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Primary esophageal malignant melanoma successfully treated with anti-PD-1 antibody for retroperitoneal recurrence after esophagectomy: A case report

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ABSTRACT

INTRODUCTION: Primary malignant melanoma of the esophagus (PMME) is a rare disease with a poor prognosis. Here, we report a case of retroperitoneal recurrence of PMME successfully treated with the anti-programmed cell death 1 antibody, nivolumab.

PRESENTATION OF CASE: A 70-year-old male with dysphagia was referred to our hospital. Esophagogastroscopy showed an elevated tumor in the lower thoracic esophagus. A histopathological examination of the biopsy revealed poorly differentiated squamous cell carcinoma. The patient was diagnosed with clinical T3N1M0 stage III esophageal squamous cell carcinoma and was treated with neoadjuvant chemotherapy followed by radical esophagectomy. A postoperative histopathological examination revealed that atypical cells with a brown pigment were scattered in the tumor. Immunohistochemical staining demonstrated positive expression of human melanoma black 45, melan A, and S100. A pathological diagnosis of PMME was confirmed. Sixteen months after surgery, abdominal computed tomography revealed solitary retroperitoneal recurrence in the lateral portion of the ascending colon. Fluorine-18 fluorodeoxyglucose positron emission tomography (PET) showed hypermetabolic accumulation with a maximum standardized uptake value of 5.8. The patient was treated with nivolumab (240 mg) every two weeks. After eight courses of nivolumab, abnormal accumulation of the retroperitoneal mass disappeared on PET, and this therapeutic effect continued for 20 months.

CONCLUSIONS: Nivolumab was effective for recurrence of PMME in our case. There are few reports of treatment with nivolumab for PMME. Further studies are necessary to establish the usefulness of nivolumab for PMME in the future.

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Abbreviations: BRAF, V-raf murine sarcoma viral oncogene homolog B1; CT, computed tomography; DCF, triple chemotherapy with docetaxel, cisplatin, and 5-fluorouracil; HMB45, human melanoma black 45; PD-1, programmed cell death 1; PET, positron emission tomography; PMME, primary malignant melanoma of esophagus; UICC, Union for International Cancer Control classification.

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1. Introduction

The incidence of primary malignant melanoma of the esophagus (PMME) is rare, accounting for 0.1–0.5% of all esophageal malignant tumors [1–3]. Furthermore, PMME has a poor prognosis, with a median survival time of 8–34.5 months, and the five-year survival rate of 10–37% [4,5]. Although common treatments for PMME include surgery, chemotherapy, and immunotherapy, standard treatment has not yet been established because only small group examinations have been carried out in previous reports. In recent years, immune-checkpoint inhibitors, such as the anti-programmed cell death 1 (PD-1) antibody, nivolumab, have been reported as effective treatments of malignant melanoma [6–8]. Few reports have used nivolumab to treat PMME [4,9–11]. Here, we report a case of PMME successfully treated with anti-PD-1 antibody

