Pleural effusion as the initial manifestation of metastatic melanoma: a case report and literature review

LiHua Yu

The Second Affiliated Hospital and Yuying Children's Hospital of WenZhou Medical University, WenZhou, China <https://orcid.org/0000-0001-9455-9232>

Duoduo Quan

The Second Affiliated Hospital and Yuying Children's Hospital of WenZhou Medical University, WenZhou, China

Zhangwei Qiu

The Second Affiliated Hospital and Yuying Children's Hospital of WenZhou Medical University, WenZhou, China

Hui Xu

The Second Affiliated Hospital and Yuying Children's Hospital of WenZhou Medical University, WenZhou, China

Jianbo He

The second Affiliated Hospital and Yuying Children's Hospital of WenZhou University, WenZhou, China

Yuanrong Dai (✉ daiyr@126.com)

The Second Affiliated Hospital and Yuying Children's Hospital of WenZhou Medical University, WenZhou, China

Case report

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Abstract

Background: Malignant melanoma (MM) is a highly invasive form of skin cancer with poor prognosis. Pleural metastatic melanoma is rare, with only a few reported cases.

Case presentation: A 47-year-old woman with a medical history of right heel melanoma was diagnosed with left-sided pleural effusion, with pleural thickening and calcified mediastinal lymph nodes, using chest computed tomography (CT). A video-assisted thoracoscopic biopsy was performed which revealed numerous pink lumps arising from the parietal pleura and viscera along the diaphragmatic surface. The pathological diagnosis was pleural metastatic melanoma and the tumor cells were immunocytochemically positive for S100, SOX10, and Melan-A.

Conclusions: The clinical manifestations of metastatic pleural melanoma are nonspecific. Pