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【 CASE REPORT 】

Amelanotic Malignant Melanoma with Dense Pleural Thickening Mimicking Malignant Mesothelioma

Takeshi Saraya[1], Masachika Fujiwara[2], Kikuko Morita[1], Takayasu Watanabe[1], Yukari Ogawa[1], Hajime Takizawa[1] and Richard W Light[3]

Abstract:
A 51-year-old man was diagnosed with stage IIC nodular malignant melanoma (T4bN0M0) of the right upper arm. The tumor was treatment-refractory, and left-sided pleural effusion emerged 1.5 years later. Aspiration of pleural fluid revealed abundant amelanotic, atypical cells that resembled epithelial malignant mesothelioma or lung adenocarcinoma cells; these cells were positive for melanoma-associated antigen recognized by T cells (MART-1)/Melan-A, HMB-45, and S-100 on immunocytochemistry. Thoracic computed tomography (CT) revealed marked diffuse pleural thickening in the left hemithorax that mimicked malignant mesothelioma; thus, the present report describes the unique cytological and radiological findings of this case.

Key words: amelanotic melanoma, malignant melanoma, nodular type, pleural effusion

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Introduction

Malignant melanoma is a rare disease in Japan (1), and only a small number of cases with pleural effusion have been reported in the literature. In this regard, the presence of melanin pigment is a hallmark of malignant melanoma that can be used to differentiate this disease from other morphologically similar malignancies, such as malignant mesothelioma and lung adenocarcinoma. However, in cases where physicians encounter patients with amelanotic and hypomelanotic melanoma, immunohistochemical and immunocytochemical staining are powerful tools for arriving at a proper diagnosis.

We herein report a case of nodular amelanotic malignant melanoma.

Case Report

A 51-year-old man was referred to our hospital following multidisciplinary treatment for malignant melanoma. The patient had been diagnosed at his local hospital with a 1-cm skin tumor of the right upper arm, and the lesion was resected using laser surgery. Due to the presence of positive margins, an additional urgent surgery to remove the residual tumor was performed, together with excision of a 2- to 3-cm margin of normal tissue (Fig. 1A) and epidermization. Hematoxylin and eosin staining revealed the presence of atypical cells in the dermis (Fig. 1B), wherein a cohesive nodule of tumor cells was noted (Fig. 1C). The patient was thus diagnosed with nodular malignant melanoma (stage T4bN0M0). The patient had no remarkable medical history; he was an ex-smoker with a history of 15 pack-years and had neither extensive dust exposure nor taken illicit drugs.

He was subsequently treated with intravenous dacarbazine (DTIC) (120 mg/m^2, days 1-5), nimustine (ACNU) (60 mg/m^2, day 1), and vincristine (V) (0.6 mg/m^2, day 1) (collectively known as DAV therapy), as well as with subcutaneous interferon-β (3 million IU/day, days 1-5) every 4 weeks. However, after completing five courses of DAV therapy, the patient experienced local recurrence. Therefore, intravenous nivolumab (3 mg/kg) and local radiation (66 Gy) were administered every 3 weeks. Metastatic lesions were also identified in the bilateral lungs, as well as in the right axillary and right inguinal lymph nodes. The *BRAF* V600E mutation was detected in the resected primary tumor using two mo-

[1]Department of Respiratory Medicine, Kyorin University School of Medicine, Japan, [2]Department of Pathology, Kyorin University School of Medicine, Japan and [3]Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, USA
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Correspondence to Dr. Takeshi Saraya, sara@yd5.so-net.ne.jp

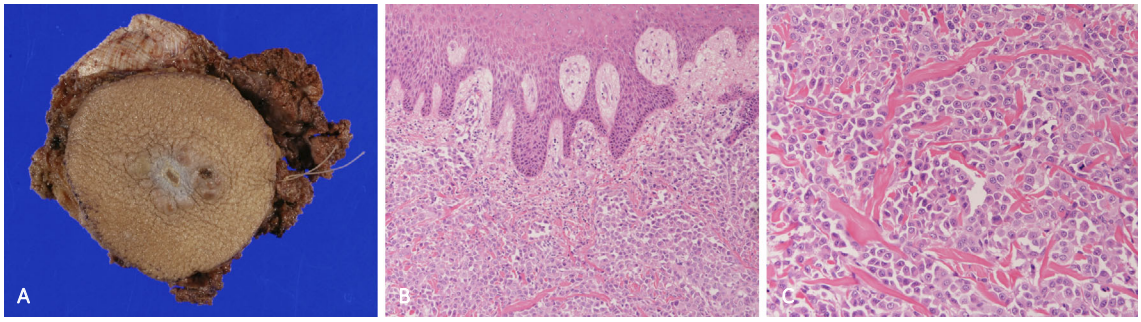

Figure 1. **(A) The tumor resected from the right upper arm. (B) Hematoxylin and Eosin staining demonstrated that the resected tumor had numerous atypical cells in the dermis. (C) A cohesive nodule of tumor cells was also noted in the dermis.**

