

Cases of primary malignant melanoma and melanocytosis of the esophagus observed by magnifying endoscopy

Application to differential diagnosis: case series

Hiroyuki Ohnuma, MD, PhD^a, Kazuma Ishikawa, MD^a, Masahiro Hirakawa, MD, PhD^a, Shohei Kikuchi, MD, PhD^{a,b}, Yasushi Sato, MD, PhD^c, Koji Miyanishi, MD, PhD^a, Junji Kato, MD, PhD^{a,*}

Abstract

Rationale: Primary malignant melanoma of the esophagus (PMME) is a rare disease with an extremely poor prognosis. In contrast, melanocytosis is a benign condition defined as melanocytic proliferation with melanin deposition. PMME is often accompanied by melanocytosis, but differentiating between them is difficult because of their similar appearance.

Patient concerns: Here, we reported 3 PMME cases, 2 with melanocytosis.

Diagnoses: Magnifying endoscopy revealed characteristic non-uniform pigmented spots along deformed intrapapillary capillary loops (IPCLs) in PMME, while melanocytosis showed fine granule-like or linearly arranged spots and intact IPCLs.

Interventions: The patients underwent endoscopic or surgical resection of each lesion.

Outcomes: Histologically, magnified images reflected melanocyte growth. For cases 1 and 2, the patients remained disease-free for 61 and 15 months after endoscopic resection, respectively. In case 3, liver metastases developed two months after surgery, and the patient died from liver failure after six months.

Lessons: This is the first report describing differences in magnified views of the 2 diseases, which aids a differential diagnosis.

Abbreviations: EGD = esophagogastroduodenoscopy, ESD = endoscopic submucosal dissection, IPCL = intrapapillary capillary loop, PMME = primary malignant melanoma of the esophagus.

Keywords: esophagus, magnifying endoscopy, malignant melanoma, melanocytosis, narrow band imaging

1. Introduction

Primary malignant melanoma of the esophagus (PMME) is a rare malignant tumor derived from melanocytes in the esophageal mucosa,^[1,2] with an estimated 12 to 13 cases per year in Japan.^[3] In comparison, melanocytosis in the esophageal mucosa is a benign condition of melanocytic proliferation with increased melanin.^[4]

PMME is very aggressive with a poor prognosis and high metastatic potential, even in its early stages.^[1–3,5] Early detection of PMME is crucial for cure since cases undergoing complete resection often experience long-term cancer-free survival.^[1–3,5]

However, distinguishing between early PMME and melanocytosis is difficult because of their similar appearance.^[6] Most PMMEs are detected at an advanced stage,^[1,5,7] presumably because many PMMEs are initially misidentified as melanocytosis and consequently remain untreated.

We present 3 resected PMME cases, 2 with concurrent melanocytoses. We compared magnified endoscopic images and histopathological findings of PMMEs and melanocytoses, and concluded these may support a differential diagnosis.

Ethics approval is not applicable to our study, because this report just reviewed previous data and did not involve any human trials. Written informed consents were obtained from the patients.

2. Case presentation

Table 1 lists three 70 to 81-year-old male patients, with multiple black pigmented mucosal lesions in the esophagus. Cases 1 and 2, symptomless and with superficial lesions, were diagnosed by esophagogastroduodenoscopy (EGD) during routine medical check-ups. Case 3, with a protruding tumor, presented with dysphagia. Patient tumors were all located in the middle to lower part of the esophagus. Cases 1 and 2 underwent endoscopic submucosal resection (ESD) in response to intramural lesions detected by endoscopy and endoscopic ultrasonography. At diagnosis, the differentiation of PMMEs from melanocytoses was difficult, despite examining biopsy specimens, so all visible lesions were resected. The histopathological examination of resected specimens revealed cases 1 and 2 had 1 PMME each, and 2 or 1 melanocytoses, respectively. Case 3 underwent an esophagectomy with extensive lymph node dissection, since the lower

Editor: Vishwas Vanar.

The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

^a Department of Medical Oncology, ^b Department of Hematology, Sapporo Medical University School of Medicine, Sapporo, ^c Department of Gastroenterology and Oncology, University of Tokushima, Tokushima, Japan.

* Correspondence: Junji Kato, Department of Medical Oncology, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo, Hokkaido 060-8543, Japan (e-mail: jkato@sapmed.ac.jp).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2017) 96:17(e6701)

Received: 6 January 2017 / Received in final form: 21 March 2017 / Accepted: 2 April 2017

<http://dx.doi.org/10.1097/MD.0000000000006701>

Table 1**Clinical characteristics of patients.**

Case	Age/sex	Symptoms	Location	Number of lesions	Size, mm	Tumor type	Treatment	Japanese classification*	Survival, mo	Outcome
1	70 Male	None	Mt	1: Melanoma 2: Melanocytosis	10 8, 12	0-IIb 0-IIb	ESD	pT1a-LPM NOMO	61	Disease-free
2	71 Male	None	Mt	1: Melanoma 1: Melanocytosis	16 10	0-IIa + IIb 0-IIb	ESD	pT1a-LPM NOMO	15	Disease-free
3	80 Male	Dysphagia	Mt–Ae	6: Melanoma	12–75	1 + 0-IIb, 0-Is, 0-IIb	Surgery	pT2 pN1M0	6	Death due to liver metastasis

0-IIa, superficial elevated type; 0-IIb, superficial flat type; 0-Is, protruded and sessile type; 1, mass type. Ae = abdominal esophagus, ESD = endoscopic submucosal dissection, Mt = middle thoracic esophagus, p = pathological findings, T1a-LPM = tumor invades lamina propria mucosae, T2 = tumor invades muscularis propria.

*According to Japanese Classification of Esophageal Cancer, 11th edition.

esophagus had a large protruding tumor and multiple superficial PMME lesions.

Endoscopic and pathological findings of PMME and melanocytosis in case 1 are shown (Figs. 1 and 2). Under white light endoscopy, both PMME and melanocytosis presented as flat, heterogeneously hyperpigmented mucosal plaques with an unclear boundary (Figs. 1A, 2A); differentiation by EGD without magnification proved difficult. However, magnifying endoscopy with narrow band imaging revealed obscure intrapapillary capillary loops (IPCLs) in faintly pigmented lesions, while amorphous dark plaques without IPCLs were observed in

hyperpigmented areas. Furthermore, IPCLs in PMME demonstrated dilatation, caliber change, and nonuniformity; irregular black granule-like spots were densely scattered along these deformed IPCLs or even replaced them (Fig. 1B, C). In melanocytosis, fine, faint spots were scattered or linearly arranged along intact, uniform IPCLs (Fig. 2B, C).

In PMME, histopathological examination revealed atypical melanocytes, with nuclear pleomorphisms and melanin granules, proliferating along the basal layers of the epithelium and IPCLs, and infiltrating toward the epithelial surface to show junctional activity. IPCLs were displaced, deformed, or replaced by invading

