

Primary malignant melanoma of the lung: A case report

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Abstract. Malignant melanoma involving the respiratory tract is nearly always metastatic from a cutaneous lesion. Primary malignant melanoma of the lung (PMML) is very rare. We herein report the case of a 61-year-old female patient with PMML who presented with a small nodule in the lower lobe of the left lung on chest computed tomography. As an intraoperative diagnosis of malignant melanoma was made, left lower lobectomy with systematic lymph node dissection were performed. Pathologically, there were no lymph node or intrapulmonary metastases. Lesions other than the pulmonary nodule were not detected throughout the comprehensive postoperative examination of all organs. Thus, the patient was followed up regularly as an outpatient. However, 1 year after the operation, multiple organ metastases developed. The patient's condition rapidly deteriorated and she succumbed to the disease 15 months after the operation, despite intensive chemo-immunotherapy.

Introduction

Malignant melanoma (MM) is a malignant skin tumor derived from melanocytes. MM is characterized as highly malignant due to its rapid growth and early metastasis. Approximately 160,000 new cases of MM are diagnosed annually worldwide (1). MM most frequently occurs on the skin, but may also arise in other organs and tissues, including the oral cavity, paranasal sinuses, esophagus, larynx, vagina and anorectal region, whereas the majority of the respiratory system cases are metastatic. Noncutaneous MM is relatively uncommon, whereas primary MM of the lung (PMML) is extremely rare. PMML accounts for 0.01% of all lung tumors, and its incidence is ~0.4% of all MMs (2), with only ~40 cases published in the English literature to date (3). We herein present the case of a

61-year-old female patient with PMML who displayed a small solid nodule during an annual computed tomography (CT) screening of the lung and discuss the clinicopathological characteristics.

Case report

A 61-year-old Japanese female non-smoker was referred to the Yao Municipal Hospital (Yao, Japan) with an asymptomatic pulmonary nodule (diameter, 6 mm) discovered on annual CT screening (Fig. 1A). The patient's medical history was unremarkable. Clinical examinations and routine laboratory tests, including tumor markers, were within normal limits. A chest CT taken after a 2-month observation revealed a homogeneous and well-defined 13mm nodule in the left basal segment (S10), without mediastinal or hilar lymphadenopathy (Fig. 1B). The nodule had rapidly increased in diameter from 6 to 13 mm over 2 months and the CT revealed disruption of the branch of the B10 bronchus by the nodule (Fig. 1B, inset).

As lung cancer or an atypical carcinoid tumor was suspected, thoracotomy was performed under the assistance of videoscopy. A wedge resection of S10 with a safe margin was performed through the left fifth intercostal space. The tumor was of soft consistency, and homogeneously black and fleshy on the cut surface (Fig. 2). Macroscopically, MM was suspected, and it was confirmed by frozen-section histology. Subsequently, left lower lobectomy with systematic lymph node dissection were performed.

Grossly, the tumor was darkly pigmented, with a solid growth pattern and measured 19x14 mm. The tumor borders were well-circumscribed by the dilated bronchial wall. Histological examination of permanent sections (hematoxylin and eosin staining) revealed multiplying spindle cells with large nuclei including clear nucleoli, and extensive brown pigmentation in the cytoplasm. The tumor extended to the bronchial epithelium (Fig. 3A) and lung parenchyma bidirectionally. However, vascular or lymphatic invasion was not detected. Immunohistochemical staining was positive for S100 protein (Fig. 3B), human melanoma black-45 (Fig. 3C) and melan-A (Fig. 3D). Fontana-Masson stain was also positive. There was no lymph node involvement. The patient was diagnosed with MM.

Postoperatively, to distinguish between primary and metastatic pulmonary melanoma, the skin, mucosae, scalp, anogenital region and eyes were thoroughly examined, but

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no melanocytic lesion was identified. Magnetic resonance imaging of the brain, upper gastrointestinal endoscopy and colonoscopy also did not identify any extrapulmonary disease. Finally, a full-body positron emission tomography scan (PET/CT) showed no evidence of malignancy. Therefore, the patient was diagnosed with PMML.

