3 biopsy cases) and compared the finding to 26 cases of ulcerated esophagitis. Cases and controls were assessed for type of necrosis, inflammatory cells, vascular thrombi, pigment deposits, granulation tissue and presence of viable mucosa. Cases were evaluated with histochemical stains for iron and microorganisms and immunohistochemical stains to inflammatory cells (myeloperoxidase, CD20, CD3 and CD163), squamous cells (pancytokeratin and p40) and muscle (smooth muscle actin). Most patients were males (60%) with an average age of 58 years. All specimens show the characteristic black discoloration of the mucosa. Microscopic examination revealed a distinct band of basophilic necrosis, Prussian blue–negative pigment deposits and fibrin thrombi in vessels. Myeloperoxidase-positive neutrophils were seen beneath the area of necrosis and CD163-positive macrophages throughout the esophagus. Basophilic necrosis was never seen in control cases. Only one control case showed intravascular thrombi and pigment deposits. We conclude that the combination of basophilic necrosis, intravascular thrombi and pigment deposits are diagnostic of AEN. We theorize that microvascular occlusion is the unifying lesion that explains the diversity of conditions associated with this disorder.

1. Introduction

Acute esophageal necrosis (AEN) also known as black esophagus is a rare severe form of esophageal injury that develops in older patients with several comorbidities [1]. It has a characteristic gross and endoscopic appearance with diffuse circumferential black discoloration of the esophageal mucosa [1-3]. Most patients present with gastrointestinal bleeding.

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Other symptoms include dysphagia, epigastric pain or those related to the underlying disorders [2-7]. To date most cases have been reported in the clinical literature and, with few exceptions, the histologic features have not been well characterized [4]. This study was planned to describe in detail the histopathologic features of this condition and to compare the findings with other cases of esophageal mucosal injury. In addition, immunohistochemical studies were performed in an attempt to characterize the type of inflammatory cells and the nature of the necrotic tissue. Based on these observations, a unifying pathophysiologic hypothesis is proposed that could explain the multiple dissimilar clinical conditions associated with this disorder and the reason why AEN is rarely seen in patients with common disorders causing visceral hypoperfusion.

2. Materials and methods

The study group consistent of six patients with AEN, three of whom were diagnosed at the time of autopsy and three by endoscopy. Demographic and clinical information regarding age, sex, and medical conditions was recorded. Autopsy and endoscopic reports were reviewed and pictures of the gross specimens and of the endoscopic findings were assessed for the location of the mucosal abnormalities within the esophagus (distal, proximal or both), distribution of the lesions (patchy *vs* diffuse) and presence of perforation. Hematoxylin and eosin stained slides prepared from biopsy and autopsy specimens were evaluated histologically for the presence and distribution of necrotic tissue, inflammatory cells, granulation tissue, intravascular thrombi, pigment deposits, bacteria, fungi and viral cytopathic changes. The residual squamous mucosa, if present, was assessed for inflammatory changes and pattern of necrosis. Cases were further evaluated with Prussian blue, Periodic acid–Schiff–diastase (PASD), Gram and Gomori methenamine silver (GMS) stains. Immunohistochemical reactions were performed in 1 autopsy and 3 biopsy specimens with antibodies to myeloperoxidase, CD20, CD3 and CD163 to characterize the type(s) of inflammatory cells, cytokeratin and p40 to define if the necrotic cells were derived from the squamous mucosa, and smooth muscle actin to highlight the muscularis mucosae. The control group consisted of 26 endoscopic biopsy specimens of patients with ulcerated esophagitis, 13 related to reflux and 13 to miscellaneous conditions (4 pill, 1 bullous pemphigoid, 1 radiation, 3 herpes and 4 cytomegalovirus esophagitis).

This study was approved by the research committee of the Department of Pathology and Laboratory Medicine, New York Presbyterian Hospital, Weill Cornell Medicine.

2.1. Statistical analysis

Statistical analysis was performed using the Freeman–Halton extension of the Fisher exact probability test for a two-rows by three-columns contingency table. Significant differences were considered with p values less than 0.05.

