

[ CASE REPORT ]

## Mediastinal Malignant Melanoma Markedly Shrinking in Response to Nivolumab

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### Abstract:

Primary malignant melanoma (MM) of the mediastinum is rare, and there is a lack of consensus regarding the preferred treatment because non-cutaneous MM demonstrates an inferior response to systemic therapy. Herein, we describe the case of a 73-year-old man with MM of the anterior mediastinum with multiple liver metastases. Even though the size of lesions increased rapidly following diagnosis, nivolumab monotherapy caused remarkable tumor shrinkage. This is the first report of mediastinal MM showing a significant response to nivolumab. We, therefore, suggest that immunotherapy may be one of the treatment options for primary mediastinal MM.

**Key words:** mediastinal tumor, malignant melanoma, nivolumab, immunotherapy

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### Introduction

The mediastinum is an extremely unusual site for primary malignant melanoma (MM), with only a few cases reported to date (1-4). A standard method for treating this disease has not yet been established. If possible, complete surgical resection to reduce the tumor mass is recommended for patients with early stage disease (1). However, due to high-grade malignancies and the high degree of invasiveness, the resection rate is generally low in this disease (3). In recent years, immunotherapy has improved the overall survival of patients with advanced melanoma (5). However, it has been suggested that the efficacy of immunotherapy is lower in non-cutaneous melanoma than cutaneous melanoma (6). To our knowledge, there have been few reports regarding the effectiveness of immunotherapy in the treatment of this disease. We describe a rare case in which nivolumab monotherapy was significantly effective against primary mediastinal MM.

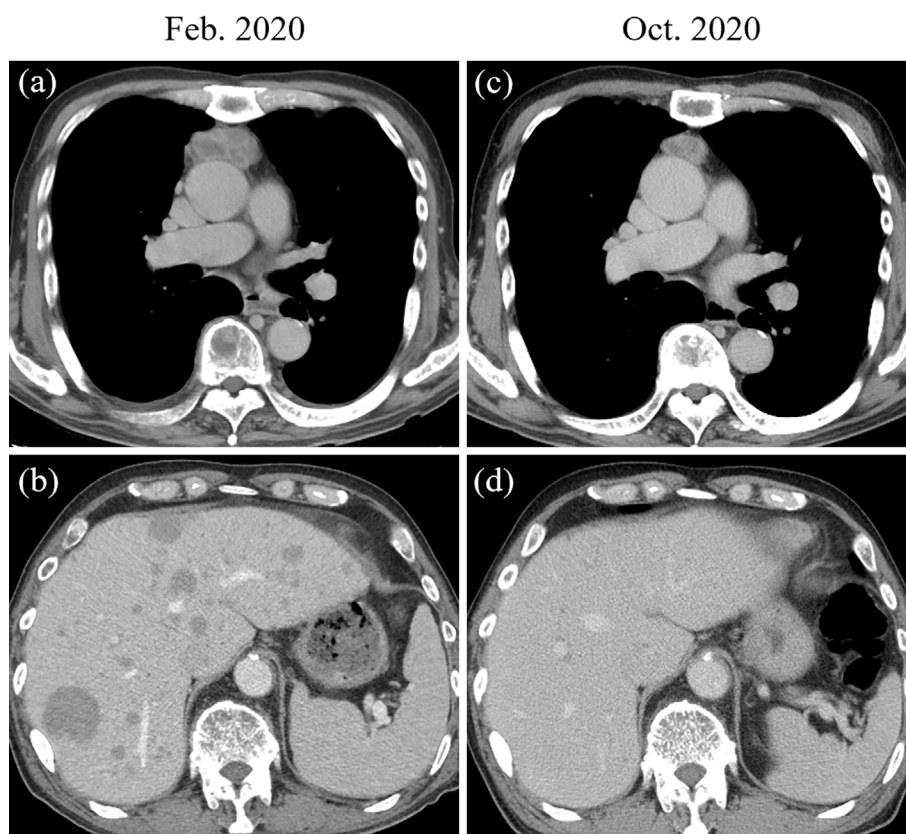
### Case Report

A 73-year-old man presented to another hospital with a one-month history of right hypochondrium pain. On physical examination, no abnormal lesions were seen on the skin, head, neck, scalp, anogenital region, and eyes. However, plain and contrast-enhanced computed tomography (CT) revealed a soft tissue density mass lesion on the right side of the anterior mediastinum (49×26 mm) (Fig. 1a) and multiple space-occupying lesions (SOLs) in the liver (Fig. 1b). To perform a pathological diagnosis using tissue samples, a CT-guided biopsy was performed. Hematoxylin and Eosin staining of the obtained tissues demonstrated that melanin pigment was present in the cytoplasm of malignant cells (Fig. 2A). Additionally, immunohistochemical analysis showed that the cytoplasm of malignant cells expressed astroglial protein (S-100), melanoma antigen (Melan-A), human melanoma black-45 (HMB-45) and preferentially expressed antigen in melanoma (PRAME) (Fig. 2B-D). Based on these results, the patient was diagnosed with malignant

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**Figure 1.** Sequential abdominal and chest computed tomography (delayed image). (a, b) A soft tissue density mass lesion on the right side of the anterior mediastinum and multiple lesions in the liver are shown. (c, d) After immunotherapy, the CT scan revealed a 40% and 100% reduction size of mediastinal mass and liver lesions according to RECIST version 1.1.

melanoma stemming from the mediastinum.

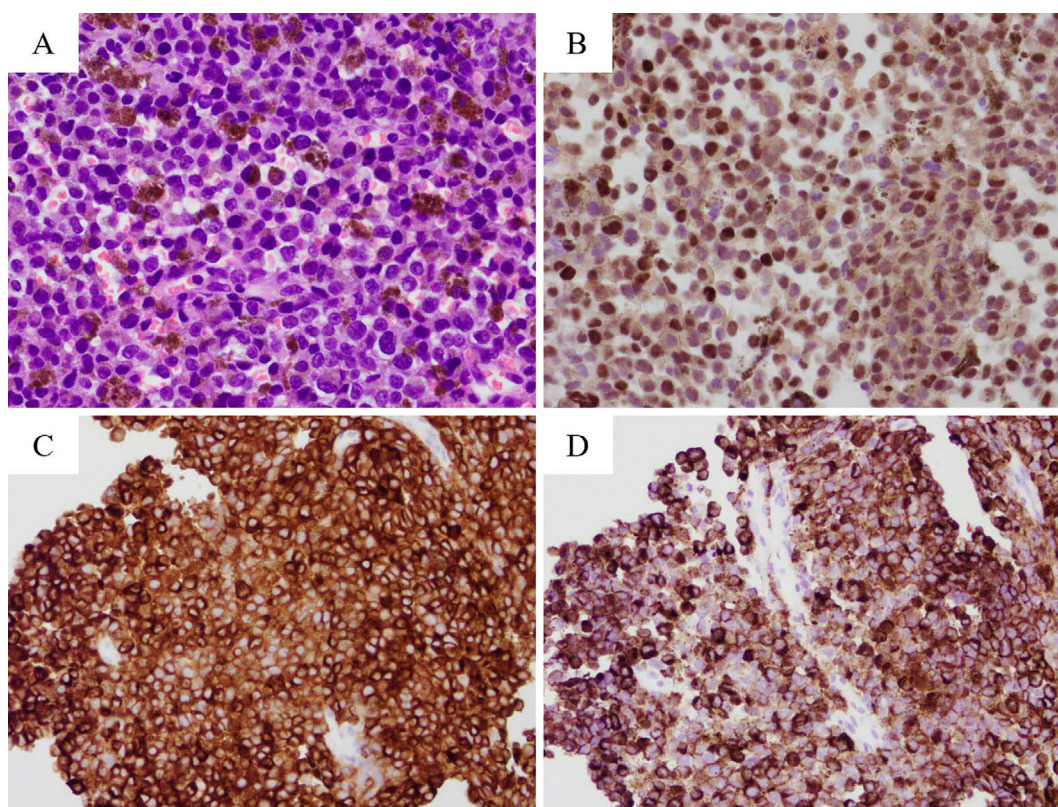
The patient was then referred to our hospital for systemic therapy. At the first visit, laboratory tests revealed anemia (7.1 g/dL), increased alkaline phosphatase (ALP) and lactic acid dehydrogenase (LDH) levels (Table). As a result of performing gastroscopy to detect the bleeding source, diffuse bluish black lesions in the whole stomach with an increased frequency in the corpus and fornix (Fig. 3), which were not found just a month earlier. We started treating him with nivolumab (OPDIVO®, ONO PHARMACEUTICAL Osaka, Japan) 240 mg every two weeks because of the presence of the wild-type *BRAF* gene, which encodes the serine/threonine-protein kinase, *BRAF*. After immunotherapy, ALP and LDH levels had decreased (Fig. 4), and the CT scan revealed a 100% reduction in the size of liver lesions according to Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (Fig. 1c, d). The patient is currently undergoing nivolumab therapy with no adverse events (AEs) noted as of the time of this publication (13 months after the initiation of immunotherapy).