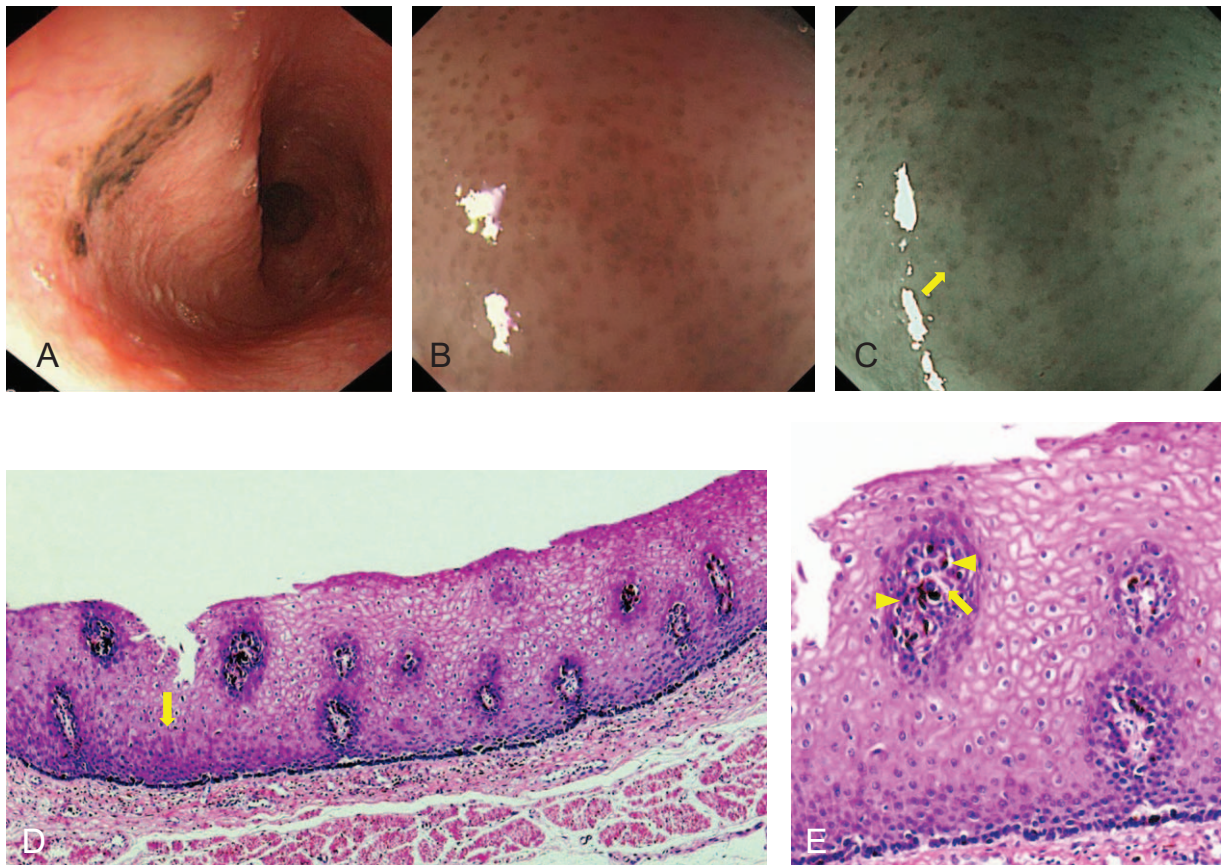


Figure 1. PMME in case 1. (A) Endoscopy showing a flat, heterogeneously hyperpigmented mucosal patch with an obscure boundary. (B) Magnified image with white light revealing irregular, black, and nonuniform granule-like spots. (C) Granule-like spots were scattered along deformed IPCLs (arrow) or replaced them as shown by magnifying endoscopy with NBI. (D) Hematoxylin–eosin stain of an endoscopic submucosal dissection. Atypical melanocytes grew along the basal layer of epithelium and IPCLs, and showed junctional activity (arrow) ($\times 50$). (E) IPCLs (arrow) deformed by invading melanocytes (arrowhead) ($\times 200$). IPCL = intrapapillary capillary loop, NBI = narrow band imaging, PMME = primary malignant melanoma of the esophagus.