3. Results

3.1. Clinical features, gross autopsy and endoscopic findings

Patients' age, sex, clinical conditions, and the type of specimen are summarized in Table 1. All patients were adults with an average age of 66 year (range 43–73 years). There were 4 men and 2 women. Conditions that were present in more than one patient included vomiting (5), hypovolemic shock (3), metastatic carcinoma (2), alcoholic liver disease (2), renal failure (2), and hypertension (2). Other associated disorders included diabetes mellitus, duodenal and gastric ulcers, and sepsis. None of the patients had a history of ingestion of corrosive substances.

Gross inspection of the autopsy specimens showed diffuse black discoloration of the entire esophageal mucosa without identifiable "islands" of residual mucosa. In one case, spotty necrotic lesions were also present in the gastric cardia and fundus and a perforation in the distal esophagus (Fig. 1A). In the other two cases, black discoloration of the mucosa was confined to the esophagus (Fig. 1B). Of the three patients that underwent endoscopic examination, involvement of all segments of the esophagus was reported in one patient while in two the proximal esophagus appeared to be spared. In one of these patients there was diffuse involvement of the distal

Table 1 Demographic and clinical features of patients with acute esophageal necrosis

Age (y)	Sex	Associated conditions	Diagnostic specimen	Follow-up
70	Male	Advanced prostate cancer, duodenal ulcer, hypovolemic shock	Autopsy	
43	Male	Diabetes mellitus, severe vomiting	Autopsy	
55	Female	Severe vomiting, hypovolemic shock	Autopsy	
55	Male	Alcoholic cirrhosis, vomiting, pancreatic mass with lymph node metastases, renal failure, hypotension	Biopsy	Died of systemic complications
66	Male	Alcoholic cirrhosis, renal failure, hypertension, sepsis, vomiting	Biopsy	Died of systemic complications
73	Female	Vomiting, gastric ulcer, severe hypertension, anemia	Biopsy	Treated successfully with PPIs