## Discussion

MM accounts for 1.5% of all cancers (2). MM generally presents as a primary neoplasm of the skin but may also arise in other organs and tissues. MM of the mediastinum is

extremely rare, both as a primary and metastatic lesion. Moreover, the prognosis has not been defined, and there is no consensus regarding the preferred treatment for primary or metastatic mediastinal melanoma (3). In the present study, immunotherapy had an obvious effect on the mediastinal and hepatic lesions. To date, there have been few reports regarding the effectiveness of immunotherapy in the treatment of this disease.

It is known that mediastinal tumors account for 50% of mediastinal masses (7). The most frequent tumors in the mediastinum are thymoma, teratoma, lymphoma, neurogenic tumors, and other rare malignancies, such as melanoma (8). Primary MM of the mediastinum is characterized by lesions only at the mediastinum. It has been reported that metastatic mediastinal melanoma in mediastinal lymph nodes arising from unknown primary tumors accounts for 1% to 8% of all melanomas (4). Primary mediastinal melanoma is only diagnosed when other primary melanoma sites are excluded from the body. In this case, the patient had lesions in the mediastinum and liver. The liver lesions showed low signal intensity on T1-weighted and high signal intensity on T2-weighted gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI). These findings are suggestive of metastatic liver cancer, and the most frequent metastasis sites of primary hepatic cancer are the lung, bones, lymph nodes, adre-



**Figure 2.** Pathological examination. (A) Hematoxylin and Eosin staining showing atypical pleomorphic melanocytes with prominent nuclei and melanin pigments ( $\times 400$ ). Immunohistochemical analysis demonstrating that tumor cells were positive for (B) S-100, (C) Melan-A, and (D) HMB-45. S-100: astroglial protein, Melan-A: melanoma antigen, HMB-45: human melanoma black-45

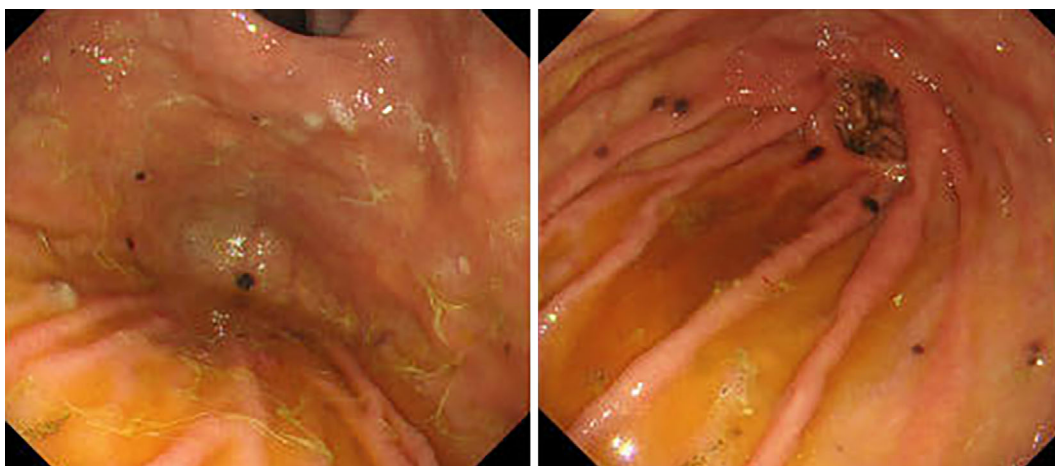
**Table.** Laboratory Data.

WBC	5,820 / $\mu$ L	$\gamma$ GTP	224 IU/L	Cl	106 mEq/L
RBC	$262 \times 10^4$ / $\mu$ L	CPK	34 IU/L	Ca	8.6 mEq/L
Hb	7.1 g/dL	Amylase	67 IU/L	t-Protein	7.0 mg/dL
Ht	22.6 %	t-Bilirubin	1.3 mg/dL	Alb	4.0 mg/dL
Plt	$34.3 \times 10^4$ / $\mu$ L	d-Bilirubin	0.4 mg/dL	FT3	1.84 pg/dL
CRP	4.06 mg/dL	UA	6.1 mg/dL	FT4	1.37 ng/dL
AST	77 IU/L	BUN	21 mg/dL	TSH	$\mu$ U/mL
ALT	52 IU/L	Cr	1.0 mg/dL	HCG- $\beta$	<0.1 ng/mL
ALP	2,033 IU/L	Na	140 mEq/L	SCC	0.4 ng/mL
LDH	2,702 IU/L	K	4.3 mEq/L	sIL-2R	887 U/mL