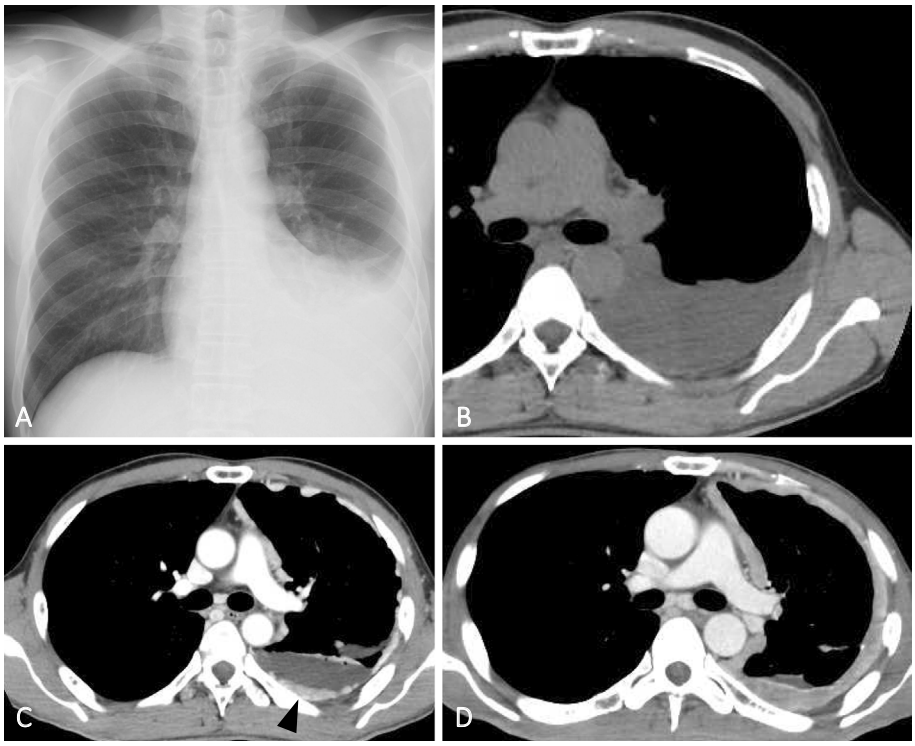

Figure 2. **(A) Chest radiograph taken 1.5 years after the patient's first visit to our hospital showed moderate, left-sided pleural effusion, which was confirmed by non-enhanced thoracic CT (B). (C) Two months later, contrast-enhanced thoracic CT demonstrated enhanced thickening of the parietal pleura (arrow head), which progressed remarkably over the next two months (D). CT: computed tomography**

lecular methods: real-time polymerase chain reaction and direct sequencing. Consequently, the oral administration of vemurafenib (960 mg twice daily), a competitive kinase inhibitor with activity against BRAF kinase mutations such as V600E, was initiated.

One and a half years after his first referral to our hospital, the patient experienced persistent dyspnea for a few weeks at a time. Chest radiographs showed left-sided pleural effusion (Fig. 2A) that was confirmed by non-enhanced computed tomography (CT) (Fig. 2B). The pleural effusion progressed over the next two months, and the patient was admitted to our respiratory department. On admission, his vital signs and physical examination findings were normal except for decreased left lung sounds and right inguinal and axillary lymphadenopathies. Serum chemistry results were normal. Pleural fluid obtained by thoracentesis was yellow and contained 4.6 g/dL of total protein, 144 IU/L of lactate dehydrogenase (LDH), 100 mg/dL of glucose, and 745 cells/μL with lymphocytes predominating (79%). A further analysis revealed normal levels of adenosine deaminase (ADA: 12.5 U/L), carcinoembryonic antigen (CEA: 0.5 ng/mL), cytokeratin subunit 19 fragment (CYFRA 21-1: 1.2 ng/mL), and hyaluronic acid (114,000 ng/mL). Following thoracic drainage, thoracic CT demonstrated an enhanced and partially thickened left parietal pleura (Fig. 2C, arrow head), suggesting pleural metastasis. This result was confirmed

