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Case Report

Effectiveness of Anti-PD-1 Antibody Monotherapy for the Primary Malignant Melanoma of the Esophagus : A Case Report

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SUMMARY

Primary malignant melanoma of the esophagus (PMME) is extraordinarily rare with a high degree of malignancy and poor prognosis, and a standard therapy remains to be established. The anti-PD-1 antibody nivolumab is a promising agent for various cancers. To our knowledge, this is the first case report of PMME where a complete response was achieved using nivolumab. We report an 80-year-old woman who was diagnosed with PMME with bone metastasis and lymph node metastases. Although dacarbazine combined chemotherapy was performed and continued for six cycles, the primary tumor progressed and liver metastases appeared. The patient then received nivolumab monotherapy. After three cycles, nivolumab monotherapy for PMME resulted in a complete response as shown by positron emission tomography, computed tomography, and esophagogastroduodenoscopy. In our case, nivolumab exerted a curative effect on PMME, thus suggesting that nivolumab can be effective in the treatment of this rare disease.

Key words : malignant melanoma, esophagus, nivolumab

INTRODUCTION

Squamous cell carcinoma accounts for approximately 90% of esophageal cancers in Japan[1~4]. Primary malignant melanoma of the esophagus (PMME) is extremely rare accounting for<0.2% of all of esophageal cancers[5] with high malignancy and poor prognosis. However, an effective standard therapy for PMME remains to be established. In recent years, immune checkpoint inhibitors have emerged as promising therapeutic agents in several cancers. Programmed death 1 (PD-1) protein/programmed death ligand-1 (PD-L1) inhibitors have been reported to demonstrate promising antitumor activity for non-small cell lung cancer, melanoma, renal cancer and such[6]. Although the anti-PD-1 antibody nivolumab was approved for unresectable malignant melanoma in Japan before anywhere else in the world, there are no reports of the anti-PD-1 antibody treatment for PMME that resulted in complete response (CR). Here, we firstly report the efficacy of the anti-PD-1 antibody for malignant melanoma of the esophagus.

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CASE REPORT

An 80-year-old woman, who had received treatment for polymyalgia rheumatica, hypertension, and hyperlipidemia, presented to another clinic complaining of progressive dysphagia in May 2015. She underwent esophagogastroduodenoscopy, and a type 1 tumor of the middle thoracic esophagus was discov-

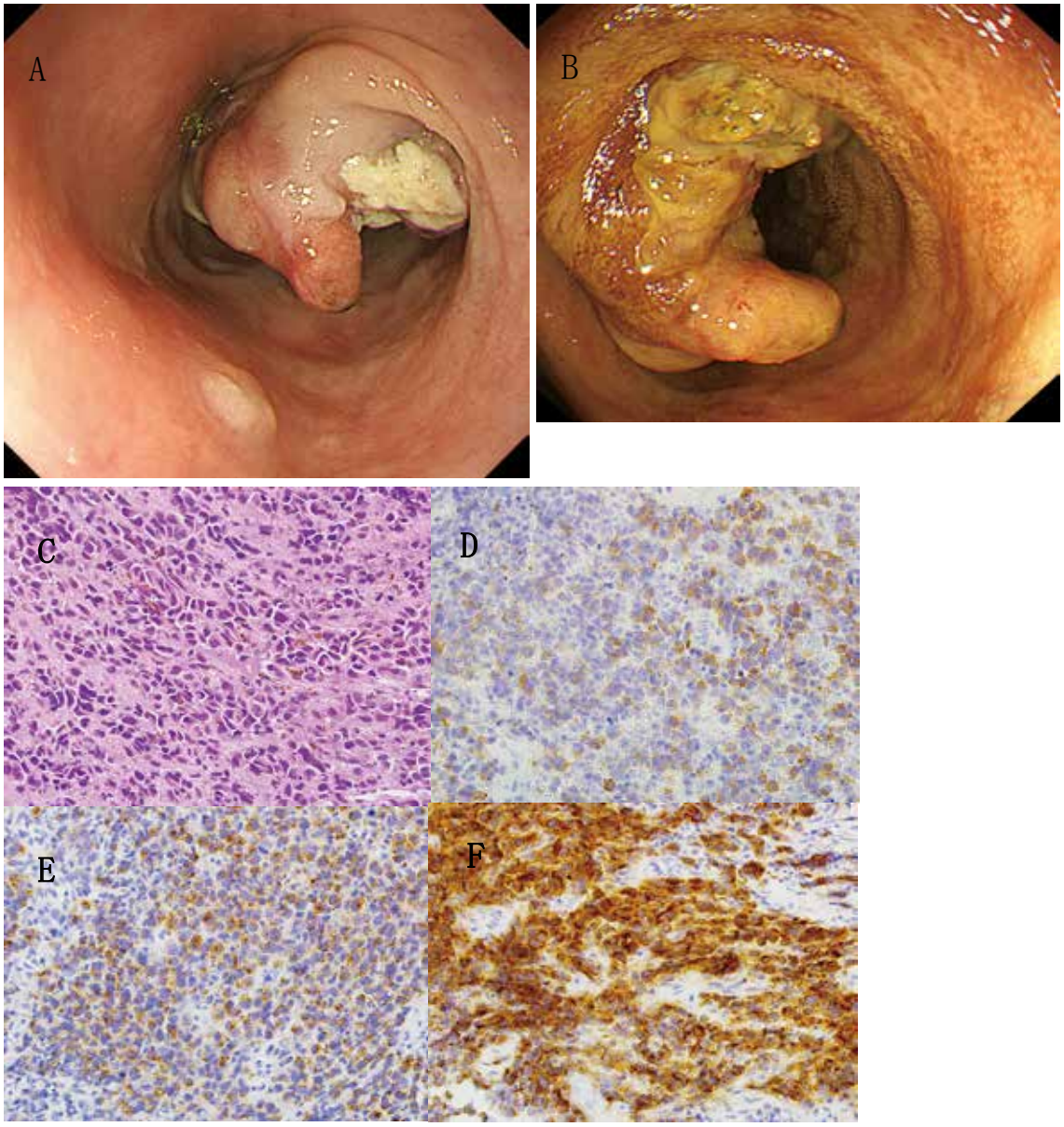

Figure 1

The first esophagoscopy before the first treatment. Type 1 tumor is located in the middle thoracic esophagus (**A**). The tumor has a Lugol-voiding lesion (**B**). Pathohistological examination and immunohistochemistry of the biopsy. Biopsy specimen showed proliferation of atypical cells that have hyperchromatic nuclei in Hematoxylin and eosin staining (**C**). Tumor cells were positive for anti-cytokeratins (AE1/AE3) (**D**), Melan-A (**E**), and human melanoma black (HMB) -45 (**F**).

ered (Fig. 1A, 1B). The patient was then referred to our institution. Routine laboratory investigation results, including tumor maker levels, were normal in June 2015. Malignant melanoma was diagnosed by the initial biopsy because the tumor cells were positive for human melanoma black (HMB)-45 and Melan A but negative for anti-cytokeratins (AE1/AE3), p40, and p63 by immunohistochemical analysis (Fig. 1C-F). There was no indication of invasion to the surrounding organs. In addition, mediastinal and abdominal lymph node metastasis, and bone metastasis of the right femur were detected by computed tomography (CT) and positron emission tomography (PET) (Fig. 2A-C, 3A-D). Finally, based on these results, we diagnosed the patient with unresectable PMME T3N1M1 (bone) Stage IV, according to UICC/TMN Classification of Malignant Tumours, 7th edition, and planned the chemotherapy.

