

CASE REPORT

Primary pulmonary malignant melanoma: Case report and literature review

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Abstract

Primary malignant melanoma of the lung is an extremely rare pulmonary carcinoma. Only 45 cases have been reported in the literature. Herein, we report a case of a 46-year-old male patient with an O Rh negative blood type who presented with pulmonary bronchial symptoms and underwent lobectomy. Genetic testing was also performed but no targetable mutations were found, and the patient's PD-L1 RNA level was low. He developed brain metastasis four months after surgery and received radiotherapy but died 21 months after diagnosis. We review the published cases of this rare pulmonary lesion.

Introduction

Malignant melanoma (MM) is a malignant tumor usually arising from the skin or mucus. The lung is a rare location for the primary site of an MM, and accounts for 0.01% of all lung tumors.¹ Herein, we present a case of a 46-year-old man with an initial diagnosis of primary malignant melanoma. He underwent surgery in our department not long after diagnosis. This case is particularly rare because the patient had an O Rh negative blood type. We present this special case and review the relevant literature.

Case report

A 46-year-old non-smoking man was admitted to our department after experiencing a cough for three months, blood in sputum for two months, fatigue, and anorexia. The patient was symptomatically treated with antitussive and hemostatic drugs for one month, but no clinical benefit was observed. His symptoms were aggravated by chest tightness but no pain, and with dark grey, fleshy tissues in

the sputum one week before admission. The patient denied a prior history of skin, ear, or ocular lesions, and declined a skin biopsy.

A physical examination showed no marked abnormality, with a body temperature of 36.5 °C, blood pressure 125/75 mmHg, heart rate 82 beats/minute, respiratory rate 20/minute, and SpO₂ of 99% at room air. No skin lesions were detected. The patient then underwent further examination. His chest computed tomography revealed two nodules in the right upper lobe of the lung, the largest of which was 3.2*2.4 cm, and a soft tissue density mass in the right hilum of the lung (Fig 1). Several mediastinal lymph nodes were enlarged.

A bronchoscopic examination showed an endobronchial mass in the right upper lobe bronchus. A biopsy was performed and immunohistochemical staining revealed atypical cells in the fibrous connective tissue expressing malignant melanoma markers, including HMB45, Melan-A, S-100 protein, and vimentin. Other immunohistochemical markers, including ALK-D5F3 (for lung carcinoma),

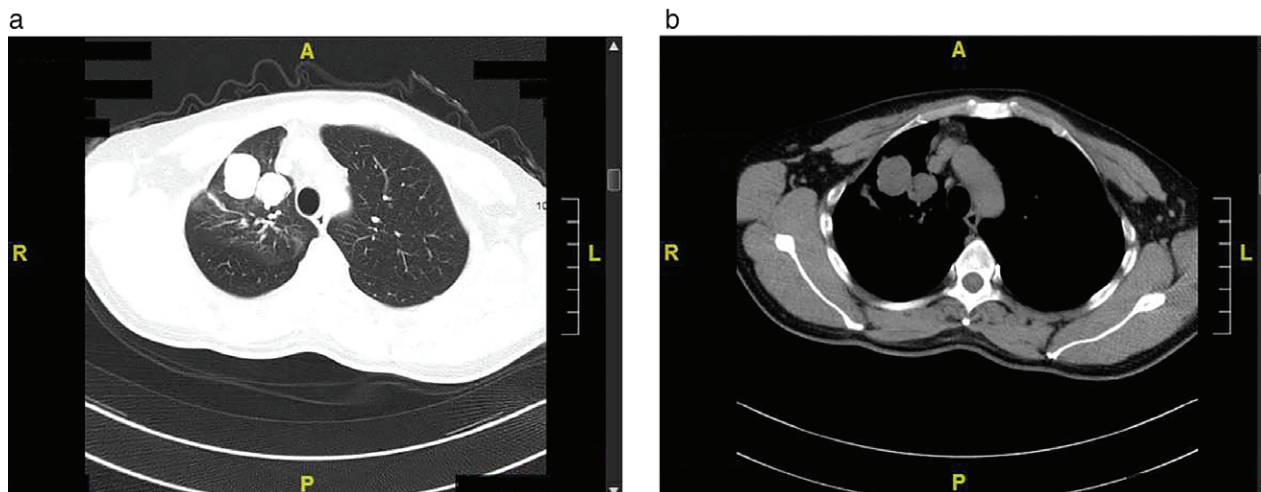


Figure 1 Preoperative computed tomography (left: lung window; right: mediastinal window).

ALK-D5F3 (negative control), CK7, P40, thyroid transcription factor-1, AE1, and AE3 were all negative.

Whole body positron emission tomography-computed tomography (PET-CT) using (^{18}F)fluorine-2-fluoro-2-deoxy-D-glucose was performed and revealed closely related nodules or a mass in the right upper lobe and the right hilum of the lung ranging in size from 2.9 to 4.0 cm, with a maximum standardized uptake value (SUV) of 11.6–14.8, indicating malignant lesions. Several 0.5–0.9 cm nodules in the mediastinum with a maximum SUV of 1.3–1.7 presented the possibility of lymphadenitis. PET-CT also revealed no abnormal metabolism increase in other sites of the body, including the head, neck, other parts of the chest, abdomen, and pelvis.

Considering that the histological result highly suggested MM and that PET-CT basically excluded the possibility of pulmonary metastasis of MM from other sites, the patient's initial diagnosis at admission to our department was primary pulmonary MM. It was noteworthy that the blood test taken before surgery showed type O Rh negative blood.

The patient underwent right open chest upper lobectomy of the lung, bronchial sleeve resection, and mediastinal lymph node dissection after the exclusion of surgical contradictions and preparation of RH(-) red blood cells and plasma. Gross examination showed a round, darkly pigmented, solid neoplasm 4 cm in diameter. The tumor was located partly in the lung tissue and partly in the bronchus. Intraoperative frozen pathology showed no tumor cells at the incisal edge of the bronchus. The final pathological report showed that the tumor measured 3.5*3.4*3.6 cm, with no pleural or bronchial involvement. All five lymph nodes detected were free of tumor cells. Immunohistochemical testing of the dissected tissue revealed

the same results as the bronchoscopic biopsy. Pathological results confirmed a diagnosis of MM (Fig 2).

At a later date we performed genetic molecular testing after the modest response achieved by targeted therapy and immunotherapy. Unfortunately the test results showed no specific mutations in PD-L1 RNA expression, *ROS1* gene rearrangement, or *MET* gene copy number (Table 1).

After several days of postoperative recovery, the patient left our department and was followed-up every three months. Four months after the surgery, brain nuclear magnetic resonance imaging was performed after the patient complained of dizziness and weakness (Fig 3). Brain metastasis was detected and he underwent whole brain radiotherapy at 2 Gy per day, reaching a total dose of 40 Gy in four weeks, together with a gross tumor volume to the right frontal lobe and right cerebellar hemisphere lesions of 3 Gy per day, reaching a total dose of 60 Gy in four weeks. Because of financial difficulties, the patient did not return after the first course of radiotherapy. The patient died 21 months after diagnosis, primarily as a result of the intracranial metastatic lesion.

Discussion

Malignant melanoma is a common tumor that ranks fifth in cancer incidence in the United States.² Ninety percent of MMs originate from the cutaneous area while unusual mucosal sites, such as the oral cavity, paranasal sinuses, esophagus, larynx, vagina, anorectal region, and liver have also been reported as sites of primary MM.^{3,4} In cases of MM in the lung, most conditions are metastatic MM from the cutaneous lesion.⁵ Primary malignant melanoma of the lung (PMML) is extremely rare, accounting for only