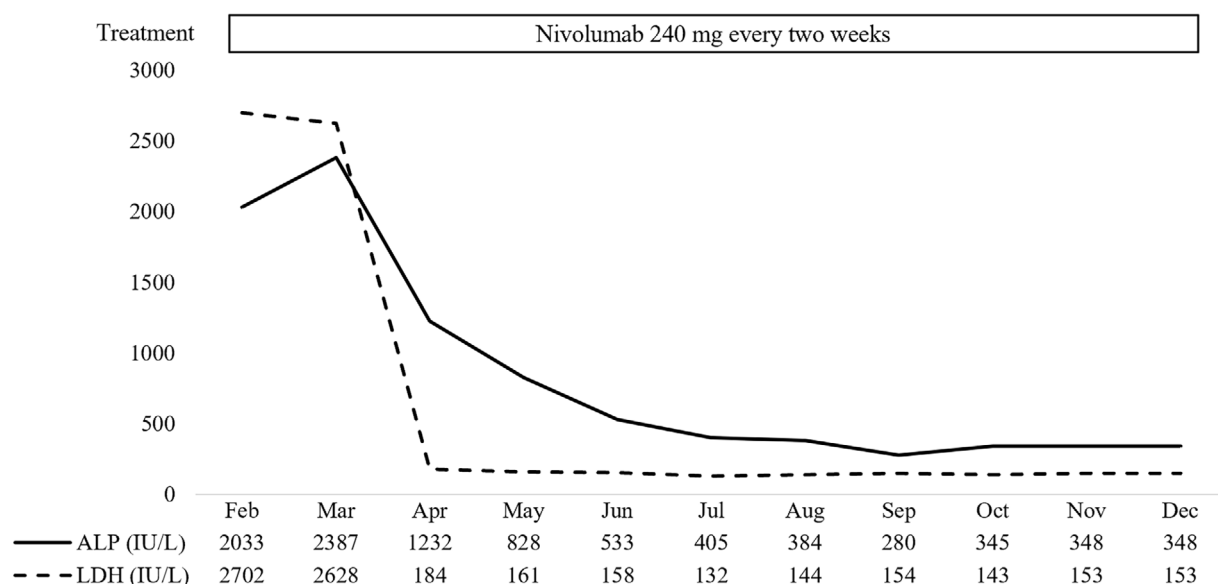
nal glands, and brain (9, 10). It is extremely rare for primary hepatic cancer to metastasize to the mediastinum. Furthermore, current studies suggests that metastasis of unknown primary malignant melanoma occurs most frequently in the lymph nodes (11). However, in this case, no structures of the lymph node was present in the sample collected by the CT guided biopsy. In addition, the patient did not present any lesion that could lead to the suspicion that the primary lesion was cutaneous. Thus, the mediastinal mass is more likely to be the primary lesion in this case.

There is no consensus regarding the treatment of primary or metastatic mediastinal melanoma. If possible, surgical resection is effective in patients with early stage disease. How-

ever, primary mediastinal MM is an aggressive malignancy and can metastasize in the early phase of disease. Hence, the resection rate of this disease is generally low (3). In recent years, immunotherapy has been a breakthrough in the treatment of MM. Ipilimumab targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA 4) was approved by the U.S. Food and Drug Administration for the treatment of unresectable MM in March 2011, and it significantly improves overall survival. Pembrolizumab and nivolumab, drugs targeting programmed death protein-1 (PD-1), have shown superior overall survival and better safety profile than ipilimumab (5). Furthermore, current evidence has shown that combination therapy with ipilimumab and nivolumab resulted in



**Figure 3.** Gastroscope showed the presence of several nonbleeding, bluish to black, gastric lesions a few millimeters in diameter. The patient underwent distal gastrectomy for gastric ulcer (Billroth I).



**Figure 4.** After immunotherapy, ALP and LDH levels significantly decreased.

a higher objective response rate than nivolumab alone. However, the incidence of treatment-related AEs was higher with combination therapy than with nivolumab monotherapy. Particularly, the frequencies of grade 3 or 4 AEs were also higher in patients who received combination therapy than in patients who received monotherapy (59% vs 21%) (5). In this case, the patient came to the hospital from a distant place and also lives alone. Therefore, the patient chose the nivolumab monotherapy because it is safer than combination therapy.

The primary sites for melanoma are the skin (82%), uvea (8%), peripheral body parts (3%), and mucous membrane (2%), with approximately 5% having an unknown primary site. Nivolumab monotherapy led to better median progression-free survival and objective response rates for primary cutaneous melanoma than for other primary melanomas (6). However, in this case, nivolumab monotherapy was significantly effective for primary mediastinal MM.

In summary, this study presents a rare case study of primary mediastinal MM. Melanoma should be considered when evaluating mediastinal masses using thoracic CT. This report suggests that immunotherapy is one of the treatment options for primary mediastinal MM.

**The authors state that they have no Conflict of Interest (COI).**

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