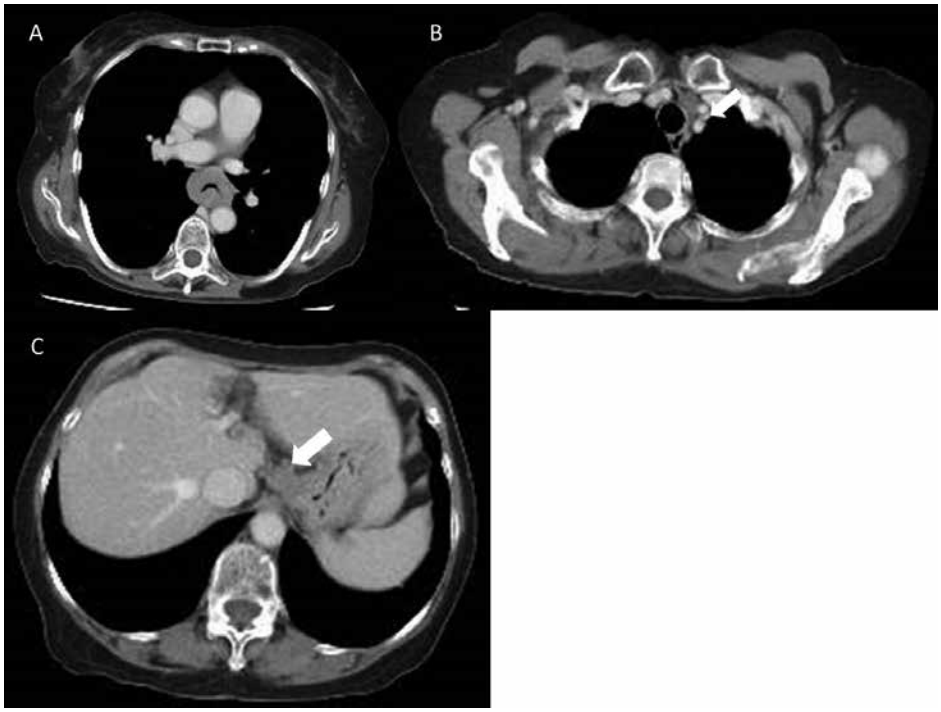

Figure 2

CT before the first treatment. CT shows primary tumor (**A**) and lymph node metastases (**B**, 5, white arrow).

