Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6657-20
Intern Med 61: 703-708, 2022
http://internmed.jp

【 CASE REPORT 】

Amelanotic Malignant Melanoma with a *BRAF V600E* Mutation Mimicking Primary Lung Cancer

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Abstract:
Amelanotic melanoma is a rare type of melanoma that shows little or no melanin pigmentation. When tumor lesions are not detected in cutaneous sites, the presence of melanin is the hallmark sign of malignant melanoma. We herein report a case of amelanotic melanoma with a *BRAF V600E* mutation mimicking primary lung cancer that was finally diagnosed on an autopsy. The current case suggests important caveats for the differential diagnosis of patients with *BRAF V600E* mutation-positive poorly differentiated lung tumors. In terms of the pathological diagnosis, routine immunohistochemical staining may be useful, especially in patients with a poorly differentiated lung tumor without TTF-1 expression.

Key words: amelanotic melanoma, lung tumor, *BRAF V600E* mutation, differential diagnosis, immunohistochemical staining

(Intern Med 61: 703-708, 2022)
(DOI: 10.2169/internalmedicine.6657-20)

Introduction

Amelanotic melanoma is rare, representing less than 2% of all malignant melanomas (1-3). This type of melanoma shows little to no melanin pigmentation on macroscopic inspections or dermoscopic evaluations (4, 5) and is therefore often mistaken for other diseases (6), with the highest misdiagnosis rate reported to be 89% (7) and nearly 60% of amelanotic melanomas completely unsuspected of being melanoma (7-9). This subtype is not only associated with a poorer diagnostic accuracy (10) than malignant melanomas that produce melanin but also a shorter survival time (11).

When tumor lesions are not detected in cutaneous sites, the presence of melanin is the hallmark sign of malignant melanoma; however, in the case of amelanotic melanoma, the lack of melanin makes the diagnosis difficult. In such cases, immunohistochemical (IHC) staining for S-100, Melan-A, HMB-45, and microphthalmia transcription factor (MITF) markers is critical for the proper diagnosis (12, 13). The S-100 and SOX10 protein is the most sensitive marker, while others are relatively specific (14).

We herein report a case of amelanotic melanoma harboring a *BRAF V600E* mutation and mimicking primary lung cancer that was eventually diagnosed by an autopsy.

Case Report

A 53-year-old Asian woman was referred to our hospital for a mass in the middle field of the lung on X-ray. Chest computed tomography (CT) revealed a 5-cm tumor in the middle lobe of the right lung with chest wall invasion, right hilar and mediastinal lymph node swelling, and pleural dissemination (Fig. 1A, B). Systemic positron emission tomography (PET)-CT (Fig. 1B) and brain magnetic resonance imaging (MRI) showed no distant metastasis, other than the thoracic lesions. The patient had no complaints about her skin or mucosa, and a visual inspection did not detect any cutaneous disorder.

A biopsy of the lung tumor revealed poorly differentiated

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Received: November 5, 2020; Accepted: June 28, 2021; Advance Publication by J-STAGE: August 24, 2021
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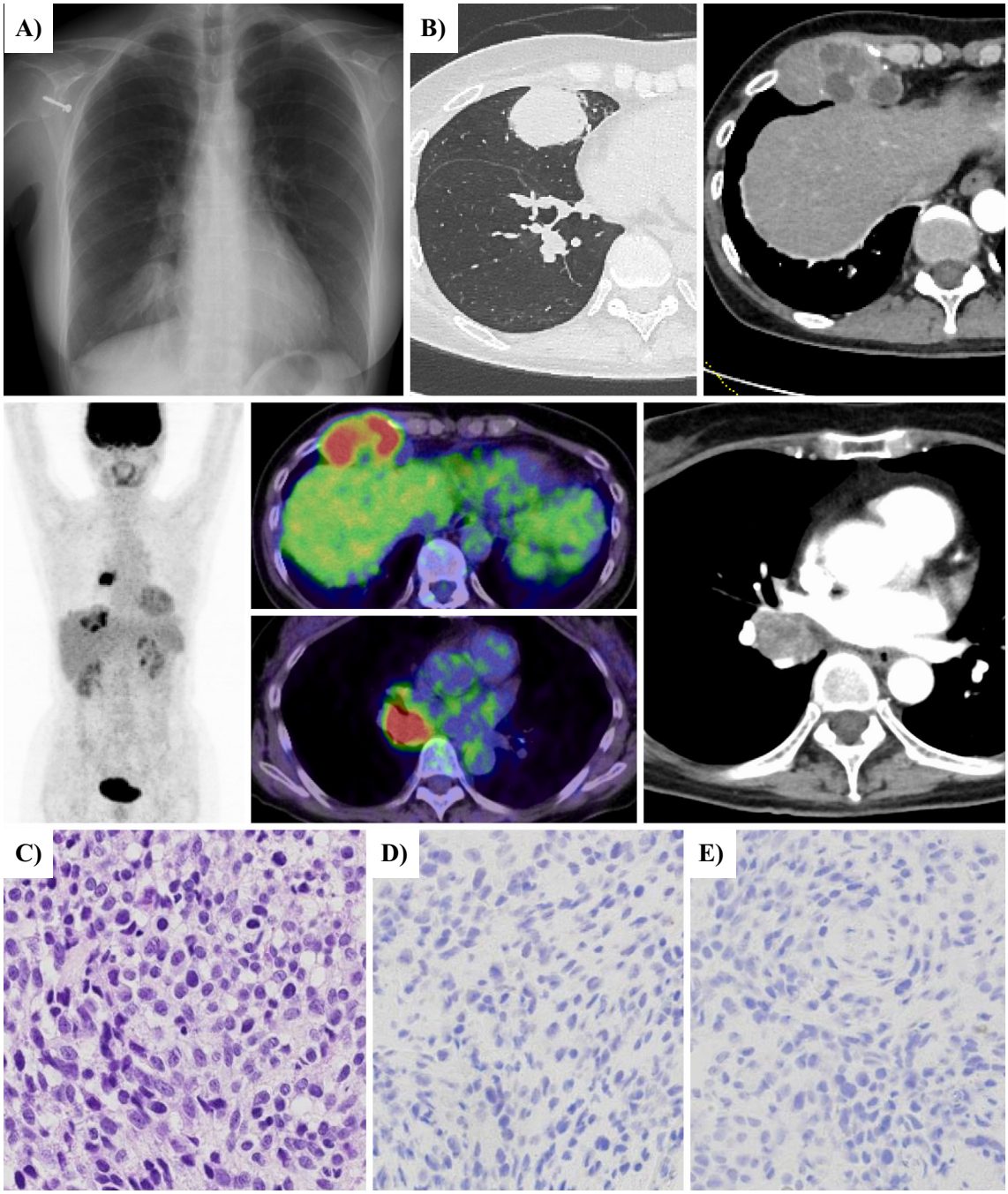

Figure 1. Examinations at the first diagnosis. (A) Chest X-ray at initial diagnosis. (B) Enhanced CT and PET-CT at the initial diagnosis. (C-J) Staining of the biopsy sample of the middle lobe of the right lung at the initial diagnosis. (C) Hematoxylin and Eosin staining shows poorly differentiated epithelial-like tumor cells (×200 magnification). (D) TTF-1 staining was negative (×200 magnification). (E) p40 staining was negative (×200 magnification).

epithelial-like tumor cells. Staining of the biopsy sample (Fig. 1C-E) was negative for TTF-1/p40 and revealed a PD-L1 tumor proportion score of 0%. Based on the radiological and pathological findings, the tumor was diagnosed as a primary lung cancer, non-small-cell lung cancer (NSCLC), not otherwise specified. A driver oncogene analysis was performed at the time of the initial diagnosis and was *EGFR* mutation-negative and *ALK/ROS1* fusion-negative. The clinical stage for the primary lung cancer was T4N2M1a, stage IVA.

First-line treatment with cisplatin plus gemcitabine, followed by second-line treatment with pemetrexed and third-line treatment with S-1 elicited no response. At the time of disease progression following the last treatment, atelectasis was observed in the middle and lower lobes of the right lung due to enlargement of the hilar lymph node metastases, and there were new multiple bone metastases.

A biopsy of the chest wall invasion was performed to evaluate targetable driver oncogenes other than *EGFR*, *ALK*, and *ROS1*. A *BRAF V600E* mutation was detected using

next-generation sequencing, and *BRAF*-targeted treatment with dabrafenib plus trametinib was started. Thereafter, the tumor in the lung and the lymph node metastases rapidly decreased in size, resulting in resolution of the atelectasis within two weeks, as observed on chest X-ray (Fig. 2A, B). Furthermore, CT revealed a remarkable response in all lesions two months after initiating dabrafenib plus trametinib therapy (Fig. 2C, D), with significant improvement in the patient's general condition. The response continued for approximately 10 months. The histological evaluation before BRAF plus MEK inhibitors revealed the existence of poorly differentiated epithelial-like tumor cells and spindle cells (Fig. 2E), suggesting a pleomorphic primary lung cancer, with a PD-L1 tumor proportion score of 80% (Fig. 2F).

The patient's disease subsequently progressed, and we performed a biopsy of the soft tissue around the right iliac bone at the time of disease progression to differentiate from an abscess, as the progression was drastic and occurred with necrosis. The histological evaluation showed poorly differentiated round cell tumor cells with spindle cells and giant cells (Fig. 2G), consistent with the earlier chest wall biopsy findings, and the PD-L1 tumor proportion score was 0%. We started atezolizumab monotherapy, but CT revealed drastic and systemic disease progression within a month, and the patient ultimately passed away. CT findings two weeks prior to the patient's death are shown in Fig. 3A.

An autopsy was performed to confirm the pathological diagnosis. Multiple white nodules were observed on the epicardial surface (Fig. 3B) and ribs (Fig. 3C). Melanin pigmentation was observed in a small section of liver metastasis (Fig. 3D). At most sites, including abdominal lymph nodes (Fig. 3E), poorly differentiated round cell tumor cells with spindle cells and giant cells were observed. In the supraclavicular lymph node metastasis, IHC staining was S-100-positive (Fig. 3F), SOX-10-partially positive (Fig. 3J), and HMB-45-, Melan-A-, and MITF-negative (Fig. 3G-I). IHC staining was performed on the initial biopsy sample based on the autopsy findings. Notably, in accordance with the autopsy findings, S-100 was positive, and Melan-A, HMB-45, MITF, and SOX-10 were negative in the initial biopsy sample (Fig. 3K-O). Furthermore, additional IHC staining was also performed on the second biopsy sample after the autopsy. S-100, Melan-A, HMB-45, MITF, and SOX10 staining findings were all negative. Based on the autopsy findings, we finally diagnosed the case as amelanotic malignant melanoma with a *BRAF V600E* mutation presenting as NSCLC.

Discussion

The current case highlights the difficulty of diagnosing amelanotic malignant melanoma presenting as a lung tumor with hilar and mediastinal lymph node swelling. To our knowledge, this is the first case of amelanotic malignant melanoma with a *BRAF V600E* mutation presenting as NSCLC.

Several findings led us to treat the tumor as NSCLC. First, the patient had no complaints regarding her skin or mucosa, and there was no fluorodeoxyglucose (FDG) uptake observed, although FDG-positron emission tomography is known to have major limitations with regard to the detection of tiny primary lesion. Second, the radiological findings were compatible with primary lung cancer with regional lymph node metastasis and pleural dissemination. Third, the initial biopsy showed no evidence of malignant melanoma, such as melanin pigmentation. Upon performing a second biopsy, we detected the *BRAF V600E* mutation of the tumor. However, the *BRAF V600E* mutation is a targetable driver oncogene in not only melanoma but also NSCLC. We noted no pigmentation findings associated with melanoma despite performing a total of three biopsies. The autopsy findings revealed multiple soft, white nodules on the epicardial surface and ribs, suggesting amelanotic melanoma. A pathological examination finally revealed melanin pigmentation in a small section of the liver metastasis, which prompted us to perform IHC screening for malignant melanoma and resulted in the detection of S-100 expression. Based on these findings, we diagnosed the case as amelanotic melanoma with a *BRAF V600E* mutation.

The *BRAF V600E* mutation is identified in 30% to 60% of malignant melanomas (15) but only 1-2% of NSCLC (16, 17). Therefore, even if radiological findings show localization of the tumor in the thoracic region, a careful examination of the skin and mucosa, including the oral cavity, genitalia, and anus, by a dermatologist is recommended to rule out the possibility of lung metastasis from malignant melanoma.

In the current case, a primary cutaneous site was not detected during the clinical course. Furthermore, visual inspection of the skin and mucosa at the autopsy also did not reveal any abnormalities, even though the autopsy was performed after identification of a *BRAF V600E* mutation, prompting the pathologists to search for the skin or cutaneous lesions with considerable care. The incidence of primary malignant melanoma of the lung is extremely low, account for just 0.01% of all primary lung tumors and less than 0.4% of all malignant melanomas (18). In contrast, the lung is one of the most common sites of melanoma metastasis. Therefore, we were unable to completely deny the possibility that the lung tumor of the current case was a metastatic lesion from undetectable primary cutaneous melanoma. However, based on the clinical course and autopsy skin findings, it was deemed reasonable to diagnose this case as primary malignant melanoma of the lung.

The response rate in unresectable malignant melanoma with a *BRAF V600E* or *V600K* mutation treated with dabrafenib plus trametinib has been reported to be 64-69% with a median progression-free survival of 9.3-11.4 months in phase III trials (19, 20). The patient in this case achieved a partial response with dabrafenib plus trametinib, and the progression-free survival was approximately 10 months, which was consistent with the efficacy noted in previous re-

