Esophageal Melanocytosis: report of two cases and review of a rare and misunderstood entity

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Abstract

Esophageal melanocytosis (EM) is a rare entity, which is characterized by a non-atypical melanocytic proliferation and melanin deposits in the esophageal mucosa. The confusion between the terms of melanosis and melanocytosis in the literature, the rarity of this lesion (less than 50 cases reported in the literature), its uncertain pathobiological course and the lack of experience of pathologists and gastroenterologists prompt us to draw the attention to this particular entity by reporting two cases and reviewing the literature. Magnifying endoscopy to observe intensive melanin accumulation followed by a biopsy are key for the diagnosis. (Acta gastroenterol. belg., **2022,** 85, **390-392**).

Keywords: melanocytosis, pseudomelanosis, melanocytic lesion, esophagus, melanosis.

Introduction

Normally, esophageal mucosa does not contain melanocytes. Esophageal melanocytosis (EM) is a very rare pathology. The presence of melanocytic cells in normal esophagus was first described in 1963 by De la Pava (1). In the literature, EM was identified more frequently in autopsy series (ranges from 4 to 7.7 %) compared to endoscopy series (ranges from 0.07 to 2.1%) (2-7). A recent review found only fifty cases of melanocytosis versus melanosis reported in the literature (2). EM is considered as a benign lesion commonly found in the middle and/or lower esophagus. However, some authors have suggested that melanocytosis might be a precursor of melanoma. Moreover, cases progressing into malignant melanoma have been reported (4,8-10). EM is more reported in male (ratio 2 :1) , middle-aged and Eastern patients (2-4). There are no specific symptoms (3,4,11).We observed a confusion in the literature between the terms of melanosis and melanocytosis. Takubo (12) described "melanosis" as "an increased amount of melanin in mucosal epithelial cells, with or without an increase in the number of melanocytes" and "melanocytosis" as " a condition of abnormal melanocyte proliferation". In concordance with the Japanese pathologists the increased number of melanocytes in the basal part of the mucosa, the melanosomal transfer to keratinocytes, stromal macrophages and fibroblasts are characteristic of melanocytosis (3,11). The term esophageal melanosis should be avoided because it does not accurately describe the proliferation of melanocytes.

No definite pathogenesis has been proposed for esophageal melanocytosis. It seems to develop secondarily to chronic stimuli such as esophageal reflux. Occasional associations are described, especially with rare systemic disorders (Albright, Peutz-Jeghers and Laugier-Hunziger syndromes, and Addison's and Celiac diseases) (3-5). Endoscopically, it appears as thin and irregular streaks or as oval to linear, flat and irregular, grey, blue, brown or black macules of 1 to 3 cm (3,6,7). Histology shows the presence of non-atypical pigmented melanocytes along the basal layer of the squamous epithelium and melanin pigment accumulation in some keratinocytes and macrophages in the surroundings. Fontana-Masson staining highlighting the melanin granules and melanocytic markers such as MART1/Melan-A, SOX10, HMB45 and PS100 allow confirmation of the cellular nature. The main differential diagnosis includes pseudomelanosis, tumoral melanocytic lesions and other rare entities as the Blue Rubber Bleb Nevus Syndrome (BRBNS) (3,5,13). The extremely rare occurrence of this entity significantly limits the experience of endoscopists especially for the diagnosis and the follow-up. We sought to draw attention on this rare entity by reporting two cases of esophageal melanocytosis and by reviewing the literature.