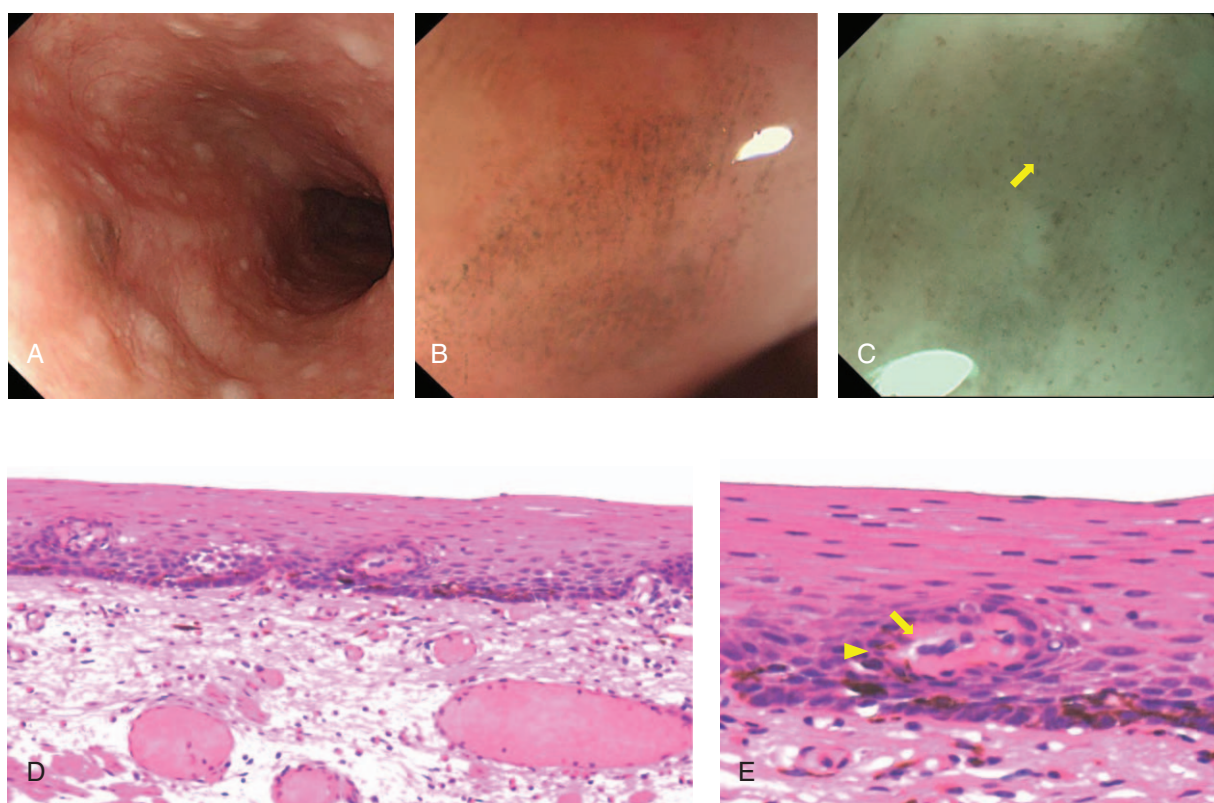


Figure 2. Melanocytosis of the esophagus in case 1. (A) Endoscopy revealed a view similar to PMME. (B) Magnifying endoscopy with white light revealed scattered or linearly arranged fine spots. (C) Magnifying endoscopy with NBI revealed faint, but intact IPCLs (arrow). (D) Hematoxylin–eosin stain of an endoscopic submucosal dissection. Spindle-shaped melanocytes grew along the basal layer of epithelium and IPCLs without junctional activity ($\times 50$). (E) IPCLs (arrow) surrounded by non-invading melanocytes (arrowhead) ($\times 200$). IPCL=intrapapillary capillary loop, NBI=narrow band imaging, PMME=primary malignant melanoma of the esophagus.

melanocytes (Fig. 1D, E). Conversely, in melanocytosis, intact melanocytes were arranged along basal layers of the epithelium and IPCLs, without any junctional activity, or destruction/infiltration into IPCLs (Fig. 2D, E). Immunohistochemically, tumor cells of both PMME and melanocytosis were positive for S-100 and Melan-A. All 3 cases showed similar endoscopic and histopathological findings (Supplementary Figs. 4–6, <http://links.lww.com/MD/B677>).

For cases 1 and 2, lesions were completely resected by ESD; invasive depth for both was T1a-LPM (lamina propria mucosae, according to Japanese Classification of Esophageal Cancer, 11th edition).^[8] Patients remained disease-free for 61 and 15 months after ESD, respectively. In case 3, despite an R0 resection, liver metastases developed 2 months after surgery, and the patient died from liver failure after 6 months.

3. Discussion

Primary esophageal cancer mainly consists of squamous cell carcinoma. PMME is extremely rare, accounting for 0.1% to 0.2% of esophageal malignancies.^[2] The male to female ratio is about 3:1, of average age, 60 to 65 years.^[1–3] Most PMMEs occur in the middle to lower 3rd of the esophagus: 47.8% are diagnosed as advanced disease, while mucosal lesion (T1a) accounted for only 11.2% of all cases.^[3] Melanocytosis is also rare, with an incidence of 0.07% to 2.1% among EGD patients,^[4] and is considered a precursor of PMME.^[9,10]

The fact that melanocytosis can transform into PMME is a crucial problem in follow-up. Although 25% to 30% of PMMEs are

accompanied by melanocytosis,^[4] the development of PMME from melanocytosis has only been formally described once.^[11] Thus, the malignant alteration of melanocytosis is supposedly a rare phenomenon, and it is therefore not meaningful to treat melanocytosis per se.