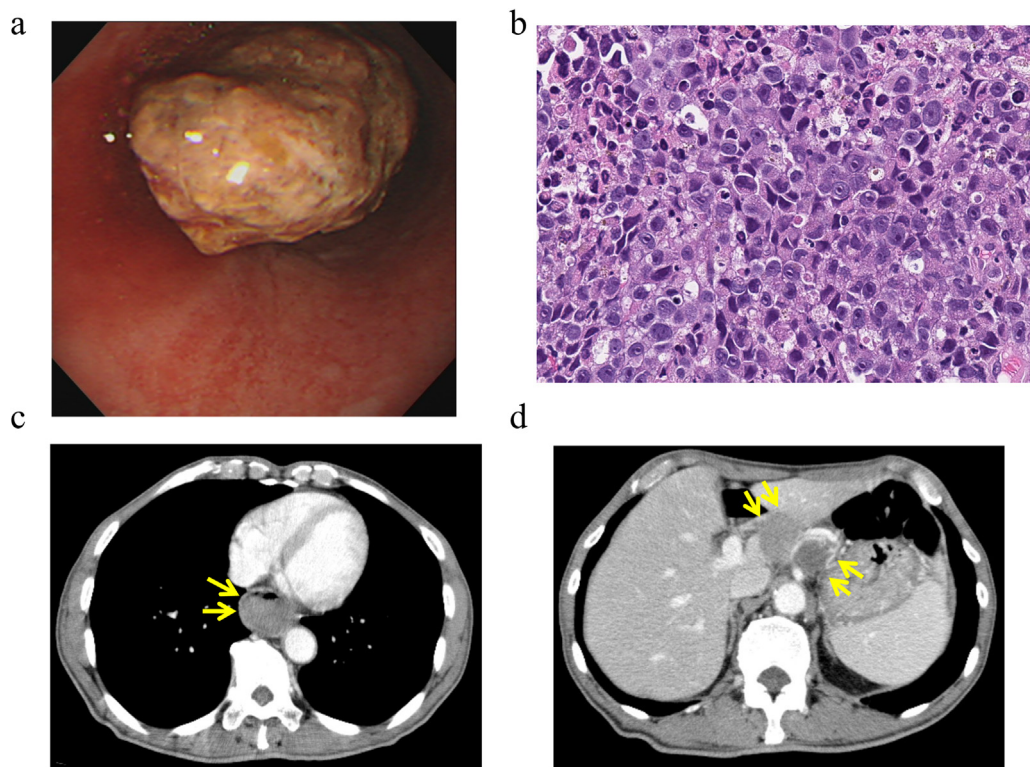


Fig. 1. Imaging findings on admission. (a) Esophagogastroscopy showed an elevated tumor in the lower thoracic esophagus. (b) A histopathological examination of the biopsy showed poorly differentiated squamous cell carcinoma. (c) Chest computed tomography showed stenosis of the esophageal lumen due to primary tumor. (d) Abdominal computed tomography showed enlarged lymph nodes along the celiac artery.

for retroperitoneal recurrence after esophagectomy. This work has been reported in line with the SCARE criteria [12].

2. Case presentation

A 70-year-old male visited a primary care doctor with a complaint of dysphagia in March 2017. The patient had a history of hypertension, untreated hyperglycemia, and brain infarction. Esophagogastroscopy revealed an elevated tumor in the lower thoracic esophagus (Fig. 1a). The tumor was white, and no black pigmentation was observed. A histopathological examination of the biopsy showed poorly differentiated squamous cell carcinoma (Fig. 1b). The patient was referred to our hospital for further examination and treatment. Esophagography revealed a 60-mm mass in the lower thoracic esophagus. Chest and abdominal computed tomography (CT) revealed stenosis of the esophageal lumen due to tumor (Fig. 1c) and enlarged lymph nodes along the celiac and common hepatic arteries (Fig. 1d), but no distant metastasis was observed. Laboratory data were normal except for hemoglobin A1c (7.8%), and the concentrations of tumor markers, including carcinoembryonic antigen and squamous cell cancer antigen, were within normal limits. There were no signs of skin melanoma or pigmentation on the whole body. The patient was diagnosed with clinical T3N1M0 stage III esophageal squamous cell carcinoma according to the 8th edition of the Union for International Cancer Control classification (UICC 8th). The patient was initially treated by triple chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF), neoadjuvant chemotherapy for esophageal cancer. The patient received docetaxel (70 mg/m² on day 1), cisplatin (70 mg/m² on day 1), and 5-fluorouracil (750 mg/m² on days 1–5) every four weeks. The therapeutic effect after chemotherapy evaluated after the two courses of DCF was stable disease. Then, the patient underwent thoracoscopic esophagectomy with two-field lymphadenectomy and gastric tube reconstruction via the poste-

rior mediastinum in May 2017. Intraoperatively, metastatic lymph nodes along the celiac and common hepatic arteries were black and invaded the hepatic plexus, which was resected curatively. The surgical duration was 370 min, and blood loss was 143 mL. The patient was discharged from hospital 16 days after surgery with no complications.