Case history

The first patient is a 57-year-old woman with a prior history of antral gastritis and bulbar ulcer treated by pantoprazole. A control endoscopy for recurrence of abdominal pain and heartburn showed fine, grayish, flat and poorly delimited macules of 1 to 3 cm in the middle and lower esophagus (figure 1). There was nothing particular in her personal or family history. She did not drink alcohol, nor take any medication leading to pigmentation but smoked a pack of cigarettes per day for twenty years. Targeted biopsies showed the presence

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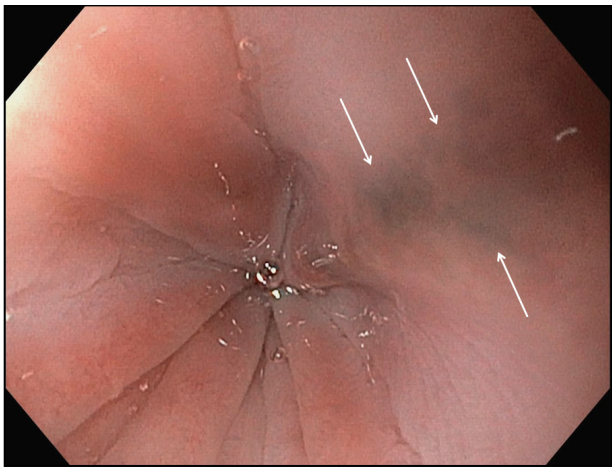

Figure 1. — Endoscopic melanocytosis : fine, grayish, flat and poorly delimited macules in the esophageal mucosa (white arrows).

of non-atypical, fusiform, dendritic cells containing dark granules in the basal layer of the squamous epithelium (figure 2A). These granules were also seen in some basal keratinocytes and macrophages. The dendritic cells were negative for PERLS and PAS stainings but presented a cytoplasmic positivity for Fontana-Masson staining (figure 2B) and for immunohistochemical stains such as MART1/Melan-A (figure 2C), PS100 (figure 2D) and HMB45, confirming their melanocytic nature. The recently introduced antibody against PRAME (PReferentially expressed Antigen in MElanoma)-RED was performed and the cell's nuclear negativity excluded their atypical character. Regular follow-up by endoscopy was performed with unchanged findings.

The second patient is a 66-year-old man, also known for gastritis, in which a discrete brownish-pigmented macule was fortuitously seen in upper esophagus during a control endoscopy. Biopsies showed the presence of non-atypical dendritic melanocytes in the basal part of the squamous epithelium, that were highlighted by Melan-A immunohistochemical stain. The patient had no particular personal or family history. He rarely drank alcohol and did not smoke.

After clinical-pathological correlation, diagnosis of esophageal melanocytosis was proposed for both patients.

Discussion

The pathogenesis of melanocytosis is not clearly defined but aberrant migration of neural crest cells during embryogenesis and differentiation of stem cells located in the basal layer of the epithelium into melanoblasts as a result of various influences are the two prominent theories (1,3,5,7). The second hypothesis seems to be preferred as melanocytosis has been associated with esophagitis and gastroesophageal reflux disease, described in patient with history of alcohol abuse and smoking, and in the surroundings of esophageal epidermoid carcinoma (14). The mutational character of molecules found in alcohol and tobacco, as acetaldehyde, and stimulating factors released by carcinomatous cells may trigger melanogenesis (5,7,14).

At endoscopy, differential diagnosis of esophageal pigmented macules includes melanocytosis, pseudo-melanosis, tumoral melanocytic lesions and other rare entities such as the BRBNS.

