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Primary malignant melanoma of the pleura with rapid progression: A case report and literature review

QIONG WANG[1], JING CHEN[1], MEERA DASSARATH[1], ZHONGYUAN YIN[1], XIUPING YANG[2], KUNYU YANG[1] and GANG WU[1]

[1]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430023; [2]Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China

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Abstract. A primary melanocytic lesion arising from the pleura is a rare occurrence. This is the case report of a 36-year-old female patient with a primary pleural melanocytic tumor. The positron emission tomography/computed tomography scan revealed multiple nodular soft tissue thickenings of the left hemipleura and a large amount of pleural effusion in the left hemithorax. The results of the histological examination confirmed the diagnosis of melanoma. The disease progressed 4 months following immunotherapy and chemotherapy and the patient succumbed to the disease 2 months later. This type of tumor appears to exhibit a highly aggressive biological behavior and responds poorly to immunotherapy and chemotherapy, which are characteristics similar to those exhibited by melanomas arising in other regions.

Introduction

Melanoma is a malignant tumor that originates from melanocytes, which are the cells that produce the pigment melanin. Melanoma is the most life-threatening and treatment-resistant skin cancer. Although 91.2% of melanomas arise from the skin, 5.3% arise from ocular tissues, 1.3% from mucosal tissues and <1% from the urethra, with the remainder being of unknown primary origin (1,2). Primary pleural melanoma is a rare occurrence. To the best of our knowledge, only three cases have been reported thus far (3-5). This is the presentation of an unusual case of primary malignant melanoma of the pleura in a 36-year-old female patient. Written informed consent was obtained from the family of the patient.

Correspondence to: Dr Kunyu Yang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430023, P.R. China
E-mail: yangky71@aliyun.com

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Case report

A 36-year-old female patient was admitted to the Union Hospital (Wuhan, China) in September, 2010 due to intermittent left abdominal pain over the previous ~6 weeks. The patient also complained of other symptoms, including dry cough and dyspnea associated with the pain. No cutaneous mass or ulceration was identified on physical examination. The chest X-ray revealed a large amount of pleural effusion in the left hemithorax. Thoracocentesis was performed at the Department of Thoracic Surgery, Union Hospital. Macroscopically, the pleural effusion was black in color, while the cytology revealed abnormalities of the red blood cells. The positron emission tomography/computed tomography (PET/CT) scanning showed multiple nodular soft tissue thickenings of the left hemipleura, inferior visceral pleura of the right lower lobe and right hilum. A lesion with high standardized uptake value (SUV) was detected and pleural effusion in the left hemithorax was reconfirmed by the scan (Fig. 1). No other high-SUV lesion was identified on PET/CT.

A thoracoscopic biopsy was performed and the histological examination of the pleural mass revealed round to polygonal cells with large nuclei. On immunohistochemical examination, the tumor cells were positive for the expression of intracellular melan-A, human melanoma black-45 (HMB-45), vimentin (Vim) and S-100 and negative for calretinin and pancytokeratin, which further confirmed the diagnosis of melanoma. The patient was then transferred to the Cancer Center of the Union Hospital and received three cycles of chemotherapy with dacarbazine (200 mg/m^2, days 1-3) and cisplatin (30 mg/m^2, days 5-7), in combination with interferon-α2b immunotherapy. Upon reevaluation, a partial response was achieved following three cycles of immunochemotherapy.

The patient declined further treatment due to grade 4 neutropenia and grade 3 thrombocytopenia; she remained asymptomatic for 2 months prior to the development of severe cough and hemoptysis and was readmitted to the Cancer Center of the Union Hospital in January, 2011. A chest CT scan revealed that the masses in the left pleural cavity had significantly increased in size. The patient was administered two further cycles of chemotherapy with dacarbazine and cisplatin, at the same dosage mentioned above.

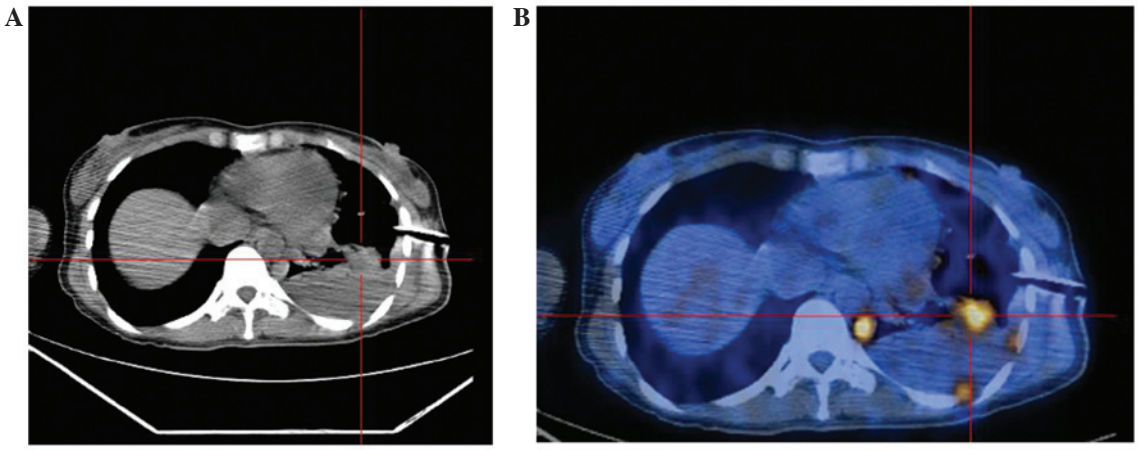

Figure 1. Pleural thickening protruding in the form of a nodular mass from the left thoracic wall prior to treatment is shown by the (A) computed tomography and (B) positron emission tomography scans.

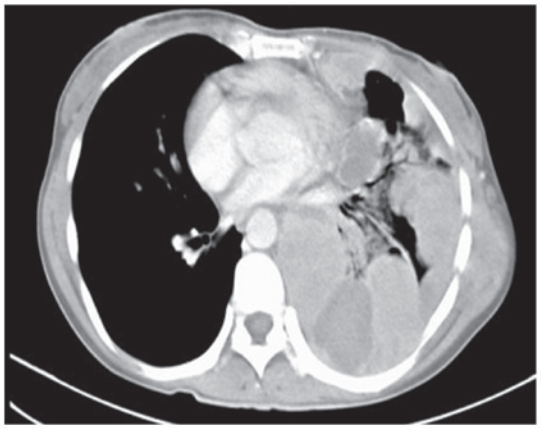

Figure 2. Computed tomography scan revealing a large mass with an unclear boundary infiltrating the interspace of the mediastinum.

However, the symptoms of cough and hemoptysis did not subside and the hemoptysis increased in severity during chemotherapy. A reevaluation chest CT scan (Fig. 2) was conducted after the fifth cycle of chemotherapy in April, 2011 and revealed that, in addition to the increased thickness of the pleura, a sizeable mass with an unclear boundary infiltrated the interspace of the mediastinum, subcutaneous tissue of the left chest wall, hilum of the left lung and right cardiac border. There were no identified metastatic nodules in the right lung. The patient was unsuccesfully palliated, exhibiting persistent cough and hemoptysis for 1 month following treatment completion. The patient eventually succumbed to the disease after 2 months.

Discussion

The incidence of melanoma has been continuously increasing over the last few decades. Despite earlier diagnosis, the prognosis of patients with melanoma remains poor. Primary pleural melanoma is a rare entity, with only three cases reported worldwide thus far (3-5). However, metastasis of malignant melanoma to the pleura or lung is relatively common. Furthermore, the symptoms of pleural melanoma are often mistaken for other types of primary pleural cancer. It is therefore important to distinguish primary pleural melanomas from metastatic or other types of primary pleural cancer.

Three basic clinical criteria should be referred to when establishing a diagnosis of primary melanoma of the pleura: i) No previously removed skin tumor, unless the pathological examination did not reveal malignancy and the slides are available for reevaluation; ii) a solitary tumor in the surgical specimen from the pleura; and iii) no demonstrable melanoma in other locations at the time of surgery (6). The present case fulfilled these criteria. The patient had not undergone any skin operation. At the time of diagnosis, only a solitary tumor on the pleura was identified on PET/CT imaging. However, metastatic lesions appeared and gradually increased in size during the follow-up period.

