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CASE REPORT

Primary malignant melanoma of the esophagus successfully treated with camrelizumab: A case report and literature review*

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Abstract

An 83-year-old Chinese woman presented with a 3-month history of dysphagia. She also had a history of hypertension, type 2 diabetes, fundus hemorrhage, and cataract but no history of cutaneous, ocular, or other-site melanomas. Upper gastrointestinal tract angiography revealed gastritis and duodenal diverticulum; thus, an endoscopic review was recommended. Enhanced computed tomography of the chest and upper abdomen revealed the following: (1) Esophageal space-occupying lesions and mediastinal lymph node enlargement (considering the high possibility of esophageal cancer, further endoscopy was recommended) and (2) A small amount of right pleural effusion, with no significant lymph node infiltration or distant metastasis. Esophagoscopy identified a bulge mass blocking the esophagus from 23 to 30 cm from the incisors. The upper mass had a spherical clustering, while the lower mass significantly festered. Pathological biopsy samples were obtained from the esophagus 23 and 28 cm from the incisors. Tissue biopsy showed proliferation of large round tumor cells and melanocytes. Immunohistochemistry showed positive findings for HMB45 and MelanA; partially positive findings for S100, CK7, CK5/6, CAM5.2, LCA, P63, and TTF-1; and negative findings for Syn. The Ki-67 positivity index was approximately 60%. Based on these findings, the patient was diagnosed with malignant esophageal melanoma with enlarged mediastinal lymph nodes. She was then treated with five cycles of camrelizumab therapy combined with chemotherapy from October 18, 2019, to May 5, 2020. Gastroscopy review following two courses of combination therapy revealed that the esophagus was 23–25 cm away from the incisors, and there were two continuous uplifted and beaded masses that had a smooth and black surface, with each of them having a length and diameter of approximately 1 cm. Melanosis of the mucosa around the lumen was observed at 40 cm from the incisors to the cardia; the dentate margin was clear; and the cardia had no stenosis. The patient then received five courses of combination therapy and became consistently stable after partial remission. No severe adverse events related to the immunotherapy were recorded. Camrelizumab may be a viable treatment option for patients with PMME. Additional evidence from future clinical trials and research is necessary to fully validate our findings.

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Key words: primary malignant melanoma of the esophagus; PD-1 mAb; camrelizumab; immunotherapy

Melanoma is the fifth most common cancer in the United States and accounts for 5.6% of newly diagnosed cancers [1]. It is characterized by uncontrolled proliferation of melanocytes mainly found in the epidermis and constitutes 91.2% of all melanomas [2]. The non-cutaneous forms of primary melanoma include ocular and mucosal lesions and represent 5.2% and 1.3% of all melanomas, respectively [2–3]. The mucosal subtypes arise most commonly in the head and neck and far less commonly in the gastrointestinal and urogenital tracts [2]. In particular, primary esophageal melanoma is exceedingly rare and accounts for 0.5% of newly identified primary melanomas [4]. Primary malignant melanoma of the esophagus (PMME) is a much extremely rare disease accounting for

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0.1%–0.2% of all malignant esophageal tumors and 0.5% of all non-cutaneous melanomas [5–6]. It is highly aggressive with a high potential for metastasis. Almost half of patients with PMME have distant metastasis upon diagnosis, and the 5-year survival rate is between 2.2% and 37.5% [7–10]. The diagnosis of PMME should be based on the combination of morphological examination, pathological examination, and immunohistochemistry findings [8]. The main treatment remains to be radical resection of the tumor. However, the optimal adjuvant therapies for PMME have not yet been established [8]. Patients with PMME tend to have a poorer response to chemotherapies than do those with other melanomas, and previous studies have indicated that the currently available treatment is insufficient. The clinicopathological characteristics of PMME have been rarely reported, and no comprehensive treatment strategy has been established because of the lack of cases and strong evidence. Recently, immunotherapy has been the preferred choice for unresectable or metastatic melanomas, and as a result, the prognosis of patients with cutaneous metastatic melanoma has improved. Camrelizumab is a fully humanized IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody. It has been shown to yield a more favorable survival benefit in previously untreated patients with metastatic melanoma not harboring a BRAF/C-KIT/NRAS mutation [11]. Herein, we report the case of an elderly patient with PMME and multiple mediastinal lymph node enlargement who was successfully treated with camrelizumab without recurrence.

