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CASE REPORT

Esophageal melanosis: Two case reports and review of literature

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Abstract

BACKGROUND

Esophageal melanosis (EM) is a rare condition characterized by melanin pigmentation in the esophageal mucosa. It is not well understood and has been documented in less than 100 cases worldwide.

CASE SUMMARY

We report two cases of African American patients who complained of significant weight loss (over 20 pounds in approximately six months) and abdominal pain during their first visit. The first case involves a 54-year female with a history of hepatic steatosis and polysubstance abuse, who also experiences nausea and vomiting. The second case is a 59-year-old male with hypertension and gastroesophageal reflux disease (GERD), who was diagnosed with esophageal squamous cell carcinoma. Both cases show benign melanocytes in the basal layer on the esophagus biopsy and are diagnosed as EM.

CONCLUSION

It is important to note that EM has been associated with malignancies such as carcinoma and melanoma. Therefore, accurate diagnosis and appropriate management are crucial. Patients with EM, especially those with concurrent risk factors (*e.g.*, GERD, smoking), should be carefully monitored for any signs of malignancy.

Key Words: Esophagus; Melanoblasts; Esophageal melanosis; Gastroesophageal reflux disease; Case report

Core Tip: Esophageal melanosis is a rare condition. Its causes and natural progression are not fully understood. Some studies have reported an association with malignancy and as a potential precursor for malignancy. Extended research is required to establish an additional correlation for this rare entity.

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INTRODUCTION

De La Pava *et al*[1] first described melanoblasts in esophageal mucosa in 1963, with its prevalence reported as 4% in autopsy cases. The recognition of this condition has been emphasized over the past few decades. While there is some correlation between microscopic and endoscopic findings, microscopic diagnosis is more common than endoscopic diagnosis due to the requirement of a large number of melanocytes to be present for it to be visible during endoscopy[2]. The specific cause of this condition and its connection to other medical conditions is still not fully understood. Some reports have suggested a link between esophageal melanosis (EM), esophageal malignancies, and esophageal injury[1,3,4]. While there is a strong connection between gastroesophageal reflux disease (GERD) and chronic esophagitis, the association with Barrett's esophagus has not been confirmed[5]. Recent reviews identified only fifty-five reported cases of EM[6-8]. This exceptionally rare condition significantly hinders the ability of endoscopists to diagnose and follow up. We aim to raise awareness of this rare condition by presenting two cases of EM and reviewing the existing literature.

This study retrospectively assessed the data of patients who underwent upper gastrointestinal endoscopy at our hospital between March 2021 and June 2024. Of these, two patients of EM were identified. The demographic, clinical, endoscopic, medication uses, histopathologic and immunohistochemical stains evaluation was conducted by two gastrointestinal pathologists independently. This retrospective study was approved by our institutional review board, which waived the requirement for informed consent. Patient anonymity was ensured prior to assessment of the data.

A review of the literature was conducted with the use of PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=esophageal%20melanosis&filter=years.1979-2024&page=8). Search terms EM were used and yielded 80 results; dates of publications were between 1980-2024. The titles and abstracts of these publications were screened, and only articles containing actual case reports were included. A total of 55 case reports were identified, and literature on EM was reviewed. Full texts of all 33 articles containing 55 reported cases were examined (Table 1)[3,5-7,9-33]. From the data collected, we proposed updates on EM's clinical, histopathologic, and immunohistochemical features.

CASE PRESENTATION

Chief complaints

Case 1: An African American female patient, 54 years old, arrived at the emergency department with sharp left-sided abdominal/chest pain, an unintentional weight loss of 20 pounds over the last six months, as well as nausea, vomiting, and poor appetite.

Case 2: A 59-year-old African American male came to the emergency department with main complaints of right upper quadrant abdominal pain and a 20-pound weight loss despite maintaining a good appetite.

History of present illness

Case 1: Patient presents to the emergency department due to hypotension, altered mental status, left-sided sharp abdominal/chest pain, and an unintentional weight loss of 20 pounds over the span of the last six months. She reported increased nausea and vomiting, along with a poor appetite, which has progressively worsened.

Case 2: The patient presented to the emergency department with chief complaints of right upper quadrant abdominal pain, which he describes as constant, sharp, and non-radiating, intermittently worsening and 20 pounds of weight loss despite maintaining a good appetite.

History of past illness

Case 1: Past medical history includes hepatic steatosis, iron deficiency anemia, polysubstance abuse (cocaine, alcohol, and marijuana), tobacco use, and hypertension (HTN).

Case 2: HTN, GERD, and seizures.

Table 1 Review of published cases of clinical and pathological characteristics of esophageal melanosis

Ref.	Age	Sex	Esophagus location	Exact location of the lesion	Country	Associated clinical diagnosis	Clinical symptoms	Medication	Smoking	Alcohol drinking
Kuo *et al*[9], 2011	76	F	NA	Not specified	Australia	Celiac disease	NA	Azathioprine	NA	NA
Dubail *et al* [7], 2022	57	F	Middle/lower esophagus	Middle and lower esophagus	Beljium	Peptic ulcer disease	NA	PPI	Yes	No
Dubail *et al* [7], 2022	66	M	Upper esophagus	Upper esophagus	Beljium	Gastritis	NA	NA	No	Yes
Horowitz *et al*[10], 1998	49	M	NA	Not specified	Brazil	Anal melanoma	NA	NA	NA	NA
Dumas *et al* [11], 1990	66	F	Lower esophagus	32-35 cm from incisor	Cedax	Mental anorexia	NA	NA	NA	NA
Bogomoletz *et al*[12], 1997	75	M	Middle esophagus	20 cm below Killian's line	France	NA	Epigastric pain, dysphagia	NA	NA	NA
Maroy *et al* [13], 2013	65	M	Middle/lower esophagus	Mid esophagus 19 cm (1st lesion) and distal esophagus 38 cm (2nd lesion)	France	Tonsil squamous cell carcinoma	NA	NA	Yes	Yes
Sarbia *et al* [14], 2012	69	M	Middle/lower esophagus	Middle and the lower thirds of the esophagus	Germany	Adenocarcinoma of the esophago-gastric junction, acanthosis nigricans of the esophagus	Pain	NA	NA	NA
Kleikamp *et al*[15], 2006	48	M	NA	No data	Germany	Adenocarcinoma of the esophago-gastric junction, acanthosis nigricans of the esophagus	Pain	NA	NA	NA
Agarwal *et al* [6], 2022	53	F	Middle/lower esophagus	Mid and lower esophagus	India	Iron deficiency anemia	NA	Iron	NA	NA
Sharma *et al* [5], 1991	50	M	Lower esophagus	Lower third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	60	M	Lower esophagus	Lower third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	68	M	Middle esophagus	Middle third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	51	F	Middle esophagus	Middle third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	57	F	Middle esophagus	Middle third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	70	M	Middle esophagus	Middle third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	45	M	Upper esophagus	Upper third of esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	55	M	Upper esophagus	Upper third of the esophagus	India	Peptic ulcer disease	NA	NA	NA	NA
Sharma *et al* [5], 1991	60	M	Middle esophagus	Middle third of esophagus	India	Peptic ulcer disease	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	50	F	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	49	M	Lower esophagus	Lower third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA

Sharma *et al* [5], 1991	40	F	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	43	F	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	48	M	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	50	M	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	58	M	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	59	M	Middle esophagus	Middle third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Kumari *et al* [16], 2016	66	M	NA	No data	India	NA	Chest pain and dysphagia	NA	NA	NA
Sharma *et al* [5], 1991	50	M	Upper esophagus	Upper third of esophagus	India	NA	Non-ulcer dyspepsia	NA	NA	NA
Sharma *et al* [5], 1991	56	M	Middle esophagus	Middle third of esophagus	India	Gastritis	NA	NA	NA	NA
Sharma *et al* [5], 1991	59	M	Middle esophagus	Middle third of esophagus	India	Gastritis	NA	NA	NA	NA
Sharma *et al* [5], 1991	48	M	Middle esophagus	Middle third of esophagus	India	Gastritis	NA	NA	NA	NA
Vincent Comraj *et al* [17], 2023	70	M	NA	No data	India	Gastritis	NA	NA	No	No
Geramizadeh *et al*[18], 2014	75	M	Middle esophagus	Middle part of the esophagus	Iran	NA	Epigastric pain and dysphagia	NA	Yes	No
Kinugasa *et al* [19], 2020	77	M	Lower esophagus	Lower part of the esophagus	Japan	Eosinophilic esophagitis	NA	Antihypertensive medications	NA	NA
Mori *et al* [20], 2005	70	M	Lower esophagus	35 cm from the incisor teeth	Japan	None	NA	NA	NA	NA
Mori *et al* [20], 2005	60	F	Lower esophagus	30 cm from the incisor	Japan	NA	Dysphagia	NA	NA	NA
Yamazaki *et al*[21], 1991	56	M	Lower esophagus	30-33 cm from incisor	Japan	NA	NA	NA	NA	NA
Yamazaki *et al*[21], 1991	62	M	Lower esophagus	35 cm from incisor	Japan	NA	NA	NA	NA	NA
Yamazaki *et al*[21], 1991	70	F	Lower esophagus	Lower third of esophagus	Japan	NA	NA	NA	NA	NA
Yamazaki *et al*[21], 1991	66	M	Lower esophagus	Lower third of esophagus	Japan	NA	NA	NA	NA	NA
Yamamoto *et al*[22], 1999	62	F	Lower esophagus	Middle esophagus 30 cm from the incisor	Japan	Laugier-Hunziker syndrome	NA	NA	NA	NA
Kaneko *et al* [23], 2022	62	M	Middle esophagus	Middle thoracic esophagus	Japan	Hypopharyngeal cancer,	NA	NA	NA	NA
Kato *et al* [24], 2013	71	M	Middle esophagus	Middle thoracic esophagus	Japan	Esophageal melanoma	NA	NA	NA	NA
Oshiro *et al* [25], 2007	71	M	Lower esophagus	35 cm away from the incisor	Japan	Esophageal melanoma	NA	PPI	NA	NA
Suzuki *et al* [26], 2008	67	M	Lower esophagus	Lower thoracic esophagus	Japan	Esophageal melanoma	NA	NA	Yes	No
Suzuki *et al* [26], 2008	62	M	Upper/middle esophagus	Upper to middle thoracic esophagus	Japan	Esophageal melanoma	NA	NA	Yes	Yes

Walter *et al* [27], 2000	64	F	Middle/lower esophagus	Lower half of the esophagectomy specimen	Netherlands	Esophageal SCC	NA	PPI	Yes	Yes
Destek *et al* [28], 2016	55	F	Middle/lower esophagus	Middle, the front incisor teeth from 20 cm to the starting 30 cm	Turkey	Gastritis	NA	NA	No	No
Chang *et al* [3], 2006 (unpublished data)	80	F	Lower esophagus	Distal esophagus 30-34 cm from the incisor teeth	United Kingdom	Gastritis	NA	NA	NA	NA
Berry *et al* [29], 1995	51	F	NA	NA	United States	NA	NA	NA	NA	NA
Nagra *et al* [30], 2020	57	F	Middle esophagus	Middle esophagus	United States	Iron deficiency anemia	NA	NA	NA	NA
Jones *et al* [31], 2005	22	M	Lower esophagus	38 cm from the incisor	United States	Addison's disease	Dysphagia	NA	NA	NA
Dinneen *et al* [32], 2014	65	F	Upper/middle esophagus	Upper and middle esophagus	United States	Esophageal wall thickening on CT	Abdominal pain	NA	NA	NA
Changela *et al* [33], 2017	48	F	Upper esophagus	Upper third of the esophagus	United States	NA	Weight loss and dyspepsia	NA	Yes	NA
Current study, 2024	59	M	Upper and lower esophagus	Upper esophagus and lower esophagus	United States	Esophageal SCC	NA	PPI	No	No
Current study, 2024	54	F	Middle esophagus	Middle esophagus	United States	None	Weight loss	Losartan	Yes	Yes

NA: Not available; PPI: Proton pump inhibitor; SCC: Squamous cell carcinoma.

Personal and family history

Case 1: Family history of colon cancer in her grandfather. No personal and family history of melanocytic lesions and malignancy.

Case 2: Family history of HTN in his mother.

Physical examination

Case 1: Normal appearance. Abdomen is flat soft on palpation with tenderness in the left lower quadrant. Bowel sounds are normal.

Case 2: He is not in acute distress. Abdomen is flat, soft and abnormal tenderness on right side and no guarding.