Pleural mesothelioma shares certain clinical and imaging characteristics with pleural melanoma. The key points for differential diagnosis lie in the expression levels of certain immunohistochemical markers: Premelanosomes, melan-A, Vim, S-100 and HMB-45 are well-defined surface markers for melanoma, while cytokeratin (CK)5/6, CK8/18, carcinoembryonic antigen, Vim, melanocortin and calretinin are considered to be mesothelioma markers.

A popular view on melanoma growth (7) is that there are eight pathological and clinical levels in a classic melanoma model of growth and development: Precursor melanocyte, commonly acquired or congenital nevus with the presence of normal melanocytes, dysplastic nevus with structural and architectural atypia, radial growth melanoma, non-tumorigenic primary melanoma without the capacity to metastasize, vertical growth melanoma, primary melanoma invading the dermis with the potential ability to metastasize and, finally, metastatic melanoma. The histogenesis of malignant melanoma of the pleura has not been fully elucidated. Patients with thick melanomas exhibit an increased risk of developing lymph node and visceral metastases (8). Therefore, it is hypothesized that the mechanism of pleural melanoma development involves cutaneous nevus cells entering dermal lymphatic vessels and subsequently traveling via the lymphatic system to the pleura. However, due to the limited number of reported cases of pleural melanoma, this theory has not been definitively proven.

Notably, it was identified that, among the four reported cases, including the present case, one patient displayed a malignant amelanotic melanoma, one case was not recent enough to obtain detailed information and the remaining two patients displayed sizeable congenital nevi. In a study by Mohanty *et al* (4), an Indian 50-year-old male farmer exhibited a giant congenital 'bathing suit' hairy nevus, ranging from small dots to extensive hyperpigmented hairy regions, extending anteroposteriorly to cover the entire lower extremity below the waist. In the present case, the 36-year-old Chinese female patient also exhibited a large congenital nevus covering almost half of the right lower extremity. Based on the abovementioned hypothesis and the latter two cases, it may be concluded that individuals exhibiting sizeable congenital skin nevi may be at higher risk of developing primary pleural melanoma. Olsen *et al* (9) reported that the highest melanoma burden is always among individuals with high nevus counts, with patients displaying ≥25 common and/or ≥1 atypical nevi constituting a high-risk group. Normal and atypical nevi are considered to be precursor lesions for melanoma and they are difficult to discriminate based on clinical or histopathological characteristics. The ABCDE rule may be applied for the clinical diagnosis of an atypical nevus: The lesion is considered atypical when it is asymmetrical (A), with uneven borders (B), multiple colors (C), diameter >5 mm (D) and elevation (E) above the surface with a maculopapular aspect (10). Although a number of findings suggest that common nevi, atypical nevi and melanomas share certain common molecular triggers that may define a pathogenic pathway (11), fluorescence in-situ hybridization (FISH) has entered the field of melanoma diagnosis in recent years. Gerami *et al* (12) reported a high sensitivity (87%) and specificity (95%) for diagnosing melanoma with a combination of four FISH probes that target 6p25 (RREB1), 6q23 (MYB), 11q13 (CCND1) and chromosome 6 centromere. However, there is no single method that allows for a definitive diagnosis of melanoma with either atypical or common nevi. Thus, it is necessary to carefully analyze the patterns of clinical expression, pathological characteristics and abnormalities of molecular genetics.

Surgery remains the mainstay of treatment for melanoma; however, its prognosis does not appear to be promising, based on our experience with pulmonary melanoma. Wilson and Moran (13) reported that five of eight patients succumbed to metastatic disease 4-32 months after their surgical procedures. The treatments approved by the Food and Drug Administration for patients with advanced melanoma are limited and they include immunotherapy, chemotherapy, molecularly targeted therapy and conventional chemotherapeutic agents. The patient in the present case received conventional immunotherapy and chemotherapy and eventually succumbed due to the rapid disease progression. There have been significant advances in the treatment of melanoma over the last few years, with an improved understanding of the involved molecular pathways and the critical role of the immune system in this process (14). Mitogen-activated protein kinase pathway inhibition and the blockade of immune checkpoints are currently the focus of investigation in the treatment of metastatic melanoma. In particular, combining active therapies to overcome resistance is key to making further advances. However, the knowledge and accumulated experience regarding the diagnosis and treatment of primary pleural melanomas are currently limited and the presentation of more cases is required to optimize treatment.

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