Case presentation

An 81-year-old Chinese woman visited the Zhengzhou Puyang People's Hospital on September 10, 2019 and presented with a 1-month history of dysphagia and consequently, weight loss. She also had a history of type 2 diabetes for 20 years, fundus hemorrhage and cataract for many years, and hypertension for 10 years but no family or medical history of other-site melanomas. On October 1, 2019, the patient visited the Liaocheng People's Hospital. Considering the presence of esophageal occupancy, gastritis, and duodenal diverticulum based on the upper gastrointestinal tract angiography findings, an endoscopic review was recommended. Enhanced computed tomography (CT) of the chest and upper abdomen (Fig. 1) conducted on October 8, 2019 upon visit to the Affiliated Qingdao Hiser Hospital of Qingdao University revealed the following: (1) esophageal space-occupying lesions and mediastinal lymph node enlargement (considering the possibility of esophageal cancer, further endoscopy was recommended) and (2) a small amount of right pleural effusion. Gastroscopy (Fig. 2) revealed that the esophagus was 23 cm from the portal bump or blocked the lumen, and the mass continued until 30 cm from the portal. The upper mass had a spherical clustering, while the lower mass showed significant ulceration. Pathological biopsy samples were obtained from the esophagus 23 and 28 cm from the incisors. Immunohistochemistry showed positive findings for HMB45 and MelanA; partially positive findings for S100, CK7, CK5/6, CAM5.2, LCA, P63, and TTF-1; and negative findings for Syn. The Ki-67 positivity index was approximately 60%. Based on these findings, the patient was diagnosed with malignant esophageal melanoma (Fig. 3). Considering the specific situation of the patient, her family refused surgery and further genetic testing. A total of five cycles of immune checkpoint inhibitor therapy combined with chemotherapy were administered from October 18, 2019, to May 5, 2020. According to the National Comprehensive Cancer Network (NCCN) guidelines for malignant melanoma treatment and based on the dominant effect of the latest domestic PD-1 mAb of camrelizumab beads in the treatment of malignant melanoma, she was started on intravenous administration of camrelizumab (200 mg, once every 3 weeks; Jiangsu Hengrui Pharmaceutical Co., Ltd., S20190027) + dacabzine (0.3 g, 1–5 days every 3 weeks; Nanjing Pharmaceutical Factory Co., Ltd., H32026231) + cisplatin (20 mg, 1–5 days; 65 mg/m^2, every 3 weeks; Qilu Pharmaceutical Co., Ltd., H20023460) + vincristine (1 mg, 1–2 days; 1.2 mg/m^2, every 3 weeks; Zhejiang Hanzheng Pharmaceutical Co., Ltd., H20043326). During chemotherapy, one to two degrees of nausea, vomiting, and loss of appetite were observed; meanwhile, no obvious myelosuppression and skin capillary hyperplasia were noted. The regimen was adjusted during cycle 4 owing to severe gastrointestinal reactions as follows: camrelizumab (200 mg, 1 day before chemotherapy, every 3 weeks; Jiangsu Hengrui Pharmaceutical Co., Ltd., S20190027) + dacabzine (0.3 g, 1–5 days every 3 weeks; Nanjing Pharmaceutical Factory Co., Ltd., H32026231) + nedaplatin (30 mg, 1–3 days; 60 mg/m^2, every 3 weeks; Qilu Pharmaceutical Co., Ltd., H20050563) + vindesine (4 mg, once every 3 weeks; Shandong Luoxin Pharmaceutical Group Co., Ltd., H20067018). During cycle 4, grade 1 fatigue was the only adverse event observed, and the partial treatment response was maintained for only 15 days. However, all treatments were discontinued for approximately 100 days owing to the nationwide coronavirus disease outbreak in 2019. Thereafter, cycle 5 was continued (protocol versus cycle 4). No severe immunotherapy-related adverse events (irAEs) were recorded. Eating limitations were significantly reduced after cycle 1 therapy combined with chemotherapy and gradually disappeared after cycle 3; thereafter, the patient gained weight. Gastroscopy (Fig. 4) conducted after two cycles of treatment on December 4, 2019 revealed the following: The esophagus was 23–25