Laboratory examinations

Case 1: White blood cell counts 8.85 × 10^9/L (3.50-9.50 × 10^9/L); hematocrit 29.7% (40%-50%); hemoglobin 9.40 g/dL, platelets 135 K/μL (150-450 K/μL); serum calcium 8.20 mg/dL (8.70-10.50 mg/dL); alanine aminotransferase 100 U/L (0-40 U/L); aspartate aminotransferase 159 U/L (0-40 U/L); serum triglycerides 568 mg/dL (30-150 mg/dL).

Case 2: White blood cell counts 10.02 × 10^9/L (3.50-9.50 × 10^9/L); hematocrit 34.6% (40.0%-50.0%); serum calcium 10.80 mg/dL (8.70-10.50 mg/dL); alanine aminotransferase 7 U/L (0-40 U/L); aspartate aminotransferase 13 U/L (0-40 U/L).

Imaging examinations

Case 1: During the upper gastrointestinal endoscopy, a normal Z-line was observed at 36 cm from the incisors, and brown/black pigmentation was seen in the middle one-third of the esophagus (Figure 1A). The abdominal X-ray showed normal results. A computed tomography (CT) scan of the abdomen/pelvis revealed the presence of uterine fibroids and bilateral hydroureteronephrosis. Additionally, an upper abdominal ultrasound indicated the presence of hepatic steatosis.

Case 2: During an upper gastrointestinal endoscopy, a narrowing was found in the upper part of the esophagus. Additionally, a single raised, cancerous-looking, and ulcerated mass measuring 50 mm in size was discovered in the lower esophagus, located 35 cm from the incisors. A CT scan of the abdomen revealed thickening of the esophageal wall

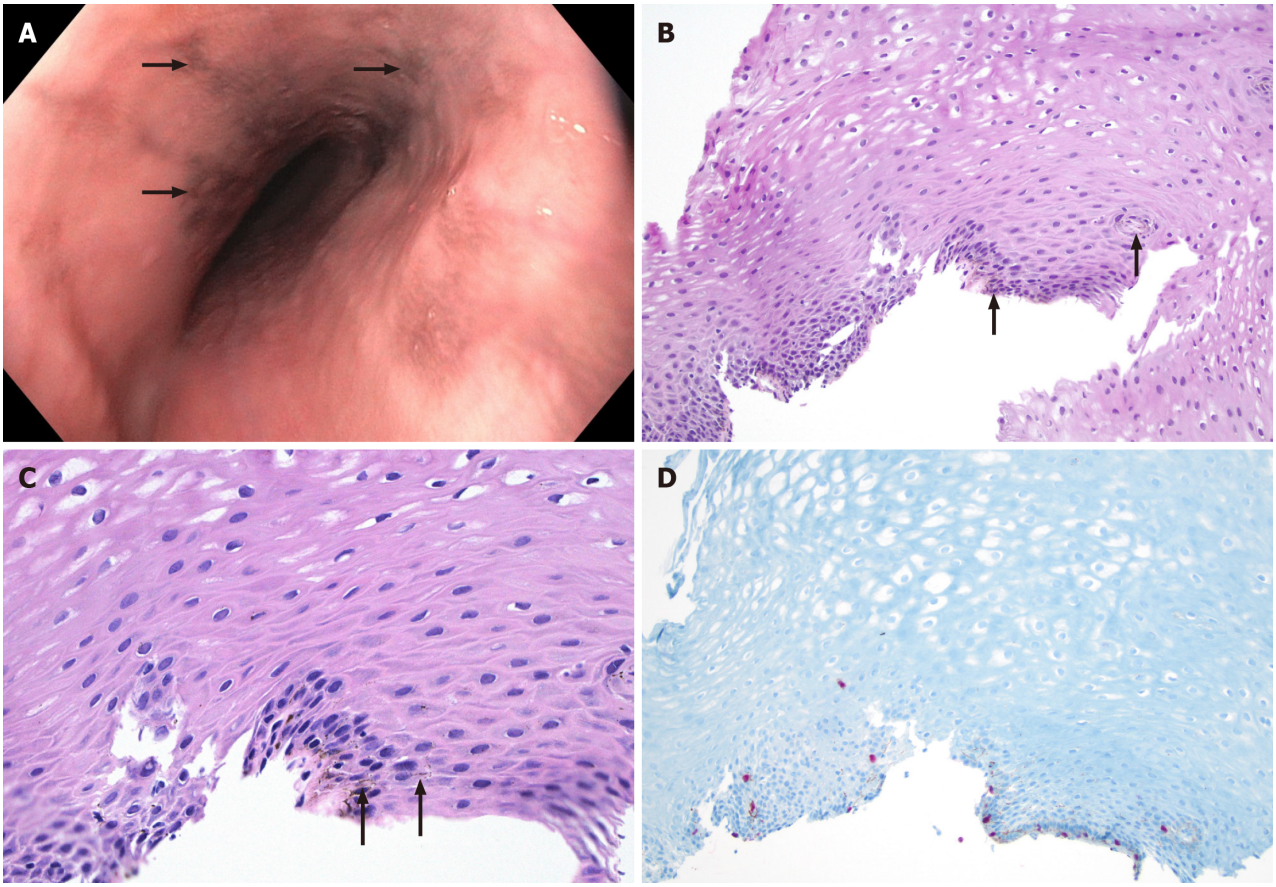

Figure 1 Imaging examinations. A: Endoscopic poorly delineated pigmented lesion (arrow) on the mucosa; B and C: Hematoxylin and eosin stain shows basal cell hyperplasia, intercellular edema, and presence on non-atypical cells with melanin deposition (arrow) along the basal layer of the epithelium, 10 × and 40 × magnification; D: SRY-related HMG box 10 immunohistochemistry red nuclear positivity in the melanocytes.

in the middle to lower part of the esophagus.

FINAL DIAGNOSIS

Case 1

On the targeted biopsies, histopathologic examination of the specimen with hematoxylin and eosin staining showed basal cell hyperplasia, intracellular edema, and melanin pigment deposition in the basal layer without atypia (Figure 1B and C). Immunochemistry stains show scattered SRY-related HMG box 10 (SOX10) (Figure 1D) and S100-positive melanocytes in the basal layer, consistent with EM. The iron stain was negative.

Case 2

The esophageal biopsies from the stricture in the upper esophagus show squamous mucosa with melanin pigment deposition in the basal layer, without atypia. Immunohistochemistry stains show scattered SOX10-positive melanocytes in the basal layer, consistent with EM. The iron stain was negative. The biopsies from the mass show moderately differentiated squamous cell carcinoma.

TREATMENT

Case 1

Antihypertensive (losartan and carvedilol) and selective serotonin reuptake inhibitors (paroxetine).

Case 2

Neoadjuvant chemoradiation therapy for squamous cell carcinoma.

OUTCOME AND FOLLOW-UP

Case 1

The patient's upper gastrointestinal symptoms have resolved at the one-year follow-up, and no follow-up endoscopy data is available.

Case 2

One year follow up imaging showed metastatic squamous cell carcinoma in thoracic vertebra.

DISCUSSION

A review of 55 reported cases and a cohort of 2 cases from our hospital (total n = 57) was performed (Table 1). Patients had a mean age of 59 (range 22-80) years, with male predominance (M:F = 1.9:1.0). Endoscopically visible pigmented lesions were present in 89% (51 out of 57) of the patients. In 84 % (n = 43/51) of the patients, the lesion is present in the middle one-third or lower one-third of the esophagus, six patients have lesions in the upper one-third, two patients have lesions in the upper and middle one-third of esophagus. A clinical association with various diseases has been reported in 38 of 57 patients. The most frequent association was present in 45 % (n = 17/38) of the patients with peptic ulcer diseases and gastritis. Other less frequent associations have been reported with esophageal melanoma (n = 4), anal melanoma (n = 1), esophageal squamous cell carcinoma (n = 3), hypopharyngeal squamous cell carcinoma (n = 1), gastroesophageal junction adenocarcinoma (n = 2), eosinophilic esophagitis (n = 1), and esophageal wall thickening (n = 1). There is a rare association with systemic disorders like celiac disease (n = 1), Addison's disease (n = 1), Laugier-Hunziker syndrome (n = 1), and mental anorexia (n = 1). No association was reported in two cases (n = 2). Medication history is available for eight patients, and four of these patients are on proton pump inhibitors, two are on antihypertensive medications (losartan), one is on iron medication, and one is on azathioprine. A clinical history of alcohol use is present in 55 % (6/11), and smoking is present in 67% (8/12) of patients.