Once patients develop a PMME, its prognosis is dismal, with extensive metastases developing in a relatively early stage.^[1–3,5] Hence, the early diagnosis of PMME is essential for cure. Makuuchi et al^[3] reported that lymph node metastasis was recognized in 54.5% of T1b-SM (submucosa) cases and 82.8% of T2 (muscularis propria) or deeper cases, and had a poor prognosis, with a 5-year survival rate of 18.1%. Meanwhile, the rate of lymph node metastasis for T1a-MM (muscularis mucosae) cases was only 6.7%, without metastatic cases for T1a-EP (carcinoma in situ) and T1a-LPM. In this report, 7 cases were treated by endoscopic resection, 4 of whom had a T1a (tumor invades mucosa) lesion, and all survived disease-free.^[3] In addition to our 2 cases, no recurrent cases were reported with T1a-EP or T1a-LPM that was completely resected endoscopically.^[3,12,13] PMME can be cured by early detection and endoscopic resection so a definitive, early diagnosis is crucial. However, differentiating a superficial PMME from melanocytosis is difficult because of similar endoscopic findings – brownish to black, flat, and irregularly delineated lesions.^[6,14]

In our 3 PMME cases, magnified endoscopic imaging revealed differences in granule-like spots and IPCLs. This suggested these findings could be applied to a differential diagnosis: uniform or linearly arranged black dots along intact IPCLs were seen in melanocytosis, whereas irregular dots of different sizes were unevenly distributed along or replaced IPCLs, which presented

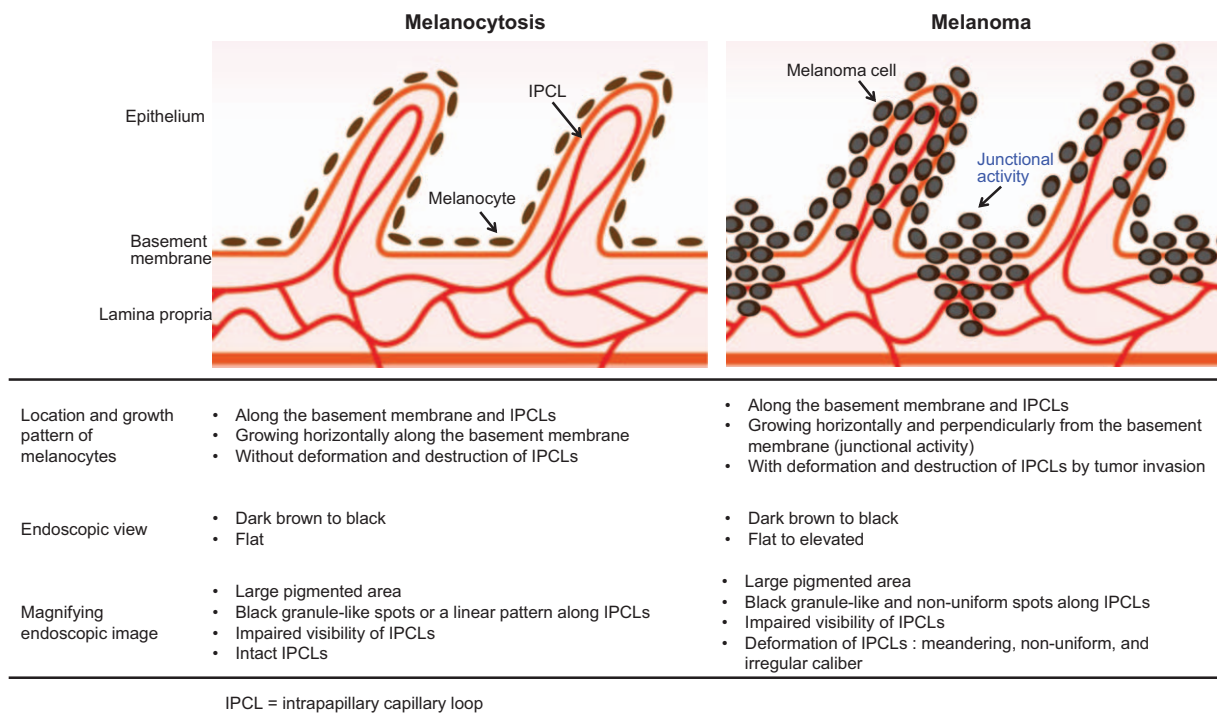


Figure 3. Schematic illustration of pathological structures and pathological/endoscopic findings of melanocytosis and primary malignant melanoma of the esophagus (PMME).

with irregularities such as meandering, dilatation, caliber change, and nonuniformity. Histological examination of resected specimens indicated magnifying endoscopic findings that reflected the growth pattern of melanocytes. That is, in melanocytosis, melanocytes were located along the basal layers of the epithelium and IPCLs without perpendicular growth and invasion into vessels, while in PMME, atypical melanocytes showed junctional activity and invasion into IPCLs, destroying normal structures. Figure 3 shows schemata and endoscopic, histological findings of melanocytosis and PMME. Additionally, endoscopy with white light was useful for observing color changes, whereas narrow band imaging was suitable for that of IPCLs, so a combination of these images was essential.