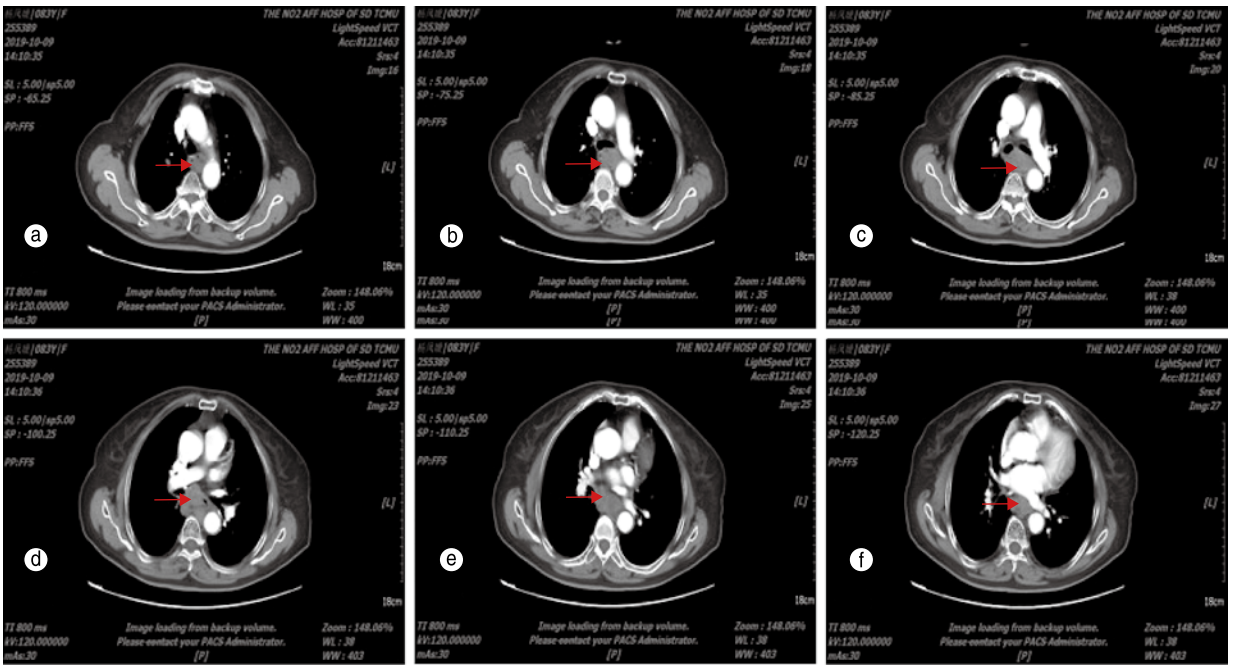

Fig. 1 CT enhancement of chest + upper abdomen on December 9, 2019 shown: esophagel occupying lesions, the lumen was significantly narrow and mediastinal lymph node enlargement (the red arrow shows); pleural effusion on the right side (small amount)