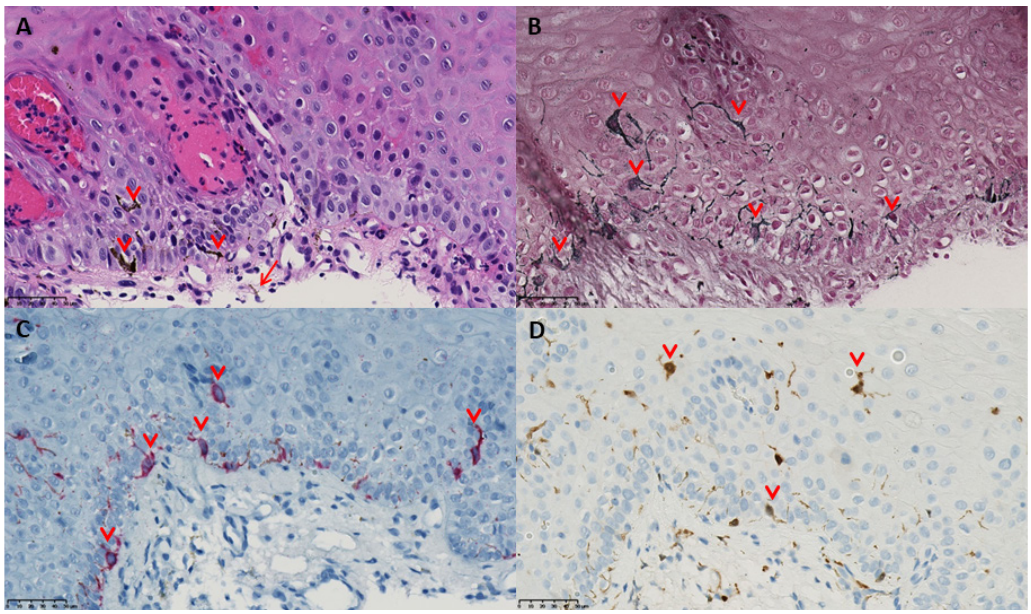

Figure 2. — Hematoxylin and eosin staining (A) shows the presence of non-atypical dendritic cells with cytoplasmic dark granules (red arrowheads) and melanin deposits along the basal layer of the squamous epithelium, associated with pigment-loaded macrophages (red arrow) in the lamina propria. Masson-fontana (B) staining highlighting dendritic melanocytes (red arrowheads) and melanin granules. Immunohistochemical stains for MART1/MELAN-A (C) and PS100 (D) show cytoplasmic positivity in the dendritic melanocytic cells (red arrowheads). (*Original magnification, 40x).*

Pseudomelanosis, which is an accumulation of various substances in macrophages, fibroblasts or epithelial cells, is caused by exogenous depositions (dye ingestion, anthracosis), hemosiderosis or hemochromatosis and lipofuscin pigment accumulation (3,5). For exogenous deposits, clinical information with a single endoscopy showing the deposits can easily give the diagnosis. PAS (Periodic-Acid-Schiff) and PERLS stainings highlighting lipofuscin pigments and iron accumulation respectively in the cells, may rapidly exclude a melanocytic lesion.

The BRBNS is an uncommon entity linked to vascular problems. Endoscopically, multiple bluish macules are observed along the esophageal mucosa. Histology exhibits various vascular alterations. Siderophages with hemosiderin accumulation can be found (3).

The most important differential diagnosis of melanocytosis has to be made with tumoral melanocytic lesions. The two main entities are melanocytic nevus and primary malignant esophageal melanoma (PMME). The first is even rarer as only one case of blue nevus has been described in the literature (13). Endoscopically, blue nevus appears as a small, flat, bluish and linear esophageal macule. Analogously to the skin, histology showed the presence of heavily pigmented melanocytes in the lamina propria without junctional activity and cytonuclear atypia.

PMME is also very rare with an incidence of 0.0036 in 100000 (3). It appears mostly as a pigmented mass or a polypoid pigmented lesion located in the middle or lower esophagus (3,6,13). Though PMME can occasionally present as flat and poorly delimited macules exhibiting the same endoscopic aspect as melanocytosis (6). A magnifying endoscopy focusing on the relation between melanocytes and the "IntraPapillary Capillary Loops" (IPCLs) and on the pigmentation pattern is encouraged by Ohnuma *et al.* (6). Indeed, in melanocytosis, the cells stay along the IPCLs and the basal membrane without deformation and destruction, while in PMME there is invasion, deformation or destruction of those structures. The pigmentation pattern is linear and well-arranged in melanocytosis while it is non-uniform and irregularly distributed in PMME. Histologically, PMME shows infiltrating nests of epithelioid cells or fascicles of spindle cells but can also stay *in situ* (lentiginous spread) and in that specific case, the presence of cytonuclear atypia, atypical mitoses and junctional activity are crucial to differentiate it from other melanocytic entity.

Because of the rarity of melanocytosis, and subsequent lack of data in the literature, there are no guidelines regarding management and surveillance. Esophageal melanocytosis usually described as a benign lesion does not require follow-up or treatment. However, as for some authors it might be a precursor of melanoma (4,8-10), an endoscopical follow-up with multiple biopsies or a complete resection by laser or mucosectomy is suggested to avoid a potential malignant transformation.

