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CASE REPORT

A case of primary malignant melanoma of the esophagus with a widely expanded surface area

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Abstract

Primary malignant melanoma of the esophagus (PMME) is rare but aggressive. PMME accounts for approximately 0. 1% of all malignant esophageal neoplasms occurring worldwide, and is usually diagnosed during the advanced stage. A 67-year-old man underwent an esophagogastroduodenoscopy (EGD) at our hospital and confirmed 20 mm of black pigmentation in the lower esophagus in the chest area. Pathological biopsy findings of the black-pigmented epithelial tissue revealed the presence of tumor cells with brown granules, leading to the diagnosis of malignant melanoma. Owing to difficulty in accurately diagnosing the range in this PMME case, we performed thoracoscopic esophagectomy. Pathological organisation test results were pT1a-LPM, INFb, pN0, and pM0, which were diagnosed at pStage I. The lesion expanded extensively, measuring > 10 cm in diameter. The tumor cells, which were centrally located in the black-pigmented area, were observed to have proliferated beyond the surrounding brownish area into the mucosa, but no findings were found in the endoscopic examination. As in this case, because PMME may diffusely spread along the basal layer outside the range of pigmentation, endoscopic diagnosis of the extent of disease spread may be impossible; hence, it is important to keep this phenomenon in mind while performing resection to treat PMME.

Keywords Primary malignant melanoma · Esophagus · Range diagnosis · Endscope

Introduction

Primary malignant melanoma of the esophagus (PMME) is rare but aggressive. PMME was reported for the first time in 1964, and currently, it accounts for approximately 0. 1% of all malignant esophageal neoplasms occurring worldwide [1]. Because the onset is mainly non-specific, PMME is usually diagnosed during the advanced stage. The most commonly metastasised organs of PMME are the liver, mediastinum, lung, and brain [2].

However, because a comprehensive understanding of PMME is challenging due to the rarity of this disease, an optimal treatment strategy, including aggressive esophageal resection, has not yet been established. To date, adjuvant chemotherapy, radiation therapy, and conventional immunotherapy have not proved to be effective [3]. A follow-up study of patients with PMME who underwent esophagectomy revealed a recurrence rate of 70% and a mortality rate of 50% [4]; it demonstrated that all patients with lymph node (LN) metastasis experienced recurrence within a year and

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that esophagectomy may be beneficial for PMME patients without LN metastasis [5].

Even in its early stages, PMME is found to be aggressive, with a poor prognosis and high metastatic potential [6, 8]. Complete resection is important for treating PMME because several cases in the literature have reported long-term relapse-free survival of patients who underwent this procedure at the time of initial PMME detection [6–8].

In this article, we report a case of superficially spreading PMME confined to the mucosa.

Case report

A 67-year-old man underwent an esophagogastroduodenoscopy (EGD) at our hospital as a follow-up reflux esophagitis. Although EGD performed 1 year prior did not reveal abnormal findings, EGD performed in March 2017 confirmed 20 mm of black pigmentation in the lower esophagus in the chest area. In addition, the flat dye exudated to the mucosal epithelium surrounding the black pigmentation (Fig. 1a). The aforementioned mucosal epithelium housing the black pigmentation lacked vascular permeability and possessed small, diffusely scattered black dots. Magnified observation of the black-pigmented interior revealed a dark blue-colored epithelium and unevenly distributed black spots (Fig. 1b).

Using NBI (narrow band imaging) findings, we observed the accumulation of pale black dots in the black-pigmented epithelium, and a portion of those dots had an IPCL-like microvascular pattern in the centre (Fig. 1c). Although iodine staining showed pale dyeing areas, it did not coincide with black pigmentation or areas where the surrounding vascular permeation had disappeared, and no obvious unstained area was recognized (Fig. 1d). Pathological biopsy findings of the black-pigmented epithelial tissue revealed the presence of tumor cells with brown granules, leading to the diagnosis of malignant melanoma.

In addition, we did not find any signs indicative of malignant melanoma of the skin spreading to other parts of the body. No abnormal accumulation was recognized in the PET-CT scan. Based on the abovementioned findings, we made the diagnosis of PMME, with an invasion depth of EP-LPM. Owing to difficulty in accurately diagnosing the range in this PMME case, we performed thoracoscopic esophagectomy, gastric tube reconstruction, and LN dissection.