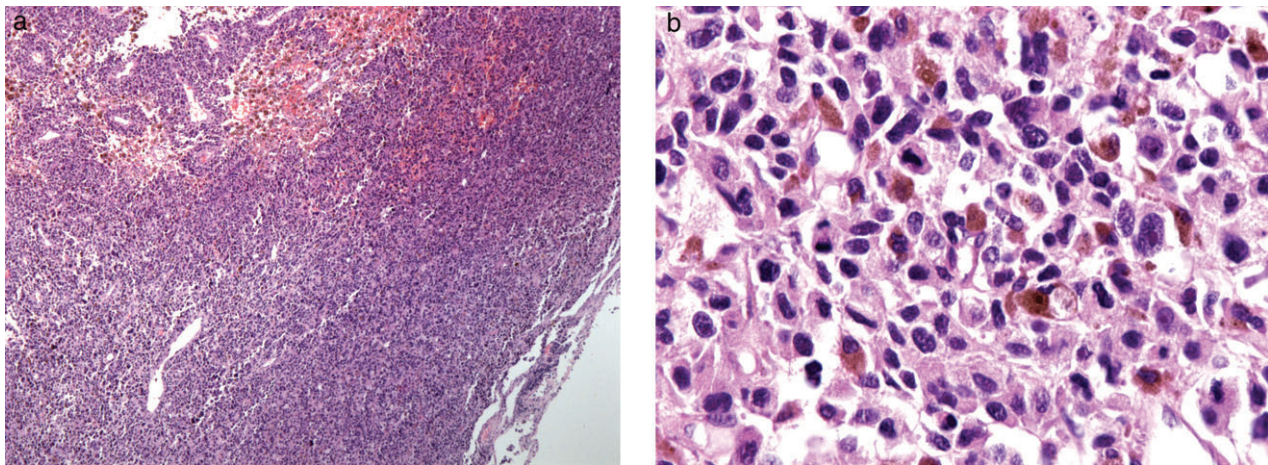


Figure 2 (a,b) Pathological section biopsy showing infiltration by melanocytes containing melanin pigmentation from the lung lesion (hematoxylin and eosin staining, magnification: (a) 40x; (b) 400x).

Table 1 Partial results of genetic testing

Test Items	Values	Results
<i>BRAF</i> mutation	Wild-type	No mutation
PD-L1 RNA level	≥ 1.8%	Low

0.001% of all pulmonary tumors.¹ Only 45 cases have been reported in the English literature to date.

Ost *et al.* and Kyriakopoulos *et al.* conducted systematic summaries in 1999 (*n* = 20) and 2017 (*n* = 41), respectively.^{6,7} Kyriakopoulos *et al.* showed a median age of onset of PMML of 59.1 years (range: 29–90) and no significant gender difference was observed (21 men vs. 19 women).

Moreover, smoking history has not been considered as strong predisposing factor correlated with the development of PMML, although it has been hypothesized that cigarette smoking may cause squamous metaplasia.⁸ Interestingly, the ABO blood group antigen is suspected to contribute to the development of cancer. De Giorgi *et al.* found a slightly increased risk of MM in patients with the O Rh-negative blood type, consistent with our patient.⁹ Respiratory symptoms are common clinical manifestations, including a reproductive cough, hemoptysis, and occasionally, mild chest pain, dyspnea, or weight loss. Thirty percent of cases are incidental findings on chest radiography or CT without any symptoms.⁶