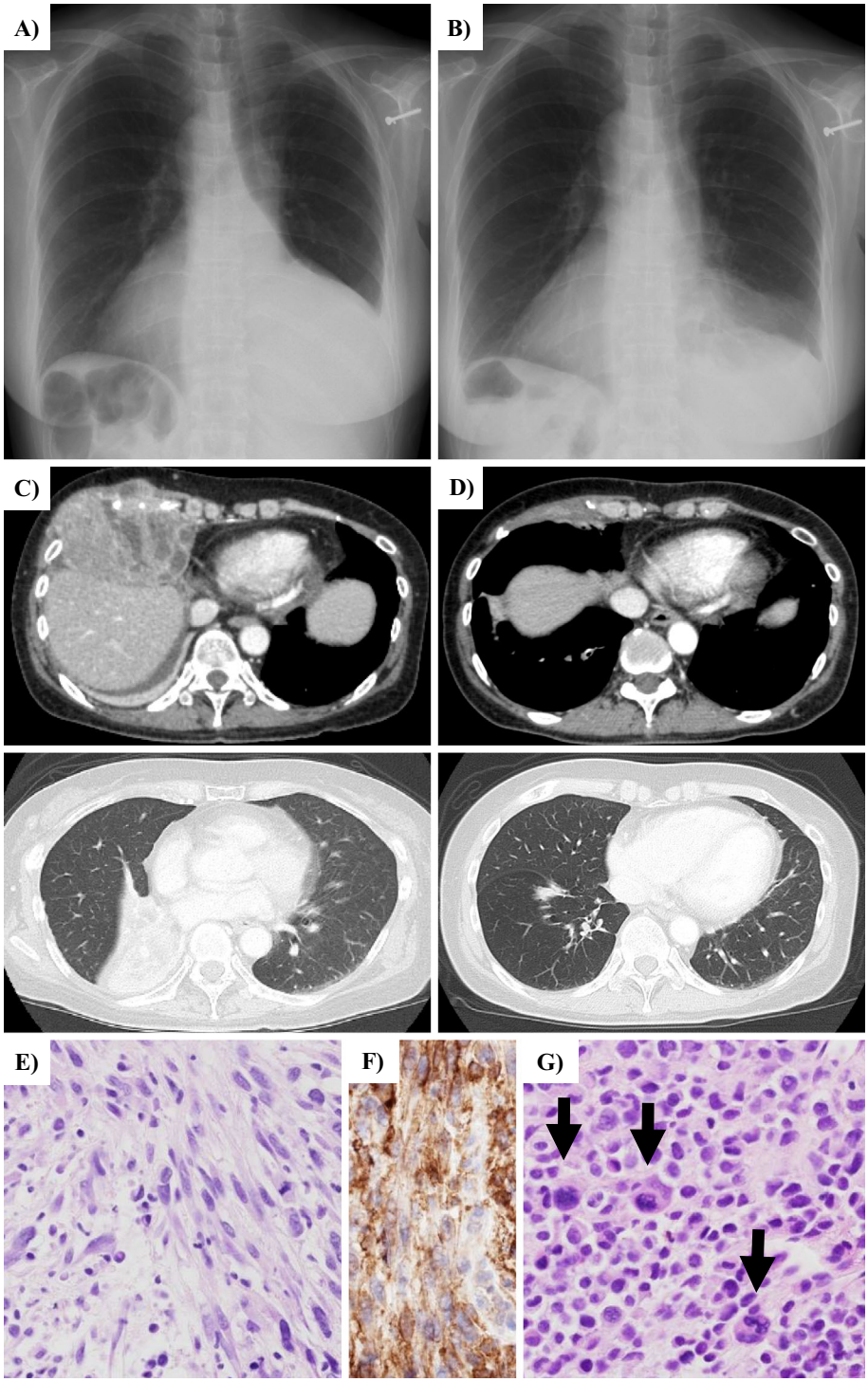

Figure 2. **Examinations at the timing before and after dabrafenib plus trametinib therapy. (A) Chest X-ray prior to dabrafenib plus trametinib therapy. (B) Chest X-ray showing that atelectasis resolved within two weeks. (C) CT prior to dabrafenib plus trametinib therapy. (D) Primary site and lymph node metastases had almost disappeared after two months of dabrafenib plus trametinib therapy. (E) A needle biopsy from the chest wall prior to dabrafenib plus trametinib therapy, with Hematoxylin and Eosin (H&E) staining (×200 magnification). Poorly differentiated epithelial-like tumor cells with spindle cells were observed. (F, G) A needle biopsy from the chest wall prior to dabrafenib plus trametinib therapy. (F) PD-L1 (×200 magnification). (G) A needle biopsy from the soft tissue metastasis after dabrafenib plus trametinib therapy, with H&E staining (×200 magnification). Poorly differentiated epithelial-like tumor cells with spindle and bizarre giant cells (arrows) were observed.**