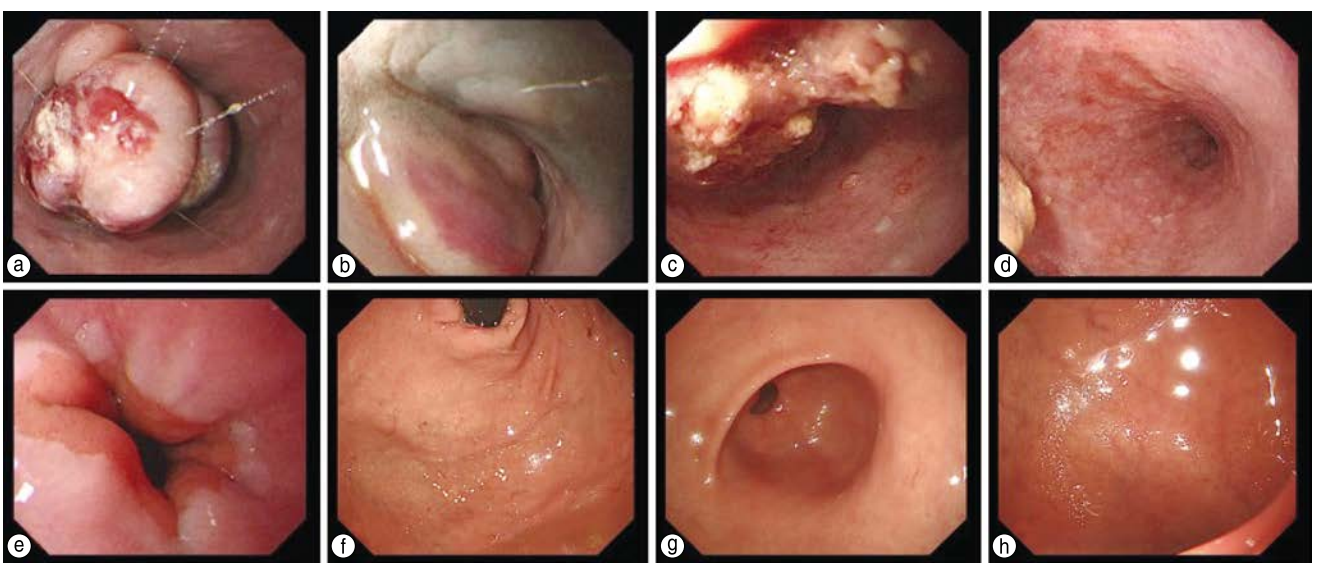

Fig. 2 Gastroscopy shown: (a) incisor to esophagus 23 cm (b) incisor to esophagus 23 cm, (c)incisor to esophagus 28 cm, (d)incisor to esophagus 30 cm, (e) dentate margin, (f) fundus ventriculi, (g) sinuses ventriculi, (h) duodenal bulb; The esophagus from the incisor 23 cm bulge mass block lumen, lumen stenosis, the endoscope is blocked, the mass continued to the esophagus 30 cm from the incisor, the upper segment of the mass is cluster spherical, bright surface sense, local surface ulceration with bleeding, the lower mass ulceration is obvious, covered with moss. From 35 cm from the portal to the cardia, the tooth line is clear and the cardia is not narrow. The gastric floor mucosa is congested and edema, clear, extended after inflation, and the mucus lake is clear and medium. The gastric is curved. Gagastric sinus mucosa congestion and oedema. The door is round, comfortable contraction. The duodenal bulb and lower mucosa are smooth and smooth without stenosis. The esophagus was taken on biopsy 23 cm from the inciaors and 28 cm from the mass,and the upper segment was more brittle and suffered more bleeding. The lower segment of the mass is hard, bleeding can be

cm from the incisors, with two continuous beaded-like bulge masses that had a smooth and black surface and a diameter of approximately 1 cm; melanosis of the mucosa around the lumen was observed at 40 cm from the incisors to the cardia; the dentate margin was clear; and the cardia had no stenosis. Endoscopic ultrasound ring scan (Fig. 5) revealed that at the esophageal bulge, there was a lesion of approximately 1 cm in diameter located in the mucosal

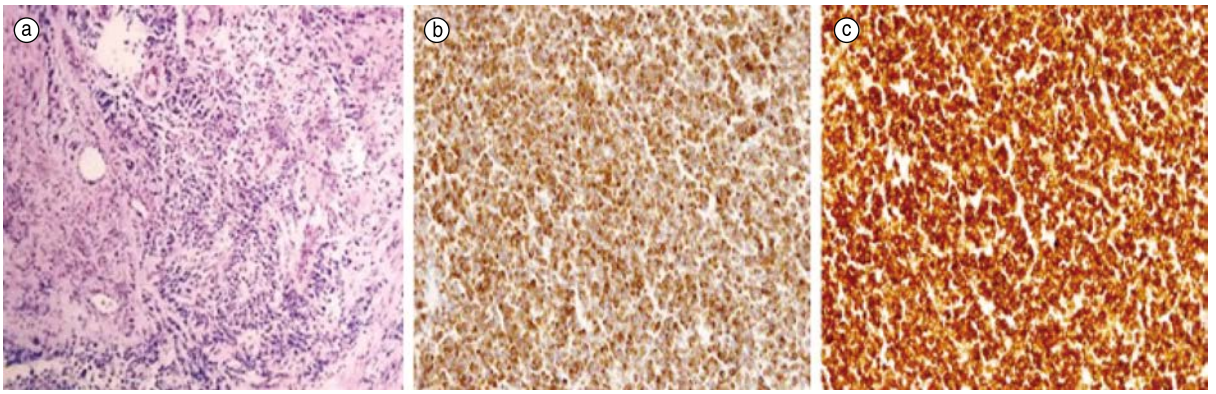

Fig. 3 (a) There was solid proliferation, and tumor cells had large round nuclei. Melanin pigmentation was sparse (HE staining × 100); (b) Tumor cells were difusely positive (HMB-45 immunostaining × 100); (c) Tumor cells were difusely positive (Melan-A immunostaining × 100)