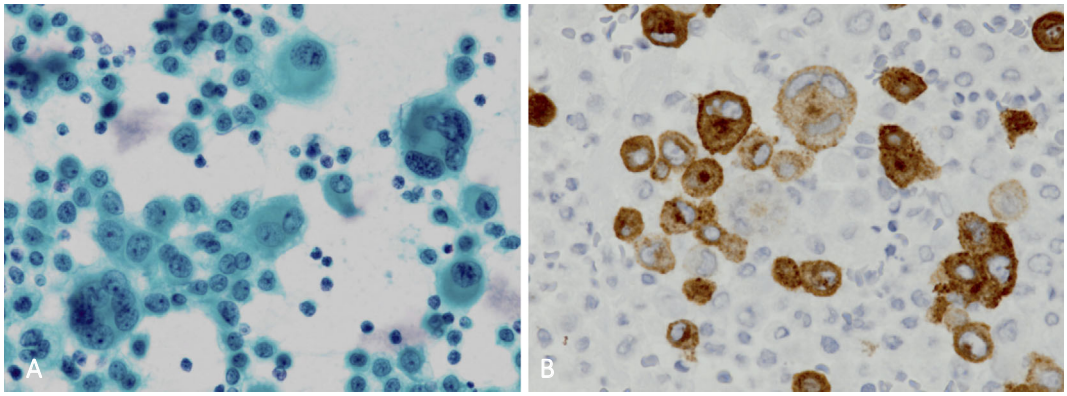

Figure 3. **(A) Papanicolaou staining of pleural effusion fluid revealed many large, multinucleated, atypical cells (magnification: ×400) resembling malignant mesothelioma (epithelioid type) or lung adenocarcinoma cells. (B) However, these cells were positive for MART-1/Melan-A (magnification: ×400) on immunocytochemical staining. MART-1: melanoma-associated antigen recognized by T cells**

with a Papanicolaou smear, which showed that the specimen contained large, multinucleated, atypical cells (Fig. 3A) that resembled malignant mesothelioma (epithelioid type) or lung adenocarcinoma cells. However, upon an immunocytochemical analysis, the atypical cells were positive for melanoma-associated antigen recognized by T cells (MART-1)/Melan-A (Fig. 3B), HMB-45, S100 protein, and vimentin and were negative for cytokeratin AE1/AE3, calretinin, and D2-40. Therefore, the patient was diagnosed with malignant melanoma.

Surprisingly, within two months, the pleural thickening rapidly expanded to 15 mm in diameter and eventually encompassed the entire left hemithorax (Fig. 2D). Thereafter, the tumor was refractory to treatment and the patient died of respiratory failure two years after his initial referral to our hospital.

Discussion

Malignant melanoma is a rare disease in Japan; the incidence rate per 100,000 people per year is 0.93, which is markedly lower than that of the European Union (12.41) (1). With regard to melanomas that occur at common sites (e.g., the sole of the foot), World Health Organization guidelines classify the majority of these cancers into four major subtypes: superficial spreading, nodular, lentigo maligna, and acral lentiginous. In Japan, acral lentiginous melanoma is the most prevalent subtype (48.7%), followed by nodular melanoma (25.8%), superficial spreading melanoma (17.5%), and lentigo maligna melanoma (8.0%) (2). Of these subtypes, nodular melanoma is associated with the worst prognosis (survival rate: 47.3% over an 80-month follow-up period) due to the heightened risk of metastasis (2), as in the present case. Melanoma can spread cutaneously, to distant lymph nodes, and to visceral organs, such as the lung (18-36%), liver (14-20%), brain (12-20%), and bone (11-17%) (3). Thus, although the lung is the most common site of metastasis, pleural effusion alone can be the initial sign of this disease (4).

Although the presence of melanin granules in the cytoplasm of tumor cells is a characteristic of malignant melanoma, all melanoma subtypes may present as amelanotic or hypomelanotic lesions both clinically and cytologically (5, 6). This feature is most commonly observed in the nodular and desmoplastic subtypes. Accordingly, the present case was confirmed as nodular melanoma with no evidence of melanin granules.

With respect to differential diagnoses, we did not evaluate the patient's serum levels of soluble mesothelin-related peptides, which is a reliable diagnostic marker for malignant mesothelioma. However, the levels of other markers in the pleural fluid, including CEA, CYFRA 21-1, hyaluronic acid, and ADA, were normal, indicating that a diagnosis of malignant mesothelioma, lung cancer, or tuberculous pleuritis was unlikely.