The resected specimen was a multinodular, elevated, and pigmented tumor measuring 75 × 40 mm (Fig. 2a). A postoperative histopathological examination revealed that atypical cells with irregularly sized nuclei and brown pigment were scattered in the tumor (Fig. 2b). Immunohistochemical staining demonstrated positive expression of human melanoma black 45 (HMB45) (Fig. 2c), melan A (Fig. 2d), and S100. No melanosis was observed in normal esophageal mucosa. A pathological diagnosis of T3N1M0 stage III PMME was confirmed according to the UICC 8th classification. A molecular study indicated no mutation in V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E and V600 K. No residual tumor or distant metastasis was revealed on postoperative fluorine-18 fluorodeoxyglucose positron emission tomography (PET)-CT. As adjuvant therapy, weekly subcutaneous injection of interferon α was performed until recurrence was confirmed. The patient was followed up every three months with chest and abdominal CT.

In September 2018, 16 months after surgery, the abdominal CT revealed a 36-mm mass in the retroperitoneum at the lateral portion of the ascending colon (Fig. 3a). PET-CT showed hypermetabolic lesions in the retroperitoneum with a maximum standardized uptake value of 5.8 (Fig. 3b). The PET showed no other lesions with abnormal accumulation. The patient was diagnosed with retroperitoneal recurrence of PMME. He was started on nivolumab treatment (240 mg), which continued every two weeks. Abdominal CT showed that retroperitoneal metastasis had reduced in size in response to nivolumab treatment with a maximum diameter of 18 mm after 2 courses (Fig. 3c), 14 mm after

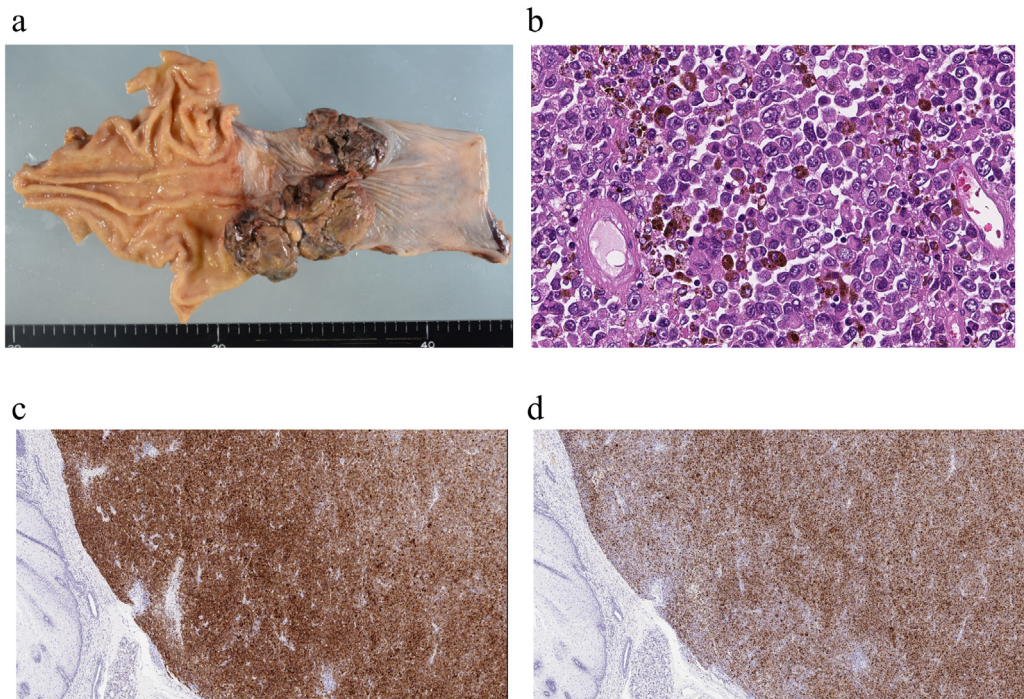


Fig. 2. Macroscopic and microscopic findings of the resected specimen. (a) Surgical specimen of the esophagus. The resected specimen was a multinodular, elevated, and black-pigmented tumor. (b) A histopathological examination using hematoxylin–eosin stain showed that atypical cells with brown pigment were scattered in the tumor. (c) Tumor cells stained positive for human melanoma black 45. (d) Tumor cells stained positive for melan A.