An endoscopic image contrasted with pathological findings of the PMME is shown in Fig. 2a. Tumor cells stayed in the epithelium in the large part (the yellow line region); however, they still destroyed IPCL structure in the region of the green line. Furthermore, tumor cells diffusely infiltrated the lamina propria of the mucous membrane at its deepest

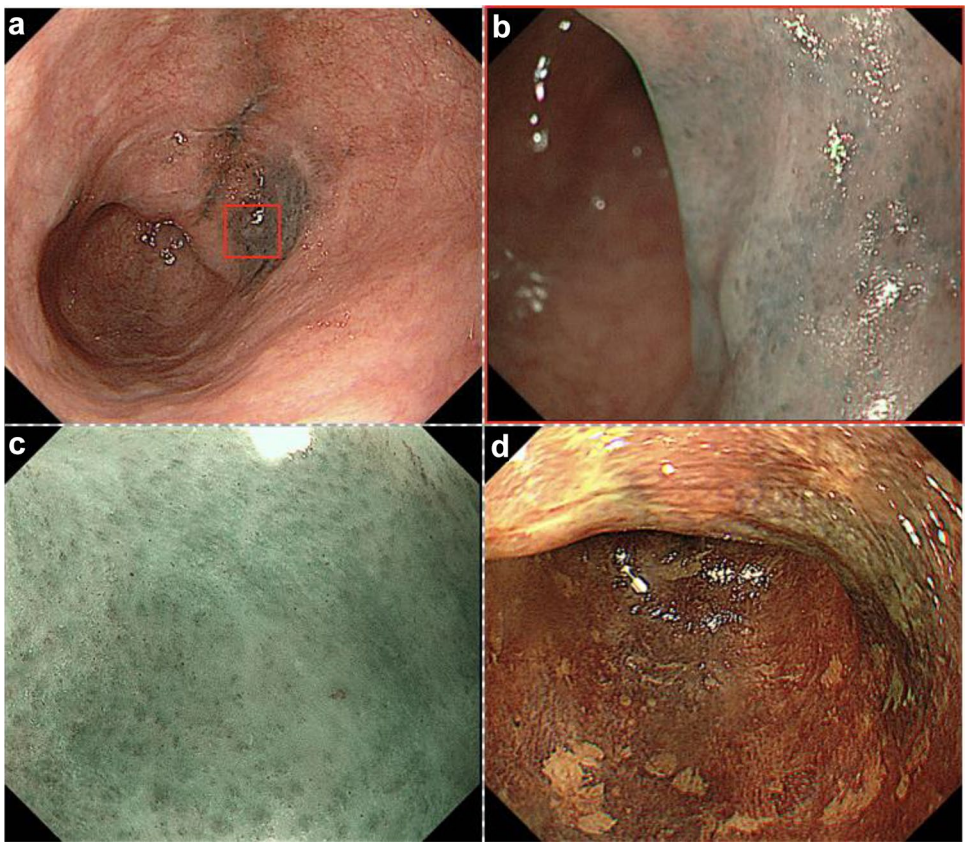

Fig. 1 **a** Under white light observation, black-pigmented spots measuring 20 mm in diameter were observed in the lower esophagus in the chest area and dye exudation was observed in the surrounding areas. **b** In the magnified observation of the black-pigmented region, black dots were observed in the background of dark blue-colored mucosa. **c** In the magnified NBI observation of the black-pigmented region revealed disappearance or deformation of IPCL and accumulation of black dots. **d** Iodine staining demonstrated a mottled pattern, but no area was left unstained

