



Case Report

A Case of Primary Malignant Melanoma of the Lung with BRAF V600E Mutation and Distinctive Bronchoscopic Features

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Abstract

A 79-year-old male patient was referred to our healthcare facility because of an abnormal CT shadow detected during follow-up of prostatectomy. The nodules revealed a tendency of increasing in size, and primary lung cancer was suspected. The patient underwent a right lower lobectomy and mediastinal lymphadenectomy via video-assisted thoracic surgery. As there was no evidence of primary disease in other organs, we diagnosed the patient with primary malignant melanoma of the lungs (PMML). Postoperative pathological examination revealed no lymph node metastasis. However, bronchoscopy revealed slight brownish-toned changes in the resection margins of the right lower lobe of the bronchus. Biopsies of the resected margins confirmed the presence of malignant melanoma cells. Owing to the presence of BRAF mutated cells in the surgical specimen, dabrafenib/trametinib treatment was initiated. Subsequent bronchoscopy revealed new brownish-toned changes in the bronchial mucosa from the trachea to the right bronchus, suggesting malignant melanoma. The patient underwent regular bronchoscopic examinations from that time with no major deterioration and is still undergoing treatment. Although PMML has a poor prognosis, in this case, disease control was achieved over a long period through molecular targeted therapy for the BRAF mutation, and bronchoscopy was useful in determining the therapeutic effects.

Keywords: Lung cancer; malignant melanoma; BRAF

Background

Malignant melanoma is a neoplasm of the skin with a poor prognosis that predominantly originates in the integumentary system, mucosal linings, or ocular structures. Primary malignant melanoma of the lungs (PMML) is exceedingly rare, accounting for only 0.01% of all primary pulmonary malignancies [1]. Herein, we report a case of BRAF- mutated PMML that showed melanoma-like bronchoscopic findings and was managed with molecular targeted therapy.

Case Presentation

A 79-year-old male was referred to our healthcare facility for further evaluation of an abnormal computed tomography (CT) shadow detected during follow-up of a prostatectomy. The patient had a history of smoking 20 cigarettes per day for 32 years and was previously diagnosed with atrial fibrillation and prostate carcinoma. The patient remained asymptomatic, and physical examination of the skin, head, neck, and ocular regions was unremarkable. Chest radiography revealed a high-density opacity in the right lower lung field (shown in Fig. 1A), and CT revealed a nodular shadow measuring 25 mm located in the right lower lobe and a peripheral infiltrative opacity (shown in Fig. 1B). Although nonspecific inflammation was initially suspected, subsequent surveillance showed an escalating growth trend, and a malignant tumor of the lung was suspected. 18-FDG positron emission tomography (PET)-CT revealed an abnormal tracer uptake (maximum standardized uptake value, 4.13) at the suspected tumor. One and

a half years after the referral, the patient underwent a right lower lobectomy and mediastinal lymphadenectomy via video-assisted thoracic surgery. The tumor measured 25 mm ×35 mm and was filled with a black mucous plug-like obstruction in the expanded bronchus. The bronchial lumen was the main site of the lesion, with atypical cells and prominent melanin granules (shown in Fig. 2A). Immunohistochemical staining was positive for HMB-45, Melan A and SOX10 (shown in Fig. 2B-D), which was consistent with malignant melanoma. Although an inspection with reference to the whole body was performed, no findings indicating the primary site in dermatology, urology, or gastroenterology were found, and we finally diagnosed the patient with PMML. Postoperative pathological examination revealed no lymph node metastasis; however, a resection margin was involved. Bronchoscopy revealed edematous, brownish-toned changes at the resection margin of the right lower lobe of the bronchus (shown in Fig. 3A). Biopsies of the resected margins confirmed the presence of malignant melanoma cells. Owing to the presence of BRAF V600E-mutated cells in the surgical specimen, dabrafenib/trametinib treatment was initiated. Five months after the start of the treatment, CT revealed no obvious worsening of the disease. Bronchoscopy showed 1) improvement of the brownish tone of the resection margin (shown in Fig. 3B) and 2) a new brownish-toned change from the trachea to the right bronchus (shown in Fig. 3C-D). We performed biopsies of both the lesions. We were not able to pathologically confirm the presence of malignant cells in the lesions but a cluster of melanocytes without atypia. These pathological results led to the decision to continue with the treatment. Subsequently, the brownish tone tended to shrink. Treatment was ongoing for 1 year and 10 months and to monitor the cancer status, regular bronchoscopies were performed.