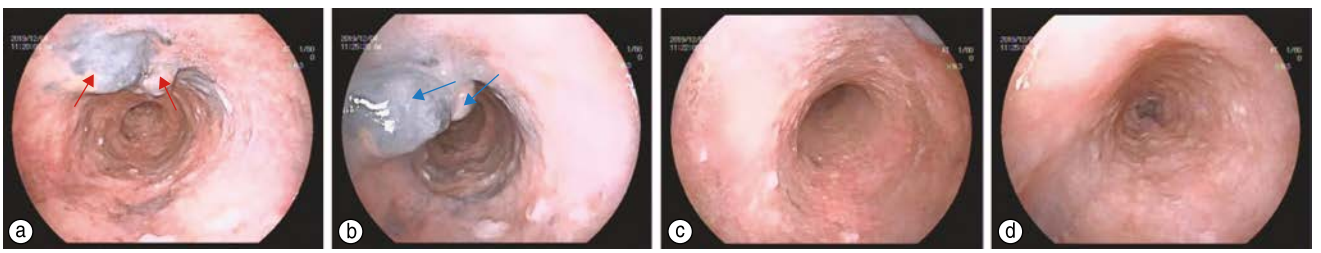

Fig. 4 Review occurred after 2 cycles of treatment on 4 December 2019, as indicated by gastroscopy: the esophagus is seen 23 to 25 cm from the incisors in two continuous bulge masses (red arrow), beaded-like, each raised about 1 cm in diameter, with a smooth black; from aisors 40 cm to the cardia with clear dentate margin (purple arrow) and no atenosis in the cardia (green arrow)

layer, and the echo was heterogeneous. CT (Fig. 6) after two cycles of treatment revealed a significantly better disease status reaching partial remission. CT (Fig. 7) after four cycles of treatment showed that the esophageal tumor continued to shrink; normal swallowing function returned; and the patient condition became stable.

Discussion

Malignant melanoma of the gastrointestinal tract is usually a metastasis from a primary cutaneous source. PMME is extremely rare, accounting for only 0.1%–0.2% of all tumors of the esophagus [12–13]. The incidence of malignant melanoma has increased over the past few decades, and approximately 132,000 individuals develop malignant melanoma each year worldwide [11]. Almost all malignant melanoma cases arise from the skin, and it is reported that only 1% of melanomas arise from the mucosa (head and neck, eyes, and genitourinary and alimentary tracts) [14]. PMME most commonly occurs in men, with a male-to-female sex ratio of 2:1, and the average age of onset is 60.5 years. The tumor is usually located in the middle and lower third of the esophagus (76.2%) [15–16]. Herein, we report a case of recurrent PMME successfully treated with camrelizumab. After the treatment, the difficulty in swallowing and weight loss symptoms dramatically decreased; the patient condition became stable and the survival rate increased; and no irAEs were observed. The patient received camrelizumab therapy for 5 months and showed no further signs of clinical disease progression. Although melanomas arising from the mucosa generally have a worse prognosis than those arising from cutaneous sites, no intrinsic risk factors and specific treatment options have been established. Furthermore, there is no evidence of a difference in sensitivity to camrelizumab therapy between skin and mucosal melanomas. Wang *et al.* [13] reported that in 76 patients, PMME occurred more commonly in men, with a male-to-female sex ratio of 2.17:1. The majority of patients with PMME are symptomatic on diagnosis, with dysphagia being the most common major symptom, as was observed in our case. Concerning the locations of PMME tumors, 92.1% are located in the middle and lower portions of the esophagus, while half of the tumors invade the muscularis propria or further. On endoscopy, PMME usually presents as a well-circumscribed, solid, polypoid tumor with black or purple pigmentation on the surface, sometimes accompanied by ulcers and bleeding [16–17]. In contrast, metastatic melanoma usually has multiple nodular lesions and may be distributed in various parts of the gastrointestinal tract [18]. However, some PMME cases present as a flat lesion [19] or as multinodular lesions that

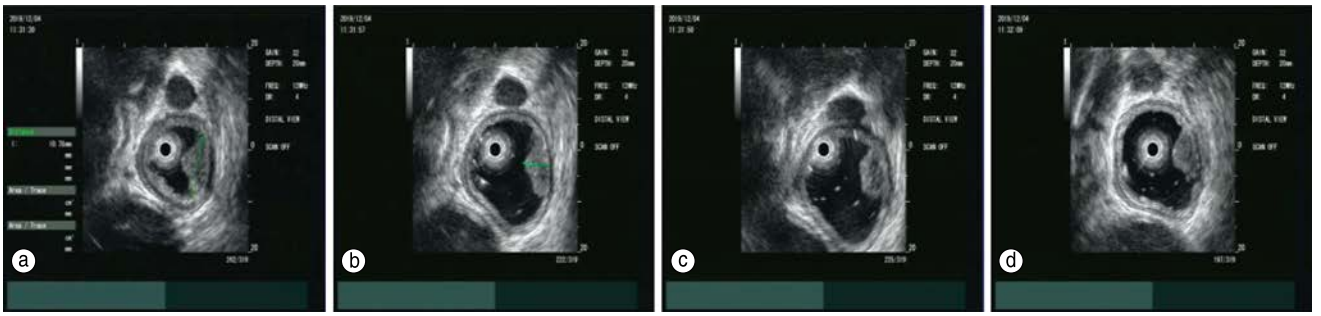

Fig. 5 Ultrasound endoscopic ring scan: At the esophagel bulge, see a lesion of about 1 cm in diameter, located in the mucosal layer, and the echo is heterogeneous