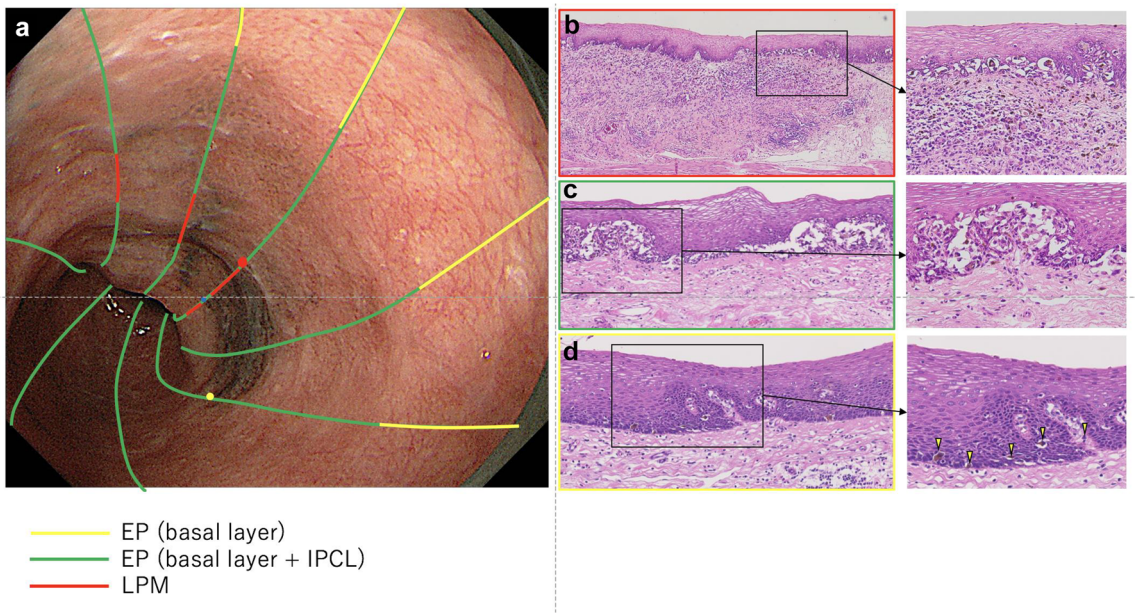

Fig. 2 **a** An endoscopic image mapping tumor depth. **b** Tumor cells infiltrated the mucosal lamina propria, and the area was accompanied by an interstitial reaction. **c** Tumor cells are present mainly in the mucosal basal layer, and IPCL is destroyed/replaced by tumor cells. **d** Tumor cells are diffusely present in the mucosal basal layer

region and were surrounded by fibrotic tissues (the red line region).

Moreover, round or spindle-shaped tumor cells of high nuclear grade had melanin granules in the mucosal epithelial basal layer and IPCL (Fig. 2b). The tissues surrounding the black-pigmented region lacking vascular permeation, tumor cells were found around the mucosal epithelial basal layer and in the epithelium, in the form of destroying the basal layer and destroying/replacing IPCL (Fig. 2c). In addition, in the outermost region, destroying/replacing IPCL by tumor cells was not observed, but round or spindle-shaped tumor cells were found to be scattered along the basal layer and the form of destroying the basal layer (Fig. 2d). In the mapped image of the biopsy specimen, the tumor cells, which were centrally located in the black-pigmented area, were observed to have proliferated beyond the surrounding brownish area into the mucosa, but no findings were found in the endoscopic examination (Fig. 3).

Pathological organisation test results were pT1a-LPM, INFb, v0, ly0, pN0, and pM0, which were diagnosed

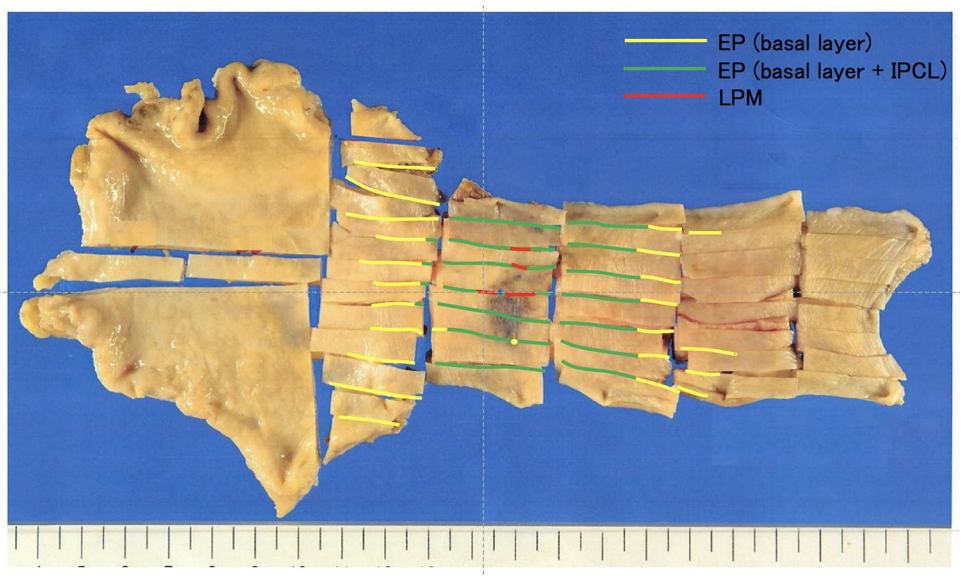

Fig. 3 Tumor cells expanded to the surrounding brownish region and further outside it; thus, they were centrally located in the black-pigmented region. The diameter of the tumor was as large as 10 cm

at pStage I. The lesion expanded extensively, measuring > 10 cm in diameter. After surgery, as per the patient's will, he did not undergo chemotherapy, and only follow-up observations were performed. It is 18 months after surgery and survives without relapse.

Discussion

Primary esophageal cancer mainly consists of squamous cell carcinomas in East Asia, or adenocarcinoma in Western countries. PMME is extremely rare, accounting for 0. 1–0. 2% of esophageal malignancies worldwide. The male-to-female ratio is approximately 3:1, and the average age of affected patients ranges between 60 and 65 years [2, 6]. PMMEs mostly occur in the middle and lower third region of the esophagus; of all PMME cases, 47. 8% are diagnosed in the advanced stage, whereas mucosal lesions (T1a) account for only 11. 2% [6]. The pattern of lymph node metastasis was somewhat similar to that of esophageal squamous cell carcinoma, but the most common form of recurrence for PMME was distant hematogenous metastasis rather than lymph node or regional recurrence, and almost all the patients with tumor later than Stage Ib recurred within about 1 year after operation [9].