Endoscopic biopsy is sometimes carried out to achieve a definitive diagnosis. With regard to a report describing the lack of difference in 5-year survival rates between patients with or without biopsy,^[15] minimal biopsy may be allowed. However, junctional activity, essential for diagnosis, may not necessarily be detected in a tiny biopsy specimen. Also, positive immunohistochemical markers for PMME, such as S-100, HMB-45, and Melan-A, are also positive in melanocytosis and consequently useless for a differential diagnosis.^[4] The accuracy rate of diagnosis from a biopsy remains approximately 80%,^[5] so a magnified view may be helpful. If a lesion is suspected of a superficial PMME by biopsy and endoscopy, an endoscopic resection may then apply. Meanwhile, observation is recommended when melanocytosis is suspected.

In conclusion, we have identified a possible method for a differential diagnosis of PMME and melanocytosis by patterns of pigmentation and IPCLs that reflect the mode of melanocyte invasion. To our knowledge, this is the first report describing differences in magnified images of these 2 diseases. However, only a small number of patients were assessed, and so a larger study is required to verify our data.

References

- [1] Sabanathan S, Eng J, Pradhan GN. Primary malignant melanoma of the esophagus. *Am J Gastroenterol* 1989;84:1475–81.
- [2] Chalkiadakis G, Wihlm JM, Morand G, et al. Primary malignant melanoma of the esophagus. *Ann Thorac Surg* 1985;39:472–5.
- [3] Makuuchi H, Takubo K, Yanagisawa A, et al. Esophageal malignant melanoma: analysis of 134 cases collected by the Japan Esophageal Society. *Esophagus* 2015;12:158–69.
- [4] Chang F. Esophageal melanocytosis. *Arch Pathol Lab Med* 2006;130:552–7.
- [5] Yamaguchi T, Shioaki Y, Koide K, et al. A case of primary malignant melanoma of the esophagus and analysis of 193 patients in Japan. *J Jpn Gastroenterol* 2004;101:1087–94.
- [6] Dinnen HS, Protopoulos G, Fitzhugh V, et al. Darkest before dawn: esophageal melanocytosis mimicking primary esophageal melanoma. *Gastrointest Endosc* 2014;80:1203–5.
- [7] Iwanuma Y, Tomita N, Amano T, et al. Current status of primary malignant melanoma of the esophagus: clinical features, pathology, management and prognosis. *J Gastroenterol* 2011;47:21–8.
- [8] Japan Esophageal Society/Japanese Classification of Esophageal Cancer, 11th Edition: part I. *Esophagus* 2016;14:1–36.
- [9] Volpin E, Sauvanet A, Couvelard A, et al. Primary malignant melanoma of the esophagus: a case report and review of the literature. *Dis Esophagus* 2002;15:244–9.
- [10] Kreuser ED. Primary malignant melanoma of the esophagus. *Virchows Arch A Pathol Anat Histol* 1979;385:49–59.
- [11] Kanavaros P, Galian A, Périac P, et al. Primary malignant melanoma of the esophagus arising in melanosis. Histological, immunohistochemical and ultrastructural study of a case. *Ann Pathol* 1989;9:57–61.
- [12] Osuga T, Sagawa T, Satou Y, et al. Primary malignant melanoma of the esophagus treated by endoscopic submucosal dissection. *Gastrointest Endosc* 2014;56:2156–62.
- [13] Miyatani H, Yoshida Y, Ushimaru S, et al. Slow growing flat-type primary malignant melanoma of the esophagus treated with cap-assisted EMR. *Dig Endosc* 2009;21:255–7.
- [14] Choudhary N, Puri R, Goel R, et al. Primary malignant melanoma involving the whole esophagus: a rare case with rarer presentation. *Endoscopy* 2014;46: E621–612.
- [15] Yamaguchi T, Shioaki Y, Koide K, et al. A case of primary malignant melanoma of the esophagus and analysis of 193 patients in Japan. *J Jpn Gastroenterol* 2004;101:1087–94.