Conclusion

Esophageal melanocytosis is a rare but well characterized entity. As EM can be treated conservatively, knowing its existence may be important to take into account in the differential diagnosis of esophageal mucosa pigmented lesions. Moreover, we should keep in mind that pathogenesis and natural course remain uncertain and a subsequent follow-up by gastroenterologist may be useful.

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Conflict of Interest statement

All authors read the manuscript and confirmed that they have nothing to disclose.

References

1. DE LA PAVA S., NIGOGOSYAN G., PICKREN JW., CABRERA A. Melanosis of the esophagus. *Cancer.,* 1963; 16: 48-50.
2. MONTGOMERY E., VOLTAGGIO L. In : Wolters Kluwer. Biopsy Interpretation of the Gastrointestinal Tract Mucosa. Volume 1. 3d ed. Philadelphia, 2018. Chap 1: 8-9.
3. CHANG F., DEERE H. Esophageal Melanocytosis : morphologic features and review of the literature. *Arch Pathol Lab Med*., 2006; 130: 552-557.
4. OHASHI K., KATO Y., KANNO J., KASUGA T. Melanocytes and melanosis of the oesophagus in Japanese subjects – analysis of factors effecting their increase. *Virchows Arch A Pathol Anat Histopath*., 1990; 417: 137-43.
5. DESTEK S., GUL V., AHIOGLU S., ERBIL Y. A rare disease of the digestive tract: Esophageal melanosis. *Gastroenterol Res.* 2016; 9(2-3): 56-60.
6. OHNUMA H., ISHIKAWA K., HIRAKAWA M., KIKUCHI S., SATO Y., MIYANISHI *K. et al.* Cases of primary malignant melanoma and melanocytosis of the esophagus observed by magnifying endoscopy: Application to differential diagnosis : case series. *Medicine.,* 2017; 96: 17.
7. SHARMA S., VENKATESWARAN S., CHACKO A., MATHAN M. Melanosis of the esophagus : an endoscopic, histochemical, and ultrastructural study. *Gastroenterology.,* 1991; 100(1): 13-16.
8. KANAVAROS P., GALIAN A., PERIAC P., DYAN S., LICHT H., LAVERGNE A., Primary malignant melanoma of the esophagus arising in melanosis : histological, immunohistochemical and ultrastructural study of a case. *Ann pathol*. 1989; 9(1): 57-61.
9. MAROY B., BAYLAC F., Primary malignant esophageal melanoma arising from localized bening melanocytosis. *Clin Res Hepatol Gastroenterol.* 2013Apr; 37(2): e65-7.
10. OSHIRO T., HIDEAKI S., FUMIAKI M., NOBUFUMI U., FUKUNORI K., NAKAYAMA T., *et al.,* Primary malignant melanoma of the Esophagus arising from a melanotic lesion: report of case. *Surg Today.* (2007)37: 671-675.
11. YAMAZAKI K., OHMORI T., KUMAGAI Y., MAKUUCHI H., EYDEN B., Ultrastructure of oesophagal melanocytosis. *Virchows Arch A Pathol Anat Histopathol.* 1991; 418: 515-522.
12. TAKUBO K. Pathology of the Esophagus. In : Springer Verlag. An Atlas and Textbook. 2nd ed. Japan, 2010. Chap 2: 25.
13. LAM KY., LAW S., CHAN GSW. Esophageal blue nevus: an isolated endoscopic finding. *Head Neck*., 2001; 23: 506-509.
14. YOKOYAMA A., OMORI T., YOKOYAMA T., TANAKA Y., MIZUKAMI T., MATSUSHITA S., *et al.,* Esophageal melanosis, an endoscopic finding associated with squamous cell neoplasms of the upper aerodigestive tract, and inactive aldehyde dehydrogenase-2 in alcoholic Japanese men. *J Gastroenterol.* 2005; 40: 676-684.