The postoperative course was uneventful and the patient was discharged with no complications on postoperative day 14. At a regular work-up performed 1 year after the operation, multiple lung, liver and bone metastases were identified. As BRAFV600E mutation was not detected, high-dose dacarbazine (DTIC; 1,000 mg/m²) was administered. However, a clinically meaning full response was not achieved, the patient exhibited elevation of the serum lactate dehydrogenase level and her performance status deteriorated. After one course of DTIC, the patient received immunotherapy 3 times using programmed cell death protein 1 (PD-1) antibody (2 mg/kg) at 3-week intervals, but she succumbed to the disease 15 months after the first surgery for the primary tumor.

Discussion

Non-cutaneous MM is relatively uncommon, whereas PMML is extremely rare. PMML accounts for 0.01% of all lung tumors, and the incidence of PMML is ~0.4% of all MMs (1). MM involving the respiratory tract is nearly always metastatic. As previously reported, skin melanomas may spontaneously disappear after they have already metastasized (4). Distinguishing PMML from metastatic melanoma to the lung may be difficult. The definitive diagnosis of PMML is based on clinical, radiological and pathological findings. Criteria for the diagnosis of PMML were previously proposed by Allen and Drash (5), as follows: i) Junctional change with dropping off or nesting of melanoma cells just beneath the bronchial epithelium; ii) invasion of the bronchial epithelium by the melanoma cells in an area where the bronchial epithelium is not ulcerated; and iii) an obvious melanoma beneath the abovementioned changes.

The clinical criteria proposed by Jensen and Egedorf are widely accepted. The diagnosis requires four clinical criteria (6): i) A solitary lung mass or nodule; ii) typical histopathology confirmed by immunohistochemistry and/or electron microscopy; iii) no prior history of excision/fulguration of a cutaneous, mucous membrane, or ocular lesion, unless the pathological examination explicitly ruled out a melanoma; and iv) no demonstrable melanoma outside the chest at the time of diagnosis.

On the basis of these criteria, the case presented herein was compatible with a diagnosis of PMML.

The pathogenesis of PMML remains unclear. Melanocytes have been identified in the larynx and esophagus, which, along with the lower respiratory tract, are derived from the sixth bronchial arch. Thus, it plausible that PMML is derived from benign melanocytes that have migrated with the respiratory tract during embryogenesis. As shown in the inset of Fig. 1B, PMML was considered to have originated from the bronchial wall proximal to the sixth bronchial arch in the present case.

According to previous reports (7), a surgical approach with adjuvant chemotherapy/immunotherapy may enable long-term survival. The therapeutic effect of conventional

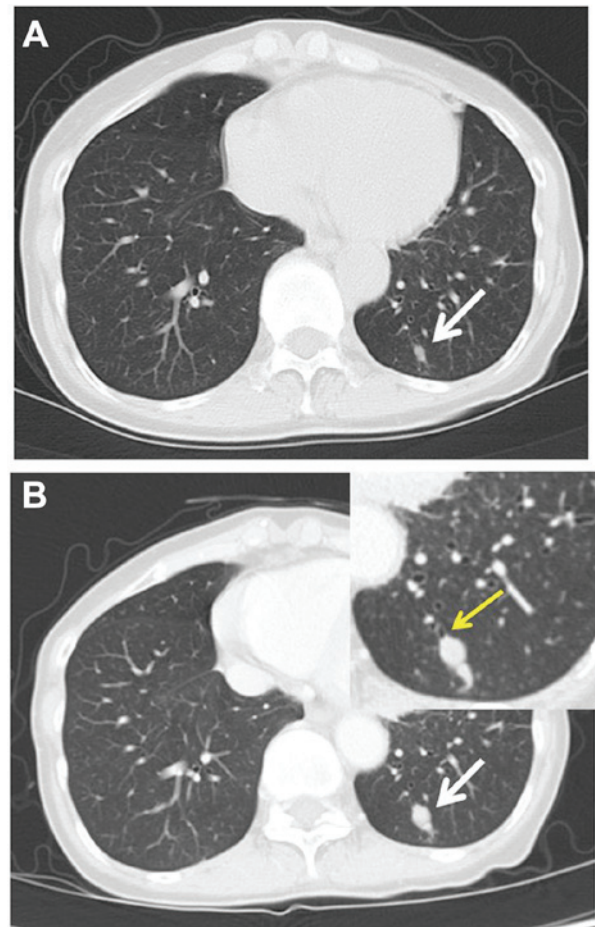


Figure 1. Chest computed tomography (CT) images captured (A) at the annual CT screening and (B) 2 months later. The tumor (white arrows) rapidly enlarged in diameter from 6 to 13 mm. Inset, disruption of the B10 bronchus by the tumor (yellow arrow).