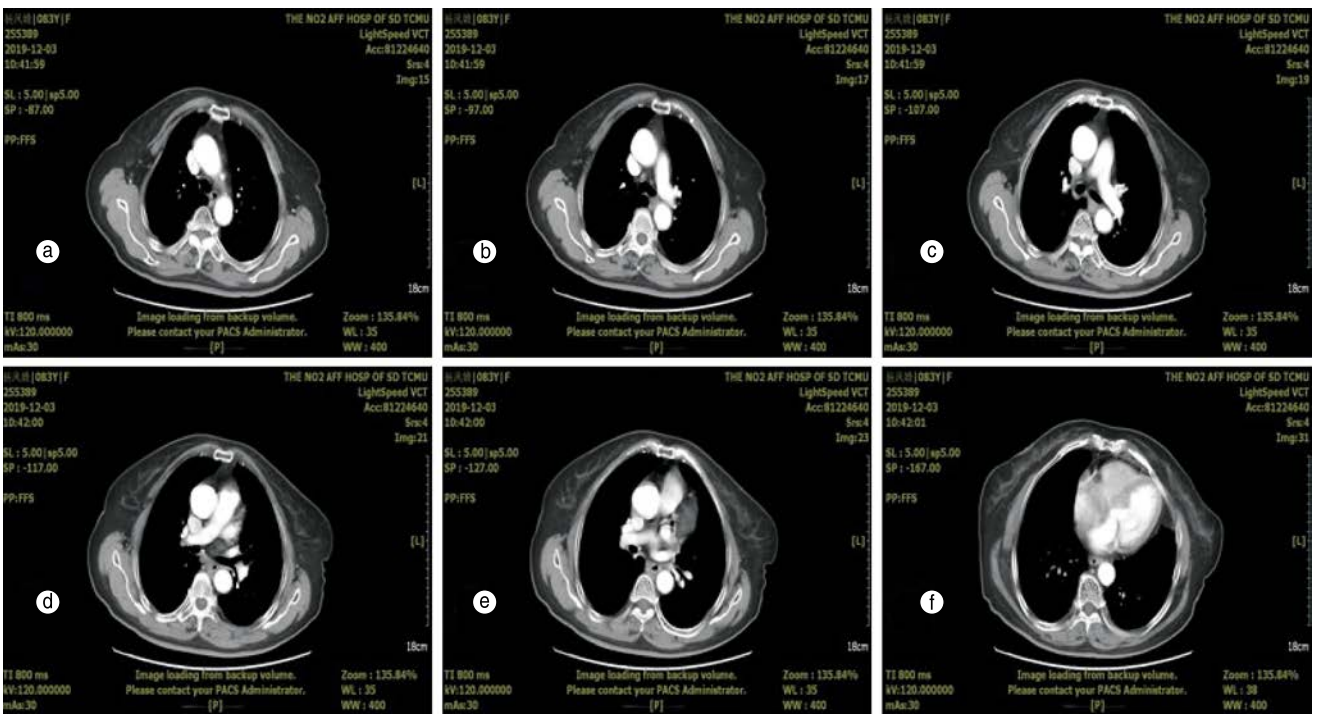

Fig. 6 CT after 2 cycles of treatmnet on December 3, 2019 shown: After esophageal melanoma chemotherapy, the review was significantly better than before, reaching partial remission. The eaophageal occupation decreased signififcantly compared with the previous one, and the mediastinal lymph nodes decreased significantly

are difficult to distinguish from metastatic lesions [20–21]. Surface pigmentation is characteristic of gastrointestinal melanoma. However, some melanomas lack melanin (i.e., the so-called amelanotic melanomas); these account for 10%–25% of all PMME cases and are extremely difficult to distinguish from other tumor types [22]. An accurate preoperative diagnosis of primary malignant melanoma is difficult to make from a biopsy specimen because the biopsy results are easily misinterpreted as indicating undifferentiated carcinoma. Repeated endoscopic biopsy may be required [23]. A definite diagnosis of melanoma depends on an immunohistochemical examination showing positive results for S100 protein, HMB45, and neuron-specific enolase [18].