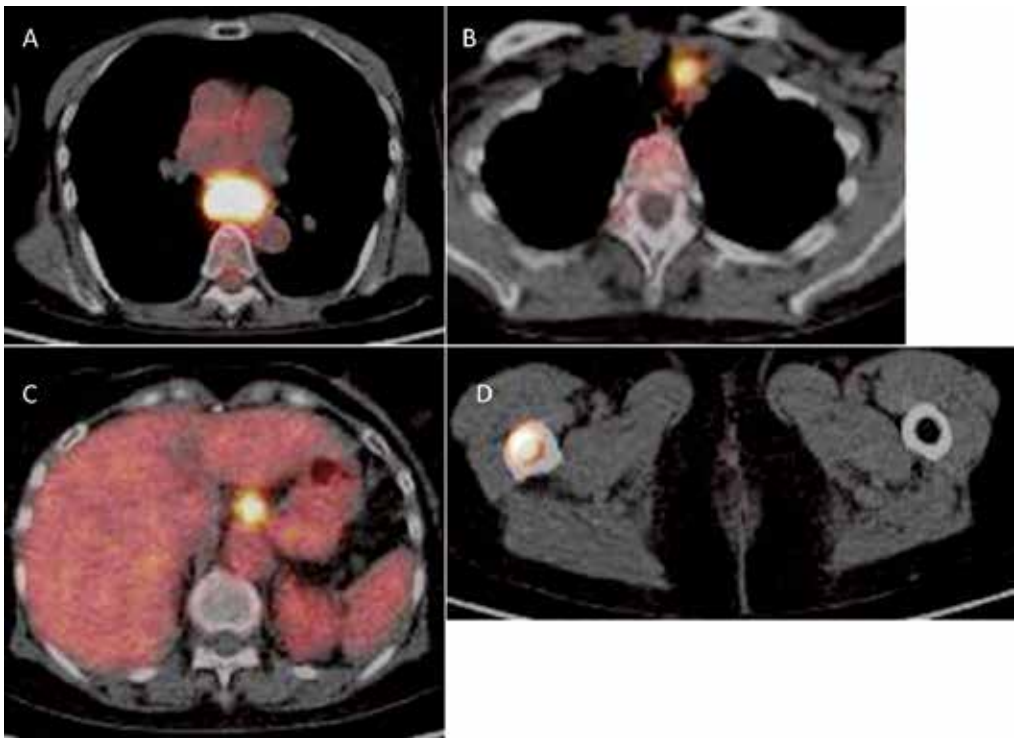

Figure 3

PET before the first treatment. Accumulation of fluorodeoxyglucose is demonstrated in middle thoracic esophagus (**A**), including lymph node (**B**, **C**) and bone metastasis (**D**).

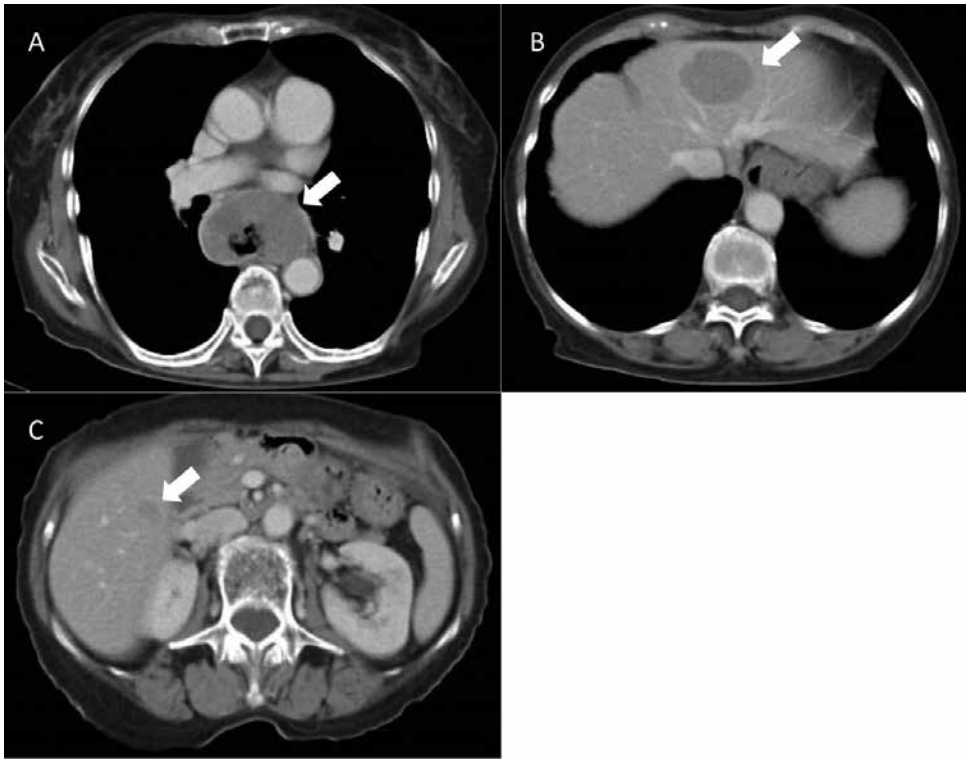

Figure 4
CT after dacarbazine combined chemotherapy. The primary tumor was enlarged (**A**, white arrow) and liver metastases appeared in S3 and S6 (**B**, **C**, white arrow).

