Primary Pulmonary Malignant Melanoma Successfully Treated with Immunotherapy in a 90-Year-Old Patient

Kohei Fujita  Koichi Nakatani  Takuma Imakita  Osamu Kanai  Tadashi Mio
Division of Respiratory Medicine, Center for Respiratory Diseases, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

Keywords
Pulmonary tumors · Malignancy · Melanoma · Immunotherapy · Older adult

Abstract
Malignant melanoma is a rare and high-grade cancer. It most commonly affects the skin, but it has the potential to involve all areas of the body. Primary pulmonary malignant melanoma is rare, accounting for only 0.01% of all pulmonary tumors. We present a case of primary pulmonary malignant melanoma in a 90-year-old patient. The pretreatment computed tomography (CT) showed a pulmonary mass in the right upper lobe, multiple pleural nodules, enlarged mediastinal lymph nodes, and bone metastases. Positron emission tomography-CT showed a region of fluorodeoxyglucose hyperaccumulation that was consistent with the abnormal shadows. Advanced stage lung cancer was initially suspected, but bronchoscopy revealed a malignant melanoma. The patient was diagnosed with a primary pulmonary malignant melanoma. Although the patient was older, he wanted to receive immediate treatment. Thus, he was treated with immune checkpoint inhibitors. He responded well to the medication, and neither major adverse events nor tumor size reduction was observed. We report a rare case of primary pulmonary malignant melanoma in an older adult. Immune checkpoint inhibitor therapy, as in this case, was a viable treatment option for older adults.
**Introduction**

Malignant melanoma (MM) is a rare and high-grade cancer. It commonly affects the skin, but it has the potential to involve all areas of the body [1]. Approximately, 90% of MMs arise from the cutaneous area, while 10% develop from other mucous membranes [2]. Primary pulmonary MM is rare, accounting for only 0.01% of all pulmonary tumors [3]. This study documents the successful treatment of a primary pulmonary MM in an older patient.

**Case Report**

A 90-year-old man with a chief complaint of back pain consulted his family doctor. He was referred to our hospital due to abnormal shadows on the chest radiograph. Computed tomography (CT) revealed a pulmonary mass in the right upper lobe, multiple pleural nodules, enlarged mediastinal lymph nodes, and bone metastases, suggesting advanced-stage lung cancer (Fig. 1a–c). Positron emission tomography (PET)-CT showed a region of fluorodeoxyglucose hyperaccumulation that was consistent with the abnormal shadows (Fig. 1d–g). A lung tissue biopsy was performed using bronchoscopy. The lung tissue histologically consisted of (Fig. 2a, b) conglomerations of round cells with round nuclei and acidophilic sporangia, surrounded by melanin deposits. The tumor stained positively for Melan-A but was negative for AE1/AE3, LCA, and CD68. These findings were indicative of a melanoma. The lesion tested negative for \textit{BRAF} mutations, and its expression of programmed death 1 ligand was less than 1%.

A PET-CT scan and close examination by a board-certified dermatologist revealed no skin lesions. Therefore, the patient was diagnosed with a primary pulmonary MM. Since the patient was at an advanced age and the malignant tumor was unresectable, palliative care was recommended. However, the patient strongly desired treatment, and accordingly, immunotherapy with immune checkpoint inhibitors was initiated. He received four cycles of combined nivolumab and ipilimumab therapy.

After four cycles of immunotherapy, the patient exhibited a partial response (Fig. 3a–c). He developed grade 1 mild skin damage during the treatment period. However, no major
immune-related adverse events were observed. Nivolumab administration was continued as maintenance therapy.

**Discussion/Conclusion**

MM is one of the most common unresectable malignant lesions. Most MMs of the lung develop via metastasis from cutaneous lesions [4]. In this case, neither the PET-CT nor detailed systemic examination by a dermatologist could detect a primary skin lesion. Therefore, the patient was diagnosed with a primary pulmonary MM. Primary pulmonary MM is rare, accounting for only 0.01% of all pulmonary tumors [3]. Its most common signs and symptoms include metastasis, cough, hemoptysis, dyspnea, chest pain, weight loss, and fever [1]. In this case, the patient initially presented with back pain, suggestive of spinal metastasis.

This case was unique compared to previous cases due to the following reasons. First, this patient was diagnosed at the age of 90 years. According to a previous review, the median age of onset of primary pulmonary MM was 60 years [1]. The diagnosis is rarely established in older patients.

Second, immunotherapy with nivolumab and ipilimumab was successful, despite the patient’s age. According to a previous review [1], surgical resection is the preferred treatment option in 70% of cases. However, in the cases included in this review, most patients were diagnosed at an early stage. In advanced stages, neither surgical resection nor chemotherapy...
is indicated. Dacarbazine is commonly used in the conventional cytotoxic chemotherapy regimen. However, it reportedly has poor therapeutic efficacy. Recently, molecular-targeted drugs have been used to treat MM with \textit{BRAF} mutations \cite{5, 6}.

The emergence of immune checkpoint inhibitors has significantly changed melanoma treatment. Two PD-1 antibodies, nivolumab and pembrolizumab, were approved for the treatment of advanced melanoma in 2014. More recently, the combined use of nivolumab and ipilimumab achieved a significantly longer progression-free survival rate than nivolumab or ipilimumab monotherapy in patients with programmed death 1 ligand negative melanomas \cite{7}. The previous clinical trials of immune checkpoint inhibitors included patients with an average age of 60 years old. Thus, their indication for 90-year-old patients should be considered with caution. Compared to the conventional cytotoxic chemotherapy, immune checkpoint inhibitors are reportedly more tolerable for older patients, as seen in the patient in the present case.

In conclusion, we encountered a rare case of primary pulmonary MM, successfully treated with a combination of nivolumab and ipilimumab. Immune checkpoint inhibitor therapy is a viable treatment option for MM, even in older patients.

\textbf{Statement of Ethics}

The study is exempt from ethics committee approval because it is a case report at the National Hospital Organization Kyoto Medical Center. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

\textbf{Conflict of Interest Statement}

The authors have no conflicts of interest to declare.

\textbf{Funding Sources}

No funding was received for this case report.

\textbf{Author Contributions}

Kohei Fujita was responsible for literature review, data collection, and manuscript writing. Koichi Nakatani, Takuma Imakita, Osamu Kanai, and Tadashi Mio cared for the patient during immunotherapy. Kohei Fujita, Koichi Nakatani, Takuma Imakita, Osamu Kanai, and Tadashi Mio contributed to the manuscript review before submission and approved the final version of the manuscript.

\textbf{Data Availability Statement}

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request because of the need to protect patient privacy and get approval from the Ethics Committee.
References

1. Paliogiannis P, Fara AM, Pintus G, Abdel-Rahman WM, Colombino M, Casula M, et al. Primary melanoma of the lung: a systematic review. *Medicina.* 2020;56(11):576.

2. Chang AE, Karmell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1998;83(8):1664–78.

3. Wilson RW, Moran CA. Primary melanoma of the lung: a clinicopathologic and immunohistochemical study of eight cases. *Am J Surg Pathol.* 1997;21(10):1196–202.

4. Shi Y, Bing Z, Xu X, Cui Y. Primary pulmonary malignant melanoma: case report and literature review. *Thorac Cancer.* 2018;9(9):1185–9.

5. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med.* 2014;371(20):1867–76.

6. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med.* 2015;372(1):30–9.

7. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med.* 2015;373(13):23–34.