Surgical resection is the most common treatment, with 77.6% of patients undergoing subtotal esophagectomy or esophagogastrostomy with lymph node dissection. Despite complete excision, recurrence occurred in 89.7% of patients in previous studies. In addition, the interval between primary surgery and recurrence was only 4.5 months [13]. The risk of recurrence is extremely high after an initial staging surgery, which likely reflects the aggressive characteristics of PMME and the important role of adjuvant therapy. Indeed, adjuvant therapy has been shown to increase recurrence-free survival (RFS) and to have varying effects on overall survival (OS) in patients with cutaneous melanoma [24]. A previous trial has suggested that temozolomide-based adjuvant

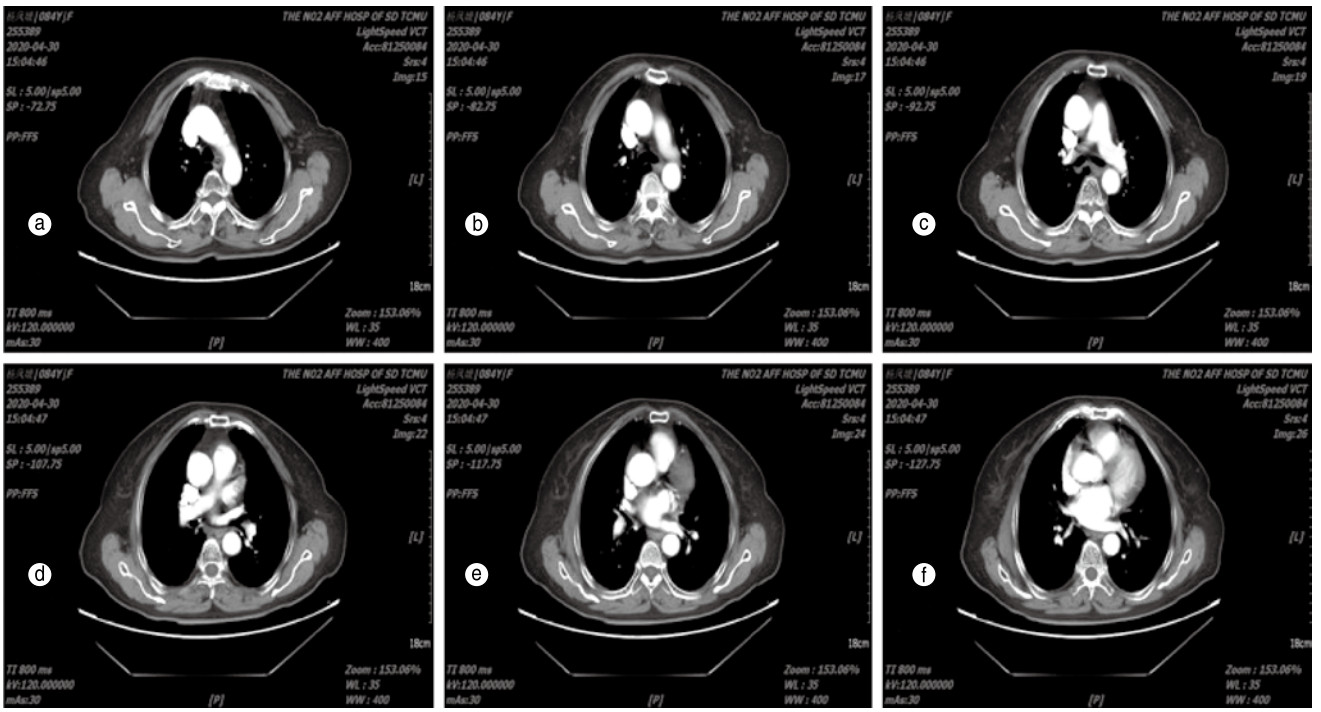

Fig. 7 After 4 cycles of treatment, the reexamination of CT on April 30, 2020 shown: esophageal tumor continued to shrink, and normal swallowing showed no uncomfortable symptoms, and the condition was stable