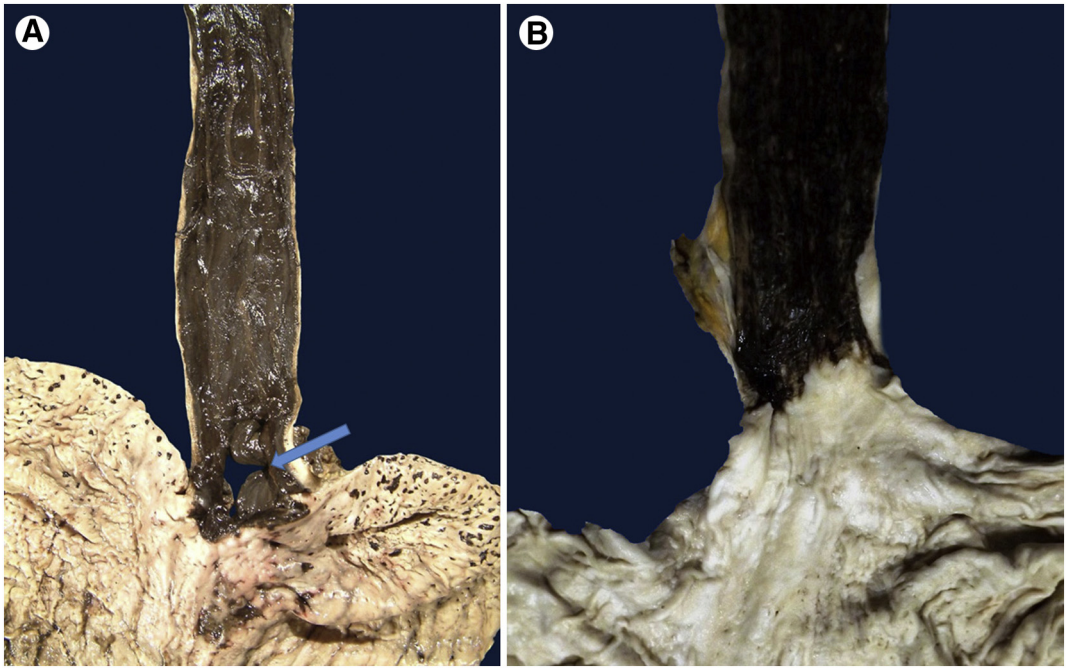

Fig. 1 Gross appearance of the esophageal mucosa in two autopsy cases of acute esophageal necrosis. There is diffuse involvement of the totality of the mucosa. Specimen A shows a perforation at the gastroesophageal junction (arrow) as well as spotty lesions in the cadia and fundus. In specimen B, the necrosis ends abruptly at the gastroesophageal junction.

esophagus without identifiable uninvolved mucosa while in the other patient patches of residual mucosa were observed.

3.2. Pathologic features

On histopathologic examination, all autopsy specimens and two of three biopsy cases show complete mucosal necrosis without residual squamous mucosa (Fig. 2). The areas of necrosis showed a band of dense basophilic poorly preserved cellular aggregates, (Fig. 3A) vessels with intravascular thrombi (Fig. 3B) and intra and extravascular golden brown pigmented granules that stained negative for iron with Prussian blue stain and were weakly positive for PASD providing support to the idea that the pigment represents lipofuscin (Fig. 3C and D). Attempts to characterize the nature of the necrotic cells with antibodies to B lymphocytes (CD20), T lymphocytes (CD3), neutrophils (myeloperoxidase) and squamous cells (cytokeratin and p40) were unsuccessful. Sections of the autopsy cases showed neutrophilic infiltrates with a band-like distribution beneath the area of necrosis which stained positive with antibodies to myeloperoxidase. (Fig. 4A). Abundant CD163-positive macrophages were observed in the areas of necrosis

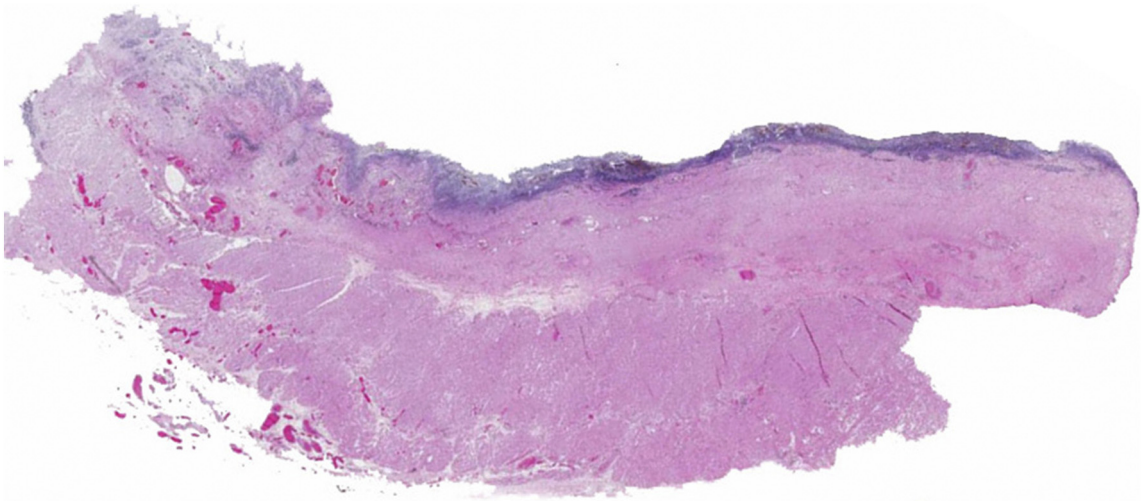

Fig. 2 Whole-mount section of the esophagus. There is diffuse basophilic necrosis of the mucosa. All other layers have a viable appearance.