DAV therapy consisting of dacarbazine (140 mg/m^2), nimustine (80 mg/m^2), and vincristine sulfate (0.8 mg/m^2) was started in August 2015. We used the World Health Organization (WHO) Response Evaluation Criteria in Solid Tumor (RECIST) to estimate the effect of the chemotherapy. Although it indicated reduction in lymph node metastases and bone metastasis after two cycles of DAV therapy, the primary tumor remained almost the same size, and also an accumulation of fluorodeoxyglucose (FDG), and a liver metastasis appeared in S3. Liver metastasis was detected only by PET. We continued to performed DAV therapy for four cycles because the primary tumor and metastases, except for the liver metastasis, were controlled and there were no adverse events. After four cycles, the lymph node and bone metastases disappeared but the primary tumor and liver metastasis progressed. In addition, a new liver metastasis appeared in S6 (Fig. 4A-C, Fig. 5A-D). Progressive disease remained after a total of six cycles ; thus, we started the anti-PD-1 antibody (nivolumab) monotherapy in March 2016. Nivolumab (2 mg/kg, every three weeks) was administered for three cycles. After three cycles, CT showed that the primary tumor and multiple liver metastases (S3, S6) had shrunken remarkably. PET also revealed the disappearance of FDG in each liver metastases and the primary tumor. Because CT and PET showed that the primary tumor and multiple liver metastases were entirely abolished, and esophagogastroduodenoscopy showed that the primary tumor was obliterated, the outcome of the PMME was graded as CR according to RECIST (Fig. 6A-C, Fig. 7A-D). There were no acute or late toxicities associated with nivolumab. The patient has received nivolumab monotherapy in our hospital and CR has been maintained for five months.

DISCUSSION

Almost all malignant melanomas have been detected in the skin. PMME is extremely rare and difficult to cure because of its remarkably aggressive malignancy with high ability to metastasize[7]. PMME commonly occurs in the sixth and seventh decades of life, with a male to female ratio of 2 : 1, and patients com-

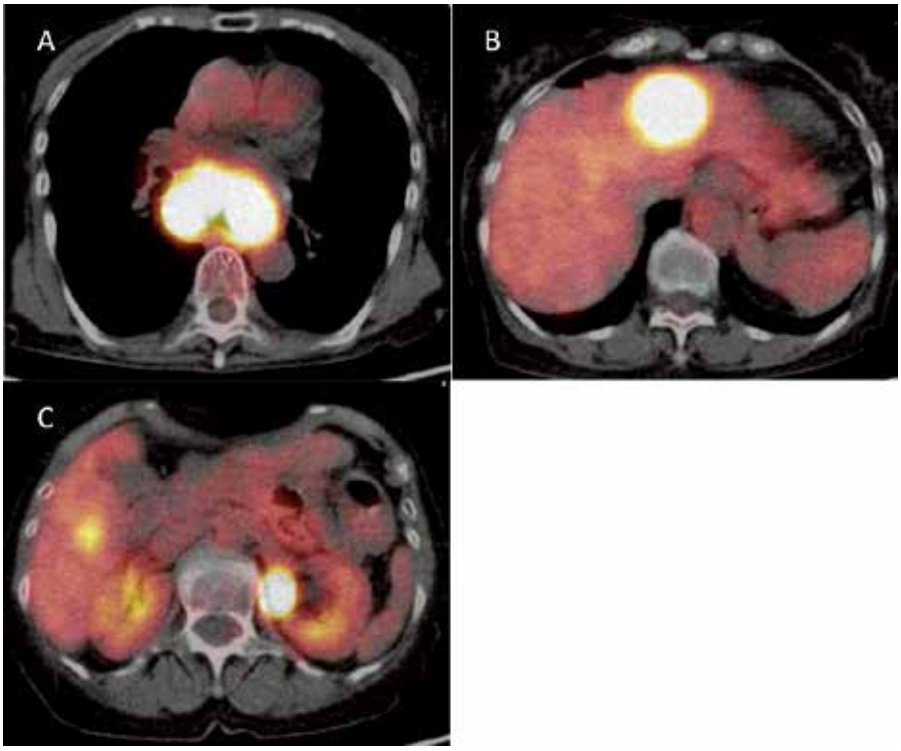

Figure 5
PET after dacarbazine combined chemotherapy. Accumulations of fluorodeoxyglucose are increased in the middle thoracic esophagus (**A**) and appeared in S3 and S6 (**B**, **C**).