Figure 1

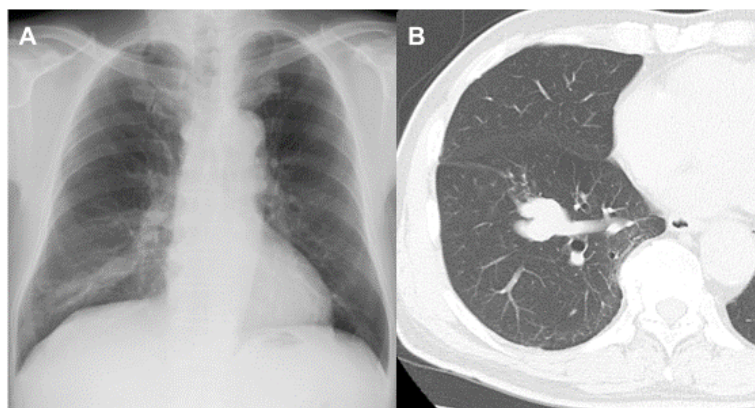


Figure 1:

A. Chest radiograph showing high-density opacity in the right inferior pulmonary field.

B. CT identified a nodular shadow measuring 25 mm located in the right lower lobe and peripheral infiltrative opacity.

Figure 2

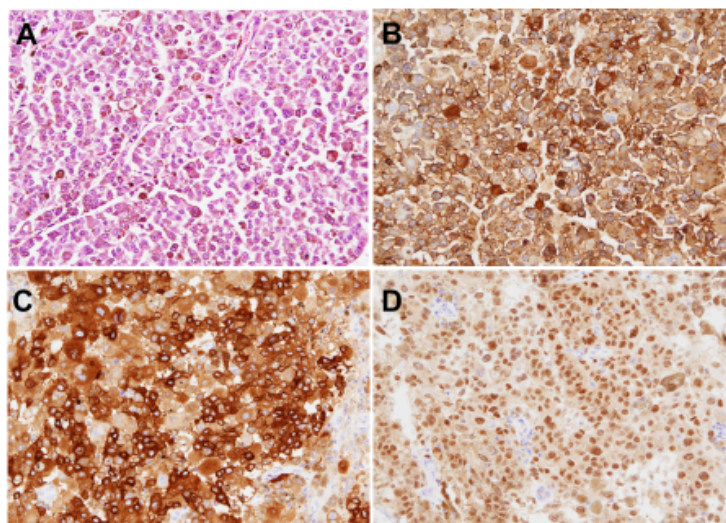


Figure 2:Photomicrograph showing atypical melanocytes (hematoxylin-eosin).

(A) Immunohistochemical features of lung tissue. Positive cytoplasmic staining of the tumor cells

(B) HMB-45, (C) Melan A, and (D) SOX10.

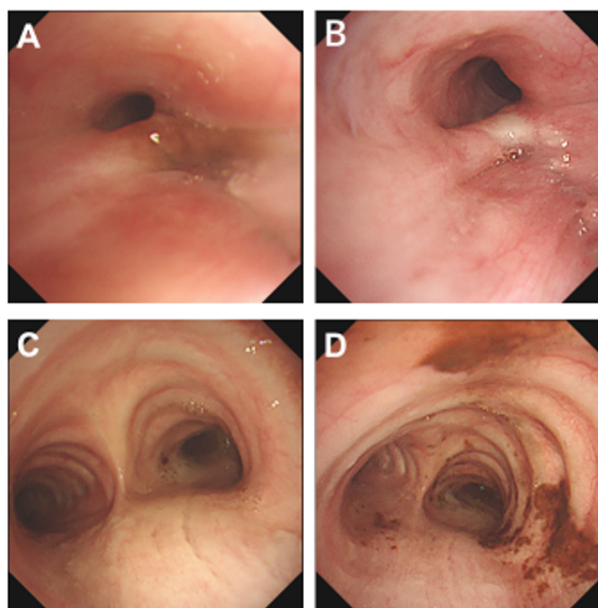


Figure 3:

- A.** Immediately after surgery, bronchoscopy showed brownish changes in the right lower lobe bronchus, and biopsy showed melanoma.
- B.** Five months after the start of treatment, bronchoscopy showed improvement of brownish changes in the right lower lobe bronchus.
- C.** Immediately after surgery, bronchoscopy showed no brownish changes from the trachea to the right bronchial mucosa.
- D.** Five months after the start of treatment, bronchoscopy revealed brownish-toned changes from the trachea to the right main bronchial mucosa

Discussion

Malignant melanoma is a malignant tumor arising from melanocytes that produce melanin and occurs in the skin as well as in mucous membranes, such as the oral cavity and vulva. Malignant melanoma rarely occurs in the lungs, accounting for approximately 0.01% of all primary lung cancers [1]. Symptoms of PMML are nonspecific, including cough, hemoptysis, dyspnea, and chest pain, and are similar to those of other chest malignancies. Malignant melanoma may spontaneously regress after metastasis [2], and it is not always easy to distinguish between primary and metastatic lung lesions. Paliogiannis, et al. reported a mean survival of 24.3 months although only for cases that were relatively early stage tumors in PMML. The mean overall survival was 14.3 months in PMML patients (76 cases), suggesting that PMML was worse than that of early or locally advanced stages of lung cancer or malignant mesothelioma, which are extremely aggressive tumors [3].

In malignant melanoma of the skin, BRAF mutations are found in approximately 30% of Japanese patients and are among the most important genetic mutations [4]. However, the incidence of genetic alterations in PMML remains unclear because of its rarity. To date, there have been only 13 reports of genetic analyses in PMML tumors, in which only 3 tumors (23%) have been reported to be BRAF-mutated [3,5,6].

Dabrafenib and trametinib are commonly used to treat patients with BRAF V600E mutated malignant melanoma of the skin [7]. Two out of three patients with BRAF V600E mutated PMML were treated with this combination therapy [3,5,6]. In our case, the patient showed disease control for approximately 2 years, indicating that this combination treatment was effective for BRAF V600E mutated PMML.

The site of occurrence of PMML is often the central bronchi, and the bronchial lumen is often occluded by brown-to-black nodular lesions on bronchoscopy [8]. In the present case, bronchoscopy revealed browned-tone changes from the trachea to the right main bronchial mucosa, which differed from previous reports [8]. Pathological analysis of the brownish tone showed the presence of clusters of melanocytes without malignant cells. Considering that melanocytes are usually absent in the lungs, the brownish changes may have been part of the melanoma; the fact that these changes shrank with treatment supports this speculation. Throughout the course, CT did not show any significant changes, and bronchoscopy was useful for determining the effectiveness of this combination therapy. These results suggest that periodic bronchoscopy and biopsy for abnormal lesions are required and are important for monitoring the PMML status before and after treatment.

There are several theories as to why melanocyte-derived tumors do not exist and develop in normal lungs. Some studies

have suggested that (1) stem cells in the lung tissue differentiate into melanocytes, (2) melanocytes migrate to the airways during embryogenesis, which later become the origin of malignant melanoma, and (3) primary skin lesions spontaneously regress after lung metastasis [9]. In this case, the pathological analysis of brownish tone changes in the bronchial membrane showed a cluster of melanocytes without atypia. This observation suggests that melanocytes in the lung tissue may have differentiated and developed into malignant melanoma.

Conclusions

We encountered an extremely rare BRAF V600E mutated primary malignant melanoma of the lungs. Treatment with dabrafenib and trametinib could be an effective strategy for BRAF V600E mutated PMML. The number of such cases is still limited; thus, further studies are needed to validate this treatment modality. Periodic bronchoscopy is important and useful for confirming the characteristic findings of PMML and monitoring the PMML status.

Declarations

Acknowledgments: Not applicable.

Ethics declarations: Ethics approval and consent to participate: This study was approved by the patient and we obtained written consent from the patient. This report was prepared in accordance with the Helsinki Declaration.

Consent for publication: We obtained written informed consent from the patients for publication of this case report and any accompanying images.

Competing interests:: The authors declare no competing interests.

Contributions: HN contributed to the patient's medical treatment and wrote the manuscript. YK contributed to the medical treatment and supervision in writing the manuscript. YM, YI, and TY contributed to the medical treatment and advice on writing the manuscript. All authors reviewed and approved the final version of the manuscript.

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