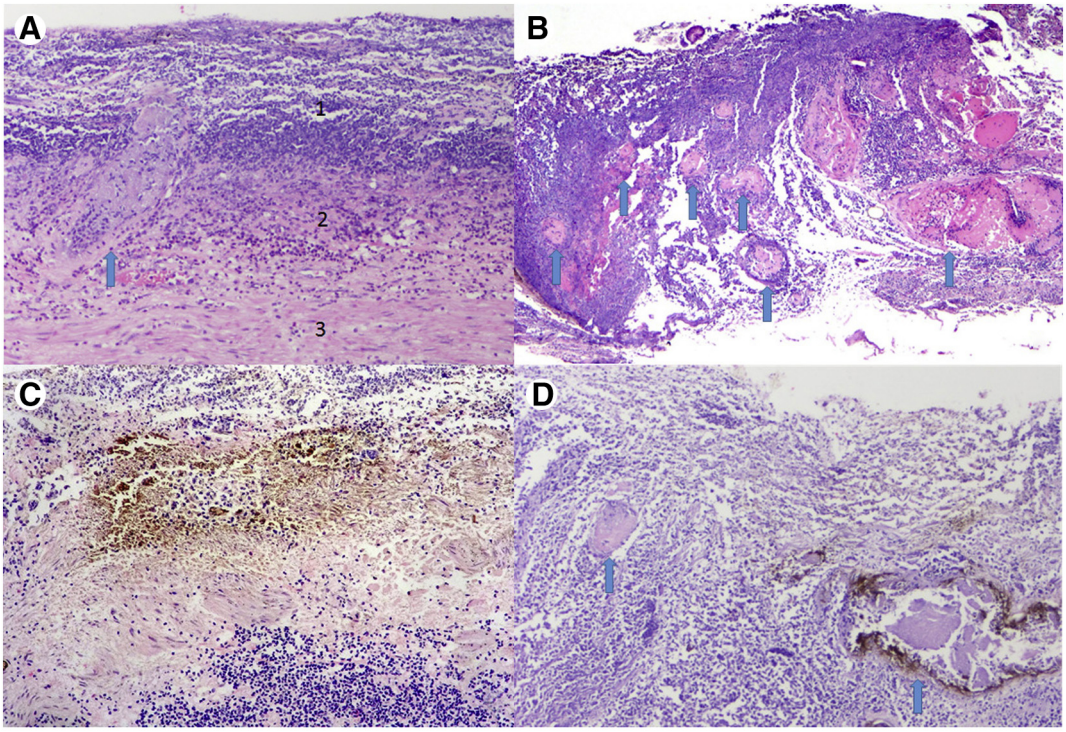

Fig. 3 A, Section from an autopsy case showing basophilic necrosis (1), neutrophil infiltrates (2) and a viable muscularis mucosae (3). The arrow point to an occluded vessels. B, Biopsy specimen showing basophilic necrosis and numerous vessels occluded by fibrin thrombi (arrows). C, Abundant dark brown pigment (same case as panel A). D, Occluded vessels (arrows) and intra- and extravascular pigment (same case as B).

in all biopsy cases as well as throughout the esophageal wall in the autopsy specimen (Fig. 4B). Confinement of the necrosis to the mucosa was demonstrated by an intact muscularis mucosae highlighted by antibodies to smooth muscle actin. (Fig. 4C) One biopsy case on endoscopic examination showed interspersed preserved mucosa (Fig. 5A). Biopsy specimens obtained from these areas showed an active esophagitis with dense mid-zonal neutrophilic microabscesses and necrosis of the overlying mucosa (Fig. 5B) while those obtained from the blackened areas show necrotic cells and pigment granules without vessels (Fig. 5C). In this case there were rare Gram-positive cocci in luminal squamous debris. Another