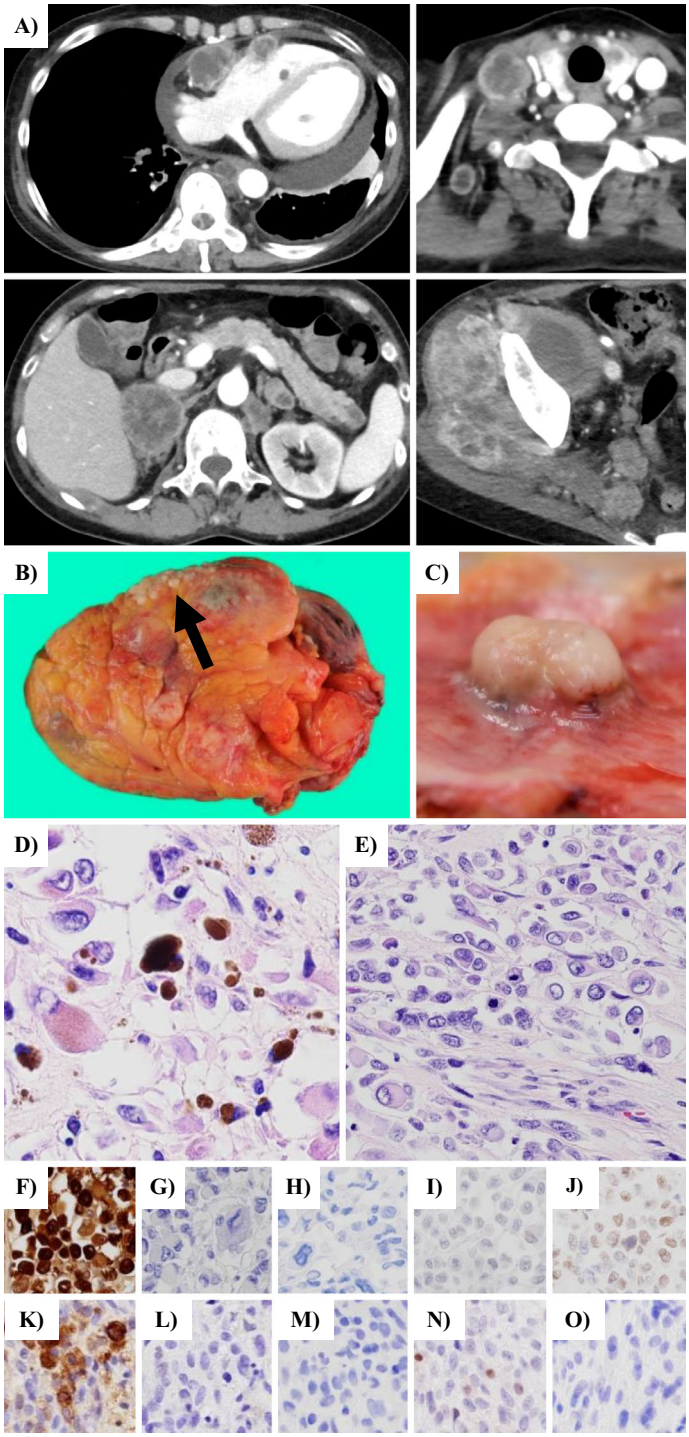

Figure 3. **Image examination findings and the autopsy evaluation. (A) CT findings from wo weeks before death. (B-J) Autopsy samples. (B, C) Multiple white nodules are observed on the (B) epicardial surface (arrow) and (C) ribs. (D) Liver metastasis with Hematoxylin and Eosin (H&E) staining (×400 magnification). Melanin pigmentation was observed in a small section. (E) An abdominal lymph node with H&E staining (×200 magnification). Poorly differentiated round tumor cells with spindle cells and giant cells were observed. (F-J) Staining of the supraclavicular lymph node. (F) S-100 (×200 magnification). (G) HMB-45 (×200 magnification). (H) Melan-A (×200 magnification). (I) MITF (×200 magnification). (J) SOX-10 (×200 magnification). S-100 was positive, SOX-10 was partially positive, and HMB-45, Melan-A, and MITF were negative. (K-O) IHC of the biopsy sample of the middle lobe of the right lung at the initial diagnosis, evaluated after the autopsy. (K) S-100 (×200 magnification). (L) HMB-45 (×200 magnification). (M) Melan-A (×200 magnification). (N) MITF (×200 magnification). (O) SOX-10 (×200 magnification). S-100 was positive, and Melan-A, HMB-45, MITF, and SOX-10 were negative.**

ports.

Conclusion

The current case suggests important caveats for the differential diagnosis of patients with *BRAF V600E* mutation-positive lung tumors. The *BRAF V600E* mutation is identified in 30% to 60% of malignant melanomas but only in 1% of NSCLC. Therefore, even if radiological findings show localization of the tumor in the thoracic region, a careful examination of the skin and mucosa, including the oral cavity, genitalia, and anus, by a dermatologist is recommended to rule out the possibility of lung metastasis from malignant melanoma. In terms of the pathological diagnosis, routine screening of S-100, HMB-45, Melan-A, and MITF may be useful, especially in patients with *BRAF V600E* mutation-positive poorly differentiated lung tumor without TTF-1 expression, as melanin pigmentation is not always identified by hematoxylin and eosin staining.

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

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