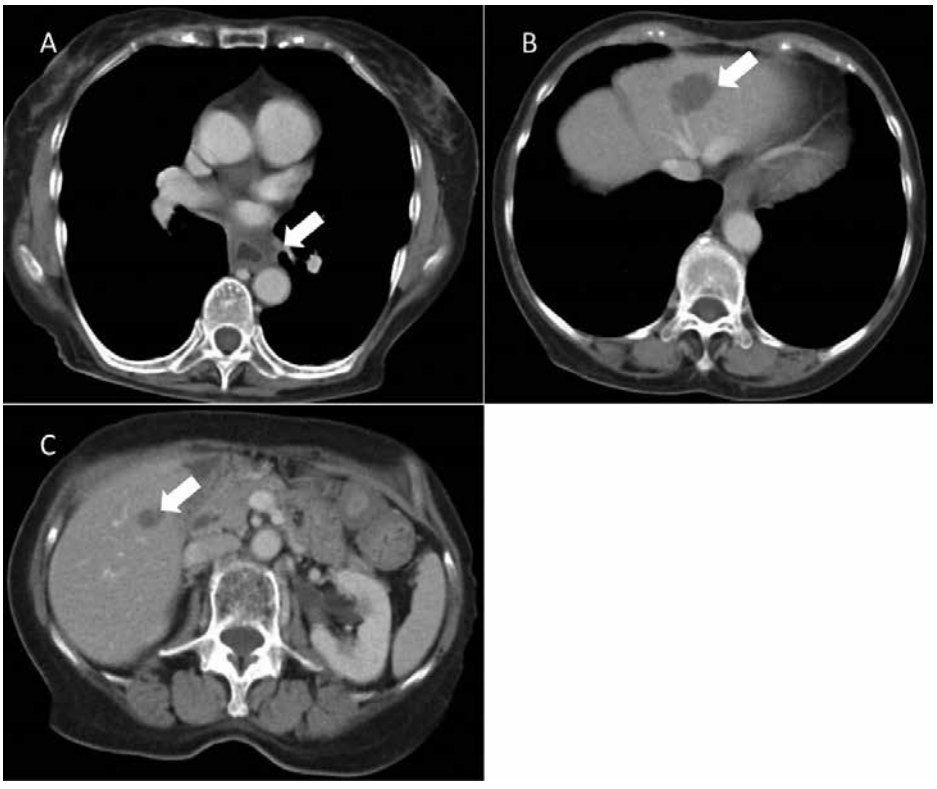

Figure 6
CT after PD-1 antibody monotherapy. The primary tumor (**A**, white arrow) and liver metastases (**B**, **C**, white arrow) shrank remarkably (**A**, white arrow).