EM is a relatively rare condition characterized by the presence of melanin pigment and melanocytes at the basal layer of the esophagus. EM was described for the first time in 1963 by De La Pava *et al*[1], and its prevalence was reported to be 4% in autopsy series. While EM is generally considered a benign condition, its clinical significance and potential association with other gastrointestinal disorders have been subjects of interest in medical literature.

Although the pathogenesis of melanocytosis is not clearly defined, there are two theories. The first is the aberrant migration of neural crest cells during embryogenesis, and the second is the differentiation of stem cells located in the basal layer of the epithelium into melanoblasts due to various injuries. The second theory seems to be preferred as melanocytosis has been associated with esophagitis and gastroesophageal reflux diseases, described in patients with a history of alcohol abuse and smoking and in the surrounding esophageal carcinomas[13-28]. One case from our cohort (case 2) also showed an association with stricture of the upper esophagus and squamous cell carcinoma of the lower esophagus. It is worth noting that this patient does not have a history of smoking or alcohol consumption. This finding may suggest that EM could potentially be considered an independent risk factor for the development of malignancy. Walter *et al*[27] reported EM associated with esophageal squamous cell carcinoma, and Dinneen *et al*[32] reported an association with esophageal wall thickness on CT scans. Sarbia *et al*[14] and Kleikamp *et al*[15] reported EM associated with gastroesophageal junction adenocarcinoma. Maroy *et al*[13] reported EM associated with tonsillar squamous cell carcinoma and esophageal melanoma. The association with other rare systemic disorders reported in the literature include Laugier-Hunziker syndrome, Addison's disease, and celiac disease[3,28,34].

The other case in our cohort (case 1) shows the presence of melanin pigment and melanocytes in the basal layer, along with basal cell hyperplasia and intercellular edema. Case series of Sharma *et al*[5] have shown an association of histological features of esophageal injury (such as basal cell proliferation, intercellular edema, and esophagitis) with EM in seven of twenty-one cases. Destek *et al*[28] and Vincent Comraj *et al*[17] reported EM in association with esophageal injury. The observed association between histological features of injury may provide support for the hypothesis that the stem cells situated in the basal layer differentiate towards the melanocytes in response to injury as one of the initial events.

The differential diagnosis of EM includes pseudomelanosis, tumoral melanocytic lesion, and other rare entities such as blue rubber bleb nevus syndrome. Pseudo melanosis is an accumulation of various substances in macrophages, fibroblasts, or epithelial cells and is caused by exogenous deposition (dye injection and anthracosis), hemosiderosis or hemochromatosis, and lipofuscin pigment deposition. Periodic-Acid Schiff and Prussian blue iron stains highlight lipofuscin and iron pigments accumulation, respectively. The most important differential diagnosis of esophageal melanocytosis has to be made with tumoral melanocytic lesions. The two main entities described in the literature are blue nevus and primary malignant esophageal melanoma (PMME). The blue nevus is rare and shows the presence of heavily pigmented melanocytes in the lamina propria without junctional activity and cytonuclear atypia. PMME is also sparce and appears mainly as a pigmented mass or a polypoid pigmented lesion in the middle or lower esophagus. Although PMME can occasionally present as flat and poorly delineated macules exhibiting the same endoscopic picture as melanosis, histologically in PMME, there is invasion and destruction of the basal lamina and nests of epithelioid cells or spindle cells with cytonuclear atypia, abnormal mitotic figures, and junctional activity[3,35,36].

CONCLUSION

EM is a rare but well-characterized condition. Although it can be treated conservatively, it is essential to consider it when diagnosing esophageal pigmented lesions. The causes and natural progression of the condition are not fully understood, but various studies have reported an association with malignancy and as a potential precursor for malignancy. We recommend following up with a gastroenterologist for further evaluation. Extended research is necessary to establish additional correlations for the condition.

FOOTNOTES

Author contributions: Kazacheuskaya L and Arora K designed the research study, analyzed the data, and wrote the manuscript; and all authors have read and approved the final manuscript.

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