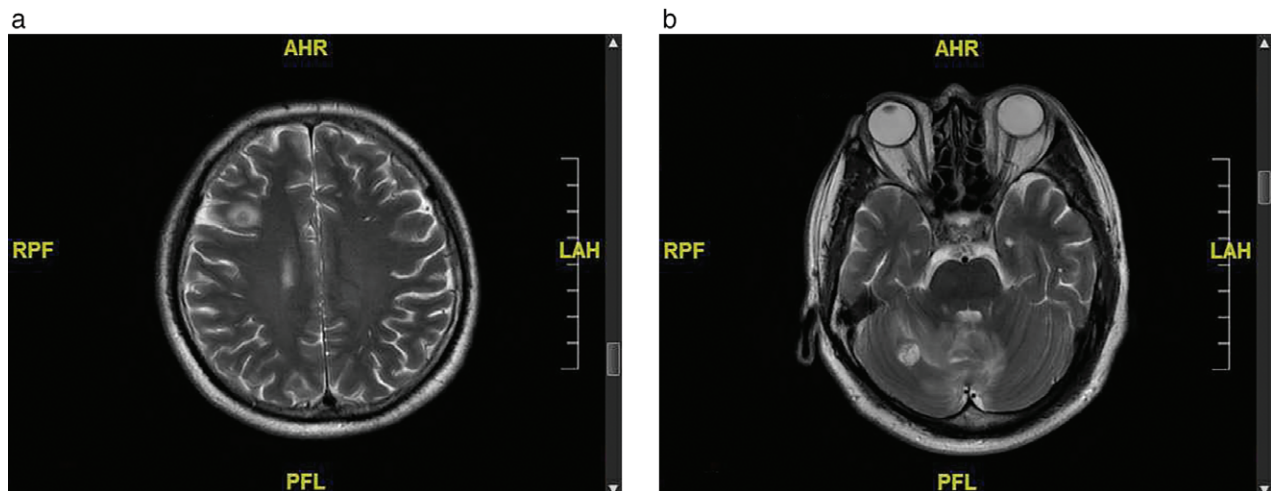


Figure 3 (a,b) Brain magnetic resonance imaging: multiple nodules are observed on the right middle frontal lobe, bilateral cerebellar hemisphere, and cerebellar tentorium, with a short T1 long T2 signal and a circular edema zone around it. Diffusion-weighted imaging showed a high signal, decreased apparent diffusion coefficient. The larger lesion (1.8*1.4 cm) was located in the cerebellar vermis and was markedly enhanced. AHR, LAH, PFL, RPF.

Diagnostic criteria have changed with further understanding of PMML. Because of the unique characteristic that cutaneous melanomas can spontaneously degenerate after metastasis, it is difficult to recognize the difference between a primary MM in a non-cutaneous site and a metastatic lesion. Jensen and Egedorf suggested six criteria to specifically diagnose PMML: no previously removed skin tumors; no previously removed ocular tumors; a solitary lung tumor; tumor morphology compatible with a primary tumor; no other organ involvement; and autopsy without primary MM demonstrated elsewhere, especially not in the skin or eyes.¹⁰ Pathologically, a diagnosis of MM is made after invasion of the bronchial epithelium by melanoma cells, junctional changes including “dropping off” or “nesting” just beneath the bronchial epithelium, and evident melanoma cells confirmed by immunohistochemical staining for S-100 and HMB-45.^{11–13} Our patient met all of the criteria for a diagnosis of pulmonary primary MM.

Although it remains controversial, the pathological progress of how primary MM develops in the lung is most likely interconnected with melanocyte migration. During embryotic development, melanocytes can migrate into the lower respiratory anlage.^{14–16} Histologically, MM of the lung is characterized by a solid growth pattern with organoid and fascicular areas. It is composed of loosely cohesive epithelioid cells with large, round hyperchromatic to vesicular nuclei and prominent eosinophilic nucleoli, together with a dark brown pigment in the tumor cells.

Lobectomy or pneumonectomy with lymph node dissection remains the first choice of treatment for PMML patients. Different types of chemotherapy, including interleukin-2 and interferon have been attempted for MM patients, as well as radiotherapy for locally advanced or distant metastatic patients, but none of the postoperative adjuvant therapies have shown a promising effect on PMML patients. Our patient developed brain metastasis four months after surgery. Although he underwent brain radiation, he died from an intracranial lesion 16 months later.^{17,18}

It is noteworthy that MM is one of the most responsive types of cancer to target therapy. Since the discovery of *BRAF* mutations in almost half of all melanoma patients, the United States Food and Drug Administration (FDA) approved a sequence of *BRAF* inhibitors, including vemurafenib and dabrafenib, together with an MEK inhibitor.^{19–21} With developments in immunotherapy in recent years, anti-PD-1 antibodies nivolumab and pembrolizumab were approved by the FDA in 2014 for treating metastatic cutaneous melanoma.²² Treatment requires an assessment of tumor PD-L1 expression. We performed genetic testing on our patient, but unfortunately no *BRAF*-V600E or *BRAF*-V600K mutations were detected and PD-L1 expression was low.

The overall prognosis of PMML is poor. Only two cases of long-term survival (10 and 11 years of disease-free

survival) have been reported to date.^{23,24} Most patients survive up to 18 months. As with other tumor types, better prognosis is achieved by early detection; some patients are incidentally diagnosed by chest radiography and do not exhibit any clinical symptoms.

Primary MM of the lung is a rare neoplasm. Most cases present pulmonary and bronchial symptoms and checking the blood type of the patient may assist in the early diagnosis of this kind of malignancy. Currently, surgery is the first choice of treatment; however, because of the lack of clinical data, the relative benefits of different adjuvant treatments are unclear. Genetic testing should become a routine test for patients diagnosed with PMML and further targeted or immune therapies are on the horizon.

Disclosure

No authors report any conflict of interest.

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