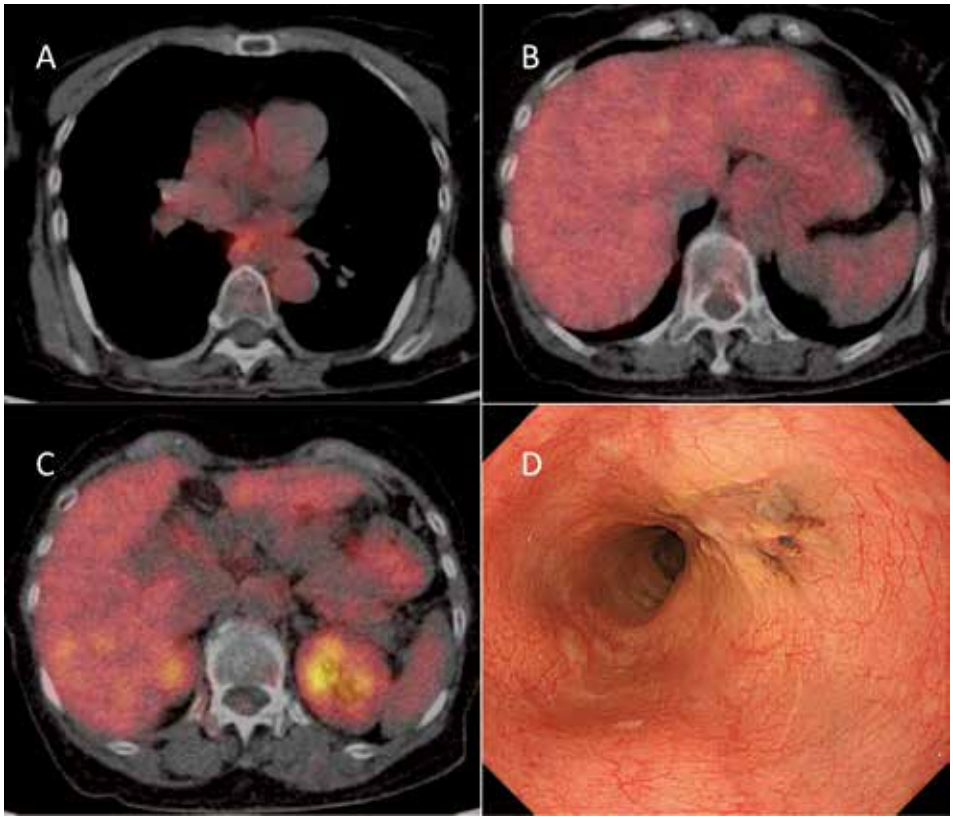

Figure 7
PET and esophagoscopy after anti PD-1 monotherapy. Accumulations of fluorodeoxyglucose are completely abolished in the middle thoracic esophagus (**A**), and S3 and S6 (**B**, **C**). Esophagoscopy also shows the absence of the primary tumor.

plain of dysphagia, similar to other esophageal cancers. A standard treatment strategy remains to be established because of the limited number of cases and a limited evidence proving their efficacy ; therefore, the current prognosis of PMME has yet to reach 40% as 5-year-survival[8,9]. Most current literature focuses on individual case reports, and the largest study of PMME was presented by Shugeng et al. in 2016, which included 17 cases[10]. Surgical resection should be the first choice of treatment when patients have no distal metastases or bulky lymph node metastases. Chemotherapy is an accepted common therapy for cases of inoperable malignant melanoma[10,11], and dacarbazine, the most widely used chemotherapeutic agent for inoperable malignant melanoma, is commonly used as monotherapy or in combination. However, current trials have shown response rates of approximately 5-12%[11~13] and these results had insufficient therapeutic efficacy. Needless to say, it is necessary to improve the current therapeutic methods.

In recent years, immune-checkpoint inhibitors have emerged as a promising therapy to improve the prognosis of various cancers. PD-1/PD-L1 signaling is one of the key interactions between cancer cells and the immune system. Nivolumab is a human IgG4 anti PD-1 monoclonal antibody that regulates T cell activation to suppress tumor cell survival. Some reports have shown that the response rate of advanced malignant melanoma treated with nivolumab therapy was approximately 28-31%[14,15] and nivolumab improved overall survival compared with dacarbazine[16].

Immune checkpoint inhibitors have the ability to induce strong tumor suppression, resulting in a plateau in the tail of the survival curve[17]. In other words, long-lasting antitumor effects and improvement of long-term prognosis can be expected in patients responding to immune checkpoint inhibitors. On the other hand, the response rate of immune checkpoint inhibitors is still inadequately low because of the lack of markers to select the population

responding to the immune checkpoint inhibitors. It is necessary to discover markers to select the responders in future studies. This case report is the first to have demonstrated that an unresectable PMME after dacarbazine combined chemotherapy gained CR by using nivolumab without acute and late toxicities. We believe this case will have a considerable impact on therapeutic strategies for PMME. It is hoped that new strategies or indications for PMME are developed.

Ethical Statement

This study followed the declaration of Helsinki on medical protocol and ethics and all participants signed an informed consent agreement.

Conflicts of Interest

Hiroto Muroi, Masanobu Nakajima, Maiko Kikuchi, Masakazu Takahashi, Yosuke Shida, Keisuke Ihara, Jun Ito, Satoru Yamaguchi, Kinro Sasaki and Hiroyuki Kato declare that they have no conflict of interest.

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