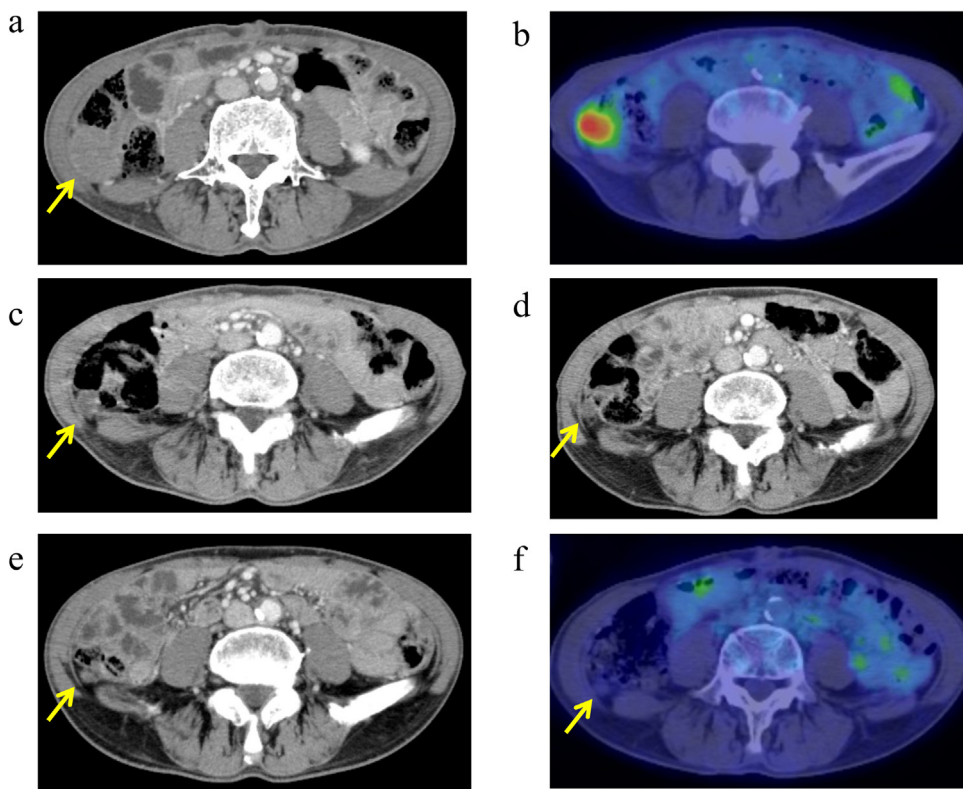


Fig. 3. Computed tomography (CT) and positron emission tomography–computed tomography (PET–CT) findings in the recurrence site. (a) Abdominal CT 16 months after surgery showed a 36-mm mass in the retroperitoneum at the lateral portion of the ascending colon. (b) PET–CT 16 months after surgery showed hypermetabolic lesions in the retroperitoneum with a maximum standardized uptake value of 5.8. (c) Abdominal CT after 2 courses of nivolumab. The maximum diameter of the tumor was 18 mm. (d) Abdominal CT after 4 courses of nivolumab. The maximum diameter of the tumor was 14 mm. (e) Abdominal CT after 6 courses of nivolumab. The maximum diameter of the tumor was 10 mm. (f) PET–CT after 8 courses of nivolumab. Although the 10-mm mass remained, abnormal accumulation of the retroperitoneal mass disappeared.

4 courses (Fig. 3d), and 10 mm after 6 courses (Fig. 3e). After 8 courses of nivolumab, although a 10-mm mass remained, abnormal accumulation of the retroperitoneal mass disappeared on PET-CT (Fig. 3f). The patient was admitted with fatigue and anorexia after 14 courses, and a decrease in serum cortisol was observed. The patient was diagnosed with grade 3 adrenal insufficiency according to the Common Terminology Criteria for Adverse Events, Version 4.0. The patient improved after administration of steroids and was discharged from hospital within 15 days of admission. Since discharge, the patient has not suffered with adverse events from nivolumab, including immune-related adverse events, and has continued with this therapy. In May 2020, 20 months after recurrence was confirmed, the disappearance of abnormal accumulation of the retroperitoneal 10-mm mass was confirmed by PET-CT after 41 courses of nivolumab.