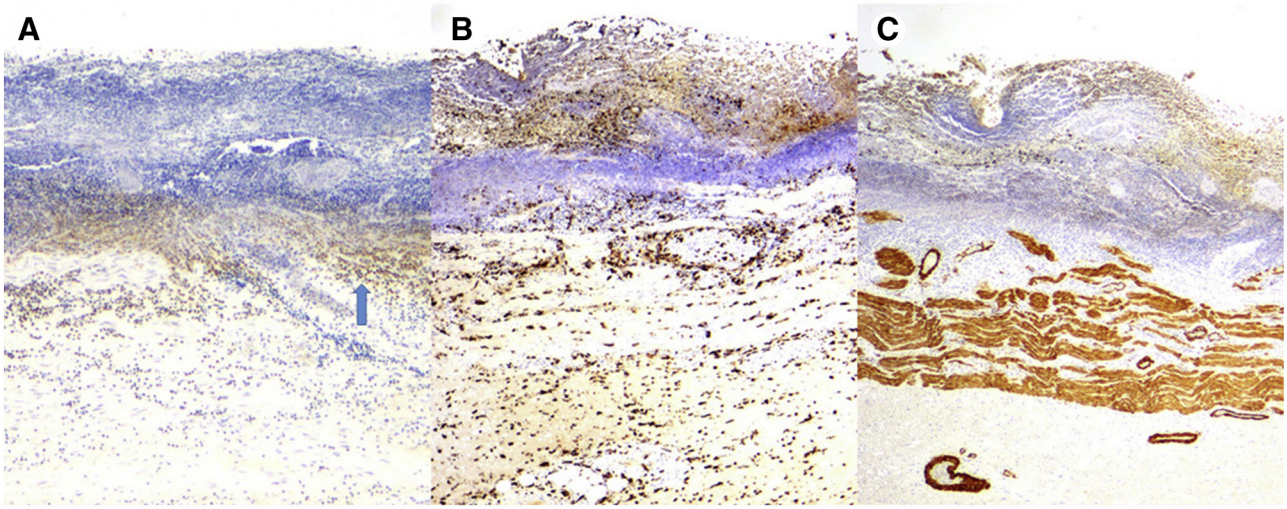

Fig. 4 A, A myeloperoxidase stain highlights the presence of abundant neutrophils beneath the areas of necrosis (arrow). B, CD163-positive histiocytes throught the esophagus. C, A stain for smooth muscle actin highlight a viable muscularis mucosae. Notice the confinement of the necrosis and inflammation to the mucosa.

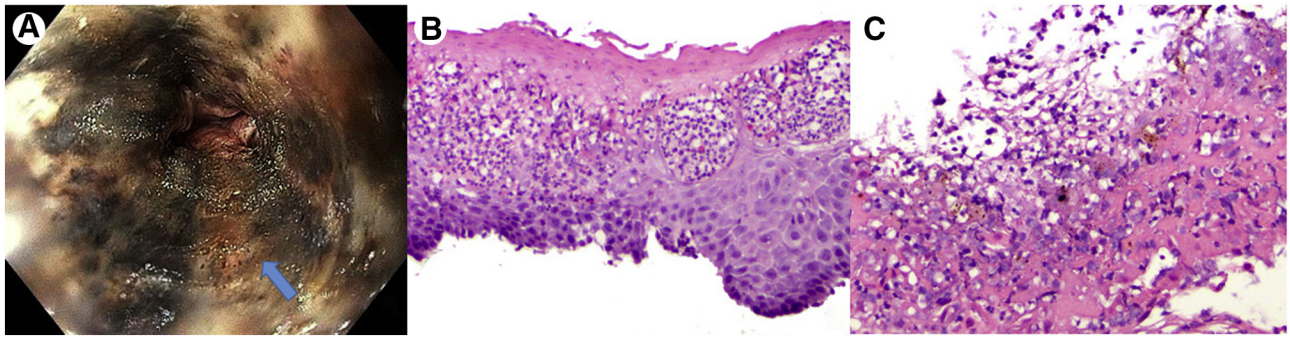

Fig. 5 A, Endoscopic appearance of a biopsy case showing partial black discoloration of the distal esophagus. Viable mucosa is indicated by the arrow. B, Neutrophilic microabscesses within the squamous epithelium (blue arrow) The overlying mucosa has a necrotic appearance (red arrow). C, Sections of the black appearing mucosa showing a fibrin, necrosis and pigmented granules.