Furthermore, tumor cells in the pleural fluid were positive for MART-1/Melan-A, S100, and HMB-45, which are indicative of malignant melanoma (6, 7) rather than the morphologically similar malignant mesothelioma or lung adenocarcinoma. We therefore did not evaluate the *BRCA1-associated protein 1* (*BAP1*) mutation status of the sample, as mutations in this gene are associated with both melanoma and a wide range of other cancers, such as lung cancer, meningioma, mesothelioma, and renal cell carcinoma (8).

Pleural thickening can be indicative of several diseases, such as primary (9) or secondary pleural lymphoma, tuberculous pleuritis (10), metastatic lung cancer, malignant mesothelioma (11), ectopic thymoma, and sarcomatoid carcinoma (12). Of note, the thoracic CT findings in our case showed dense pleural thickening that encompassed the left hemithorax, reminiscent of malignant mesothelioma. However, as described in previous reports (13, 14), this pattern of growth is rarely observed in malignant melanoma. This can lead to diagnostic challenges, especially in cases of

amelanotic melanoma.

In summary, patients with malignant melanoma require rapid and intensive treatments, and pleural thickening, such as that seen in malignant mesothelioma, is a potential radiological finding. Of note, a careful cytological examination specifically focusing on the presence of melanin pigment in tumor cells, together with immunocytochemical staining, can differentiate malignant melanoma from other malignancies with similar morphological features.

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

References

1. Tamaki T, Dong Y, Ohno Y, Sobue T, Nishimoto H, Shibata A. The burden of rare cancer in Japan: application of the RARECARE definition. Cancer Epidemiol **38**: 490-495, 2014.
2. Ishihara K, Saida T, Yamamoto A; Japanese Skin Cancer Society Prognosis and Statistical Investigation Committee. Updated statistical data for malignant melanoma in Japan. Int J Clin Oncol **6**: 109-116, 2001.
3. Velu PP, Cao C, Yan TD. Current surgical management of melanoma metastases to the lung. J Thorac Dis **5**(Suppl): S274-S276, 2013.
4. Chen JT, Dahmash NS, Ravin CE, et al. Metastatic melanoma in the thorax: report of 130 patients. AJR **137**: 293-298, 1981.
5. Longatto Filho A, de Carvalho LV, Santos Gda C, et al. Cytologic diagnosis of melanoma in serous effusions. A morphologic and immunocytochemical study. Acta Cytol **39**: 481-484, 1995.
6. Ikeda K, Tate G, Iezumi K, Suzuki T, Kitamura T, Mitsuya T. Effusion cytomorphology and immunocytochemistry of malignant melanoma: five cases of melanotic melanoma and one case of amelanotic melanoma. Diagn Cytopathol **37**: 516-521, 2009.
7. Ohata Y, Haga T, Ogata S, Nakanishi K, Kawai T. Malignant amelanotic melanoma of the pleura without primary skin lesion: an autopsy case report. Acta Med Okayama **63**: 379-384, 2009.
8. O'Shea SJ, Robles-Espinoza CD, McLellan L, et al. A population-based analysis of germline BAP1 mutations in melanoma. Hum Mol Genet **26**: 717-728, 2017.
9. Saraya T, Takei H, Fujiwara M, et al. Primary pleural lymphoma with dense pleural thickening. Pulm Res Respir Med Open J **2**: 77-80, 2015.
10. Tsujimoto N, Saraya T, Takizawa H, Goto H. Tuberculous peritonitis incidentally diagnosed on FDG-PET/CT. Intern Med **52**: 841-842, 2013.
11. Saraya T, Yokoyama T, Ishii H, et al. A case of malignant peritoneal mesothelioma revealed with limitation of PET-CT in the diagnosis of thoracic metastasis. J Thorac Dis **5**: E11-E16, 2013.
12. Inomata M, Kawagishi Y, Yamada T, et al. Two cases of pulmonary sarcomatoid carcinoma mimicking malignant mesothelioma. Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc) **48**: 33-38, 2010 (in Japanese, Abstract in English).
13. Sanno K, Sugawa K, Nakano C, Kashiwa K. Thoracoscopic findings of malignant melanoma. Intern Med **49**: 2643, 2010.
14. Wang Q, Chen J, Dassarath M, et al. Primary malignant melanoma of the pleura with rapid progression: a case report and literature review. Oncol Lett **9**: 2713-2715, 2015.