3. Discussion

PMME develops multiple metastases in its early stages [13]. PMME commonly metastasizes into the liver, mediastinum, lung, and brain [14]. Makuuchi et al. reported distant metastasis in 25 patients (18.7%), including 2 cases of retroperitoneal metastasis (1.5%), in a review of 134 patients in Japan [3]. To the best of our knowledge, there has only been one case report of retroperitoneal recurrence of PMME reviewed in previous literature in the PubMed database [15]. Kranzfelder et al. reported PMME recurrence and a possible residual tumor two months after surgery in the retroperitoneum enclosing the celiac trunk, renal vein, and superior mesenteric artery [15]. Similar to our case, postoperative solitary retroperitoneal recurrence as distant metastases in remote sites was rare.

In this case, the preoperative diagnosis was poorly differentiated squamous cell carcinoma. A previous study reported that the accuracy of biopsy is approximately 80%, and 20–50% of patients were misdiagnosed with poorly differentiated carcinoma because of absence of melanin granules [1]. Sun et al. considered the reasons for misdiagnosis as follows: 1) some tumors are grossly amelanotic, and contain no melanin granules that are observable through microscopy, 2) melanocytes tend to concentrate in foci, and may thus be missed on biopsy, and 3) primary esophageal melanoma may be covered by normal squamous epithelium [16]. In our case, a detailed re-examination of biopsy tissue later revealed melanin with hematoxylin–eosin stain. In addition, retrospective immunohistochemical staining of biopsy tissue showed positive staining for HMB45, melan A, and S100, similar to the findings of the resected specimen.

According to the current treatment strategy outlined in the National Comprehensive Cancer Network Guidelines for patients with unresectable malignant melanoma, first-line therapy for patients involves immune-checkpoint inhibitors, such as anti-PD-1 antibody (nivolumab) and anti-CTLA-4 antibody (ipilimumab) [17]. If patients have a *BRAF* mutation, a combination of molecular target drugs, such as *BRAF* inhibitors and mitogen-activated protein kinase/extracellular signal-regulated kinase activator kinase inhibitors, is available [17]. A molecular study indicated no mutation in *BRAF*, thus, nivolumab was chosen at first in this patient. In relation to the use of chemotherapy for PMME, although cytotoxic agents, such as dacarbazine, nimustine, vincristine, vindesine, tamoxifen, and cisplatin, were adopted according to cutaneous malignant melanoma, the effectiveness of chemotherapy was limited [3,4,13]. On the other hand, immune-checkpoint inhibitors, such as nivolumab and ipilimumab, and molecular target drugs were examined for their effectiveness in the treatment of malignant melanoma [6–8,18]. In recent years, several experiences of using nivolumab for PMME have been reported [10,11]. Wang et al.

reported a response rate of 75% with a median response duration of 11.4 months with nivolumab in 12 patients with PMME [9]. Nivolumab is thought to be effective as a novel treatment for PMME. Nivolumab has been approved for insurance coverage for the treatment of unresectable malignant melanoma since 2014 in Japan, and insurance was enabled in postoperative adjuvant therapy from August 2018 [19]. In this case, a definitive diagnosis of PMME was provided by examination of a surgical specimen; therefore, we performed careful follow-up with administration of interferon α as an adjuvant therapy [20]. After confirming recurrence, nivolumab was administered immediately, and tumor shrinkage was achieved. Surgical outcomes for PMME have been unsatisfactory until now, but therapeutic outcomes may improve with use of immune-checkpoint inhibitors.

4. Conclusions

The present study reports a case of successful treatment of retroperitoneal recurrence of PMME with nivolumab. A combination of surgery and immunotherapy is expected to improve prognosis for patients with PMME. Further studies with larger sample sizes are necessary to investigate the usefulness of anti-PD-1 antibody for PMME in the future.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Ethics approval

This case report is exempt from ethical approval by our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' contributions

FE and YA conceived of this case presentation and drafted the manuscript.

TI, TK, TT, KO, HiN, KK, and AS participated in the design of this case presentation.

RF, NS, HaN, SB, and MO participated in the treatment of the patient.

RS and TS determined the pathological diagnosis of the patient.

All authors read and approved the final manuscript.

Registration of research studies

Not necessary in this case report.

Guarantor

Yuji Akiyama.

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