PMME lesions with protrusions (type 0–I, type 0–IIa, type 3, etc.) account for > 70%, and usually, tumors are frequently covered by the normal epithelium. The reason for this is that PMME originates in the basal layer, grows upward, and swells in the submucosa like a bud. The eventual development of such buds appears as a series of protrusions [6].

In our case, PMME did not grow upward but grew extensively and transversely along the basal layer and invaded the mucosal lamina propria only in the central region. Pathological findings revealed that the tumors extended beyond the range of endoscopic diagnosis and that the tumor diameter was 10 cm. The reason for not being able to diagnose the extent of disease spread by endoscopy may be the initial expansion mode of PMME. During the early onset of PMME, tumor cells expanded along the basal layer and IPCL and consequently led to tissue destruction. The tumor cells surrounding the IPCL coincide with a faint black dot in the endoscopic image, which is depicted as a brownish black region due to the presence of tumor cells originating from the basal layer [10]. When we compared the endoscopic image obtained in this case with the pathological organisation, IPCL was found to be replaced by tumor cells in the area shown in green, i.e., the area where vascular permeability was absent, whereas in the area shown in yellow, the replacement of IPCL by tumor cells was not recognised and tumor cells dissimilarly existed only in the basal layer.

According to Makuuchi et al., 12 out of 134 PMME cases had tumors measuring > 10 cm in diameter, and all cases involved LN metastasis [6]. In most of those 12 cases, tumors infiltrated the muscularis propria, and the prognoses of these cases were very poor. In this case, however, despite the tumor diameter being 10 cm in size, it is rare that the invasion depth was LPM and LN metastasis was not observed.

Before invading the mucosal lamina propria, PMME often shows "junctional activity" which is defined by atypia of cells growing in the esophagus epithelial basal layer, randomness of the sequence, and discontinuity of the esophageal epithelial basement membrane [11]. In this case, IPCLs were replaced by tumor cells and tumor cells were found to be scattered along the basal layer, which is considered to be the initial image of PMME. If melanoma cells growing along the basal layer are accompanied by IPCL destruction/replacement and the basal layer destruction, vascular permeability decreases, as observed in subsequent endoscopic images. However, if melanoma cells spread diffusely along the basal layer without IPCL destruction/replacement and the basal layer destruction, endoscopic findings may not be obtained. Therefore, if vascular permeability disappears around the black-pigmented areas of PMME, it is considered that melanoma cells may be present further outside the range of diagnosis.

Histologically, melanoma is composed of epithelioid cells arranged in nests or spindle cells arranged in fascicles [11]. An endoscopic biopsy is sometimes carried out to achieve a definitive diagnosis of PMME. With regard to a report describing the lack of difference in 5-year survival rates between patients with or without biopsy [8], minimal biopsy from PMME may be allowed. However, junctional activity may not necessarily be detected in a tiny biopsy specimen. Also, positive immunohisto-chemical markers for PMME, such as S-100, HMB-45, and Melan-A, are also positive in melanocytosis and consequently useless for a differential diagnosis [12]. Therefore, an endoscopically negative biopsy is very difficult because it must be judged only by the presence or absence of a nuclear isotype in cells having melanin granules, if there were melanoma cells outside the main lesion, which is recognized as a dye exudation outside the main lesion. On the other hand, because junctional activity can be evaluated in addition to those observations, intraoperative rapid pathological diagnosis is considered useful.

Consequently, it is not possible to estimate the range of melanoma spread using an endoscope in this case. Considering that it is difficult to estimate the range of disease spread and because LN metastasis rate is high, we believe that it is appropriate to perform surgical resection in patients with PMME.

We encountered a patient with PMME having a tumor measuring 10 cm in diameter, which extensively expanded

outside the range of diagnosis by endoscopy. Although the diameter of the tumor was large, the invasion depth was LPM, and LN metastasis was not observed. Consequently, surgical esophageal resection and LN dissection were performed as curative measures. As in this case, because PMME may diffusely spread along the basal layer outside the range of pigmentation, endoscopic diagnosis of the extent of disease spread may be impossible; hence, it is important to keep this phenomenon in mind while performing resection to treat PMME.

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Compliance with ethical standards

Conflict of interest Koki Nakamura, Yuji Urabe and Shiro Oka and Masanori Ito and Takahiro Kotachi and Yuki Ninomiya and Tomoyuki Boda and Toru Hiyama and Manabu Emi and Yoichi Hamai and Noriyuki Shiroma and Shinji Tanaka and Kazuaki Chayama declare that they have no conflict of interest.

Human and animal rights statement All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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