chemotherapy can improve both RFS and OS in patients with mucosal melanoma [25]. However, because of the rarity of PMME, optimal adjuvant therapies have not yet been established. Postoperative adjuvant chemotherapy may be considered for patients with PMME because it can significantly improve RFS. However, even with adjuvant chemotherapy, the RFS is still much lower in PMME than in other subtypes of mucosal melanoma [25]. A previous phase 3 randomized trial has suggested that adjuvant therapy with ipilimumab can treat stage III melanoma based on a significantly prolonged RFS [26]. In addition, CheckMate 238 showed that among patients undergoing resection of stage IIIB, IIIC, or IV melanoma, adjuvant therapy with nivolumab resulted in a significantly longer RFS and a lower rate of grade 3 or 4 adverse events than did adjuvant therapy with ipilimumab [27]. A previous open-label phase IB trial has shown that the combination of toripalimab with axitinib was tolerable and showed promising antitumor activity in patients with treatment-naive metastatic mucosal melanoma. The patients enrolled in this previous study were all Asians, and the combination therapy used must be validated in a randomized phase III trial that includes a non-Asian population before it can become a standard of care [28]. Camrelizumab combined with apatinib for advanced acral lentiginous melanoma (ALM) phase II research has achieved excellent efficacy is known as a landmark research on acroterminal malignant melanoma. In the initial treatment of metastatic ALM, apatinib combined with camrelizumab not only was safely tolerated but also improved anti-tumor activity and progression-free survival (PFS), benefitting OS. The most common type of melanoma in Asian populations is acroral melanoma. Meanwhile, the incidence of acral melanoma in European and American populations is less than 5%, and the effectivity rate of PD-1 mAb in acroral melanoma treatment is only approximately 14%. The objective response rate (ORR) of camrelizumab combined with apatinib was 22.2%; the DCR reached 77.8%; and the median PFS reached 8 months in patients with metastatic ALM [11]. Moreover, immunotherapy may be effective as adjuvant therapy for patients with PMME.

The role of systemic therapy for metastatic or unresectable PMME remains unclear. The first-line systemic therapy for melanoma is immunotherapy, including nivolumab, ipilimumab, and pembrolizumab, according to the NCCN guidelines. In previous studies, camrelizumab also showed a better therapeutic effect. The traditional cytotoxic chemotherapies have displayed very minimal efficacy against advanced-stage PMME. The overall response rate of chemotherapy in a previous cohort study was only 10.9%, with a short PFS of only 3 months [27]. Other studies have also shown unsatisfactory results of chemotherapy. Over the past decade, the introduction of novel therapies has drastically improved the survival of patients with advanced melanoma, and these therapies are broadly grouped into immune checkpoint inhibitors

(immunotherapy) and BRAF or MEK inhibitors (targeted therapy) [29]. Immune checkpoint inhibitors nivolumab, ipilimumab, and camrelizumab are novel treatment agents for malignant melanoma. These drugs have been reported to demonstrate a substantial clinical benefit for patients with metastatic melanoma, with an ORR of 31.0%–40.0% [30]. A number of previous case reports have suggested that the usefulness of immunotherapy with nivolumab for PMME may be comparable to that for melanoma of other organs. Patients with metastases at the time of diagnosis had a median survival duration of 15.8 months, whereas those who developed metastases later or had unresected stage III disease had an average survival duration of 22.8 months from the date of first diagnosis; the median OS from the first diagnosis was 18.5 months [31]. A nationwide study revealed that marked improvements in OS were associated with the use of targeted therapy and immunotherapy in patients with stage IV melanoma with an unknown primary site [29]. Pablizumab is the first PD-1 inhibitor approved for the treatment of advanced melanoma in China, bringing the treatment of melanoma in China into the era of immunotherapy. Melanoma in Chinese populations is mainly composed of acral and mucosal types; thus, it is necessary to further conduct clinical trials and develop original melanoma-specific immunotherapy drugs suitable for the Chinese population. These findings could be used as a basis in clinical practice and the treatment of PMME; however, more studies are required to prove the benefit.

Conclusion

In conclusion, PMME is an extremely rare but highly aggressive tumor. The special pattern of pigmentation should be recognized while performing endoscopy. The diagnosis of PMME requires careful pathological examination and exclusion of other possible origins in the entire body. Early detection and radical resection of the tumor are critical to ensure favorable outcomes. The effect of adjuvant chemotherapy and radiotherapy is uncertain, and data from large clinical multicenter long-term follow-up studies are lacking. With the continuous development and progress of radiotherapy equipment, precision radiotherapy may be an effective treatment strategy for primary malignant melanoma among patients with advanced or poor general state of malignancy. Novel therapies, including immunotherapy and targeted therapy, may improve the OS in patients with PMME. PD-1 inhibitors may represent a promising option for patients with advanced PMME. However, more evidence is needed from future clinical research to further validate their role.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

Gaoyang Lin drafted the manuscript. Yufeng Cao and Xin Zheng treated the patient. Fuman Wang and Daijun Xing helped search articles. All authors have read and approved the manuscript for submission.

Data availability statement

The SEER dataset was used in the creation of this manuscript. All information of the case presentation was available from standard documentation in the patient's electronic medical record.

Ethical approval

Not applicable.

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