Table 2 Comparative histologic features of acute esophageal necrosis and ulcerated esophagitis of various etiologies

Histologic features	Reflux (n = 13)	Other esophagitis (n = 13)	AEN (n = 6)	*P*
Preservation of squamous mucosa	13 (100%)	13 (100%)	1 (16%)	<0.001
Inflammation	9 (70%)	11 (85%)	1 (16%)	0.001
Necrosis	5 (38%)	8 (62%)	1 (16%)	0.2
Ulcer				
Granulation tissue	7 (54%)	10 (78%)	0	0.006
Inflammation	9 (70%)	11 (85%)	6 (100%)	0.5
Fibrin	9 (70%)	9 (70%)	6 (100%)	0.3
Basophilic necrosis	0 (0%)	0 (0%)	6 (100%)	<0.001
Pigment	1 (8%)	0 (0%)	6 (100%)	<0.001
Fibrin thrombi	1 (8%)	0 (0%)	5 (83%)	<0.001
Viral inclusions	0 (0%)	4 (31%)	0 (0%)	0.05

Abbreviation: AEN, acute esophageal necrosis.
NOTE. Other esophagitis: Drug/pill 4, bullous pemphigoid 1, radiation 1, herpes 3 and cytomegalovirus 4).

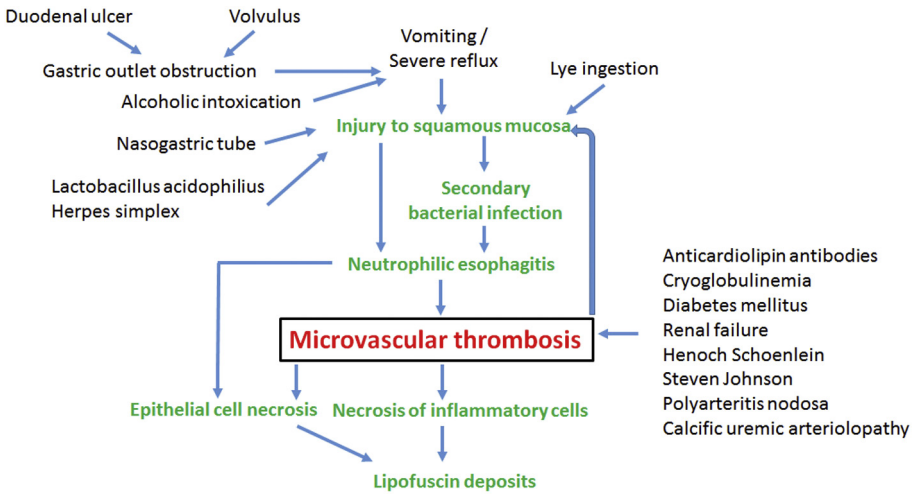

Fig. 6 Proposed pathogenesis for acute esophageal necrosis. Severe vomiting (gastric outlet obstruction, alcoholic intoxication), mechanical disruption (nasogastric tube), chemical injury (lye ingestion) or an infection (herpes virus, bacteria) damages the squamous mucosa. A neutrophilic response develops either as a result of the epithelial injury or a secondary infection. The liberation of neutrophilic enzymes and occlusion of small vessels by thrombi results in gangrenous necrosis (combination of liquefactive and coagulative necrosis) of the squamous epithelium and inflammatory cells. Occlusion of the microvasculature may be the triggering mechanism in patients with disorders associated with microvascular injury (diabetes, cryoglobulinemia, vasculitis, etc). As a result of the massive destruction of epithelial and inflammatory cell membranes, lipofuscin granules become apparent.

biopsy case showed rare fungal forms consistent with Candida. There were no viral cytopathic change.

3.3. Comparison between cases and controls

The histologic features of the mucosa in the study cases were compared with those seen in 26 cases of ulcerated esophagitis (13 related to reflux and 13 of other causes) as shown in Table 2. A noticeable difference was the presence of intact squamous mucosa in all control cases while this feature was present in only one study case. In the areas of mucosal denudation, granulation tissue was commonly present in controls while it was absent in all cases. Basophilic necrosis was observed in all cases and none of the controls. While only one reflux case showed rare intravascular fibrin thrombi and pigment granules in granulation tissue, these features were present in 5 of 6 (83%) and 6 of 6 (100%) study cases respectively.

4. Discussion

The diagnosis of acute esophageal necrosis or black esophagus has been based on the gross appearance of the mucosa either at the time of endoscopy or autopsy. At present, there is very limited information related to the histopathologic findings in this condition. Previous reports have described mucosal necrosis without specifying its microscopic characteristics [2,4]. In addition, the level of involvement of the different layers of the esophagus has not been clearly defined. The "non-specificity" of the pathologic findings so far reported have been used to support the notion that mucosal biopsies are non-contributory to the diagnosis [4]. The aim of this study is to define the histologic characteristics of acute esophageal necrosis and to evaluate the specificity, if any, of the observed features compared to other causes of esophageal injury with ulcers. We evaluated three esophagi obtained at the time of autopsy and three biopsy specimens from patients which showed on endoscopy the typical black discoloration of the mucosa. Microscopic examination revealed necrosis of the mucosa with clusters of basophilic poorly preserved cellular aggregates and granular brown pigment granules in all cases. Intravascular thrombi were present in 5 of 6 cases. By their size and distribution within the necrotic mucosa, these vessels had the features of arterioles and capillaries and were readily apparent. The single case where thrombi were not demonstrated did not have vascular structures in the sampled areas of necrosis. By comparison, basophilic necrosis was never seen in control cases. Only one control case showed focal intravascular thrombi and pigment granules in viable granulation tissue. A single endoscopic study case had a residual fragments of squamous mucosa. By contrast, viable squamous mucosa was always present in cases of ulcerated esophagitis either caused by reflux or other etiologies. This difference is explained by the diffuse distribution of the necrosis in the most cases of black esophagus. All study cases showed a preserved muscularis mucosae which indicates that necrosis is mostly confined to mucosa. A viable muscularis propria was seen in all autopsy cases including the one with the perforation which was attributed to forceful vomiting (Mallory Weiss tear).

Since the immunoreactivity of cells with coagulative necrosis is sometimes preserved, we attempted to characterize the type(s) of cells in the necrotic areas using antibodies to B and T lymphocytes (CD20 and CD3), histiocytes (CD163), neutrophils (myeloperoxidase) and squamous cell markers (cytokeratin and p40). With the exception of scattered histiocytes, there was no staining of the necrotic cellular aggregates. These negative results are most likely due to the type of necrosis which should be properly classified as gangrenous. Similar to common gangrenous necrosis of the skin of the extremities or digits, the esophageal mucosa is black and shows advanced necrosis with mixed coagulative and liquefactive features which explains the loss of antigenicity.

Acute esophageal necrosis or black esophagus is a very rare medical condition affecting primarily adult men (81%) with an average age of 67 years [1-8]. Incidence estimates based on retrospective review of large numbers of endoscopic reports have ranged from 0.01 to 0.28% [1,10]. Autopsy studies have corroborated the low frequency of this condition with reported cases ranging from 0 to 0.2% [9]. The low incidence in autopsy studies is difficult to explain if one of the key physiopathologic elements, as has been proposed, is decreased blood flow or hemodynamic instability in patients with a variety of medical disorders. Hemodynamic causes are also problematic to reconcile with the observation of frequent panesophageal mucosal involvement as happened in 4 of 6 of our cases considering the rich vascularity of this organ and the independent blood supply of each third from separate and unrelated arterial networks [10,11]. The esophagus is also protected from ischemic injury by extensive intramural vascular connections which prevent mucosal ischemia even when long segments of the esophagus are detached from their blood supply [12]. Despite these considerations, ischemia appears to be the most likely explanation for the mucosal necrosis. An observation that might solve the dilemma is the consistent presence of intravascular thrombi in mucosal vessels as discussed below.

Neutrophils with a band-like distribution under the necrotic area were present in autopsy cases. Although this type of inflammation might be secondary to the necrosis, neutrophils could play a more active role in its pathogenesis. The histologic features observed in the single case with residual squamous mucosa (midzonal neutrophilic infiltrates with necrosis of the luminal epithelium) is strongly reminiscent of the inflammatory pattern seen in the skin in patients with bullous impetigo, a condition caused by mixed infections by *Staphylococcus aureus* and *Streptococcus pyogenes* [13]. Dense neutrophilic intraepithelial infiltrates with this distribution are seen in infectious esophagitis of diverse etiologies but are not a feature of reflux injury. It is conceivable that in some cases severe damage to the squamous mucosa might predispose to a secondary bacterial infection causing inflammation,

microvascular thrombi and necrosis. The histiocytic infiltrate observed in all cases is probably triggered by the necrosis as a "clean-up/reparative" response as seen in all organs in different conditions as active inflammation and necrosis subsides.

The appearance of the mucosa in acute esophageal necrosis is reminiscent of that observed in other medical conditions. Rapidly progressing black discoloration of the skin occurs in a gamut of diseases such as cryoglobulinemia, ecthyma gangenosum, disseminated fungal infections, systemic coagulopathies (coumarin/warfarin induced skin necrosis and protein C and S deficiencies), disseminated intravascular coagulation, antiphospholipid syndromes, calciphylaxis, etc, all of which have in common cutaneous circulatory derangement related to microvascular occlusion [14]. Cryoglobulinemia, anticardiolipin antibodies, Henoch-Schonlein purpura, Steven Johnson syndrome, polyarteritis nodosa, calcific uremic arteriolopathy and other conditions with microvascular occlusion have been reported in patients with acute esophageal necrosis [11,15-18]. As previously mentioned, microvascular thrombi were present in 5 of 6 cases. Although the occluded vessels were located within the areas of necrosis and could be viewed as a secondary event, the absence of similar vascular changes in the ulcer bed of control cases makes this explanation improbable. The role of microvascular occlusion in the disease process provides a unifying explanation for the rapid evolution of the disorder, the involvement of mucosae within different vascular territories, the diversity of etiologies, the infrequent occurrence of this condition relative to systemic ischemic disorders and circumscription of the initial injury to the mucosa. A similar pathogenic sequence has been observed in other conditions characterized by widespread acute necrosis initially limited to one anatomic compartment such as necrotizing fasciitis. Triggered by infection by group A *Streptococcus*, neutrophilic infiltrates and fibrin deposits in the deep dermis and superficial fascia are followed by microvascular thrombosis causing localized necrosis with initial sparing of the deep muscle [19].

Based on these observations, we propose that microvascular occlusion is the central event that causes necrosis of the esophageal mucosa. (Fig. 6) Vessels may be injured directly by disorders that cause vasculitis, microangiopathy or occlusion, or indirectly through damage to squamous epithelium by severe vomiting, mechanical injury, infections, chemical injury etc. Disruption of the squamous mucosa may promote the recruitment of neutrophils either as a consequence of epithelial necrosis or a secondary infection. The end result is necrosis of epithelial and inflammatory cells and the appearance of pigment deposits. (Fig. 6).

In conclusion, a constellation of pathologic findings in the esophageal mucosa of patients with acute esophageal necrosis or black esophagus facilitates the recognition of this disorder in esophageal biopsy specimens. Specific features include basophilic necrosis, pigment deposits and vascular occlusion by fibrin thrombi. This "diagnostic triad" is not seen in other disorders that cause disruption and ulcers of the squamous mucosa. We propose that microvascular occlusion is the unifying pathogenic event that causes mucosal necrosis and explains the multiplicity of medical conditions associated with this disorder.

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