Figure 2. Specimen obtained by wide wedge resection. The cut surface revealed a dark pigmented tumor extending into the bronchial lumen. Arrows, bronchial wall.

chemotherapy or radiation therapy is currently considered to be poor. Novel immunotherapy, with a combination of

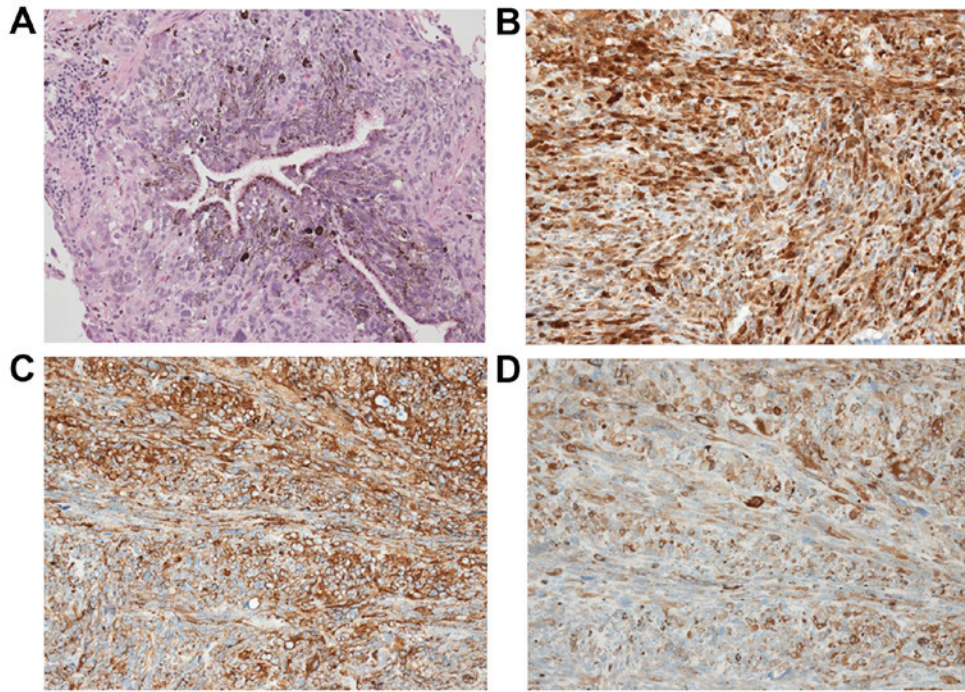


Figure 3. (A) Hematoxylin and eosin staining of the tumor cells showing extension to the bronchial epithelium. On immunohistochemical staining, the cytoplasm of malignant cells stained strongly positive with antibodies against (B) S-100, (C) human melanoma black45 and (D) melan-A. Original magnification x20.

check-point inhibitors, such as ipilimumab (anti-cytotoxic T-lymphocyte antigen-4, CTLA-4) and nivolumab (anti-PD1), has been tested in patients with advanced melanoma in several trials, with promising results (8).

The volume-doubling time (VDT) of melanoma is shorter (mean, 48 days) than in any other malignant tumors, apart from testicular and anaplastic thyroid cancer (9). However, there are no data on VDT in PMML. In the present case, the VDT of PMML was calculated to be 40 days.

Early detection and complete removal with regional lymph node dissection are crucial for long-term survival of PMML patients. As there was no lymph node metastasis or vascular/lymphatic invasion in the present case, postoperative adjuvant therapy was not performed. However, diligent follow-up taking the short VDT into consideration is mandatory for such an aggressive malignant tumor.

This rare case should raise awareness that early diagnosis prior to hematogenous spread is the most important survival factor for such a metabolically active tumor with a shorter VDT. The PET scan performed immediately after removal of the primary lesion failed to identify micro-metastases in the present case. When a small solid nodule is identified affecting the bronchus proximal to the sixth bronchial arch on high-resolution CT, particularly in the lower lobe, open thoracotomy and excisional biopsy should be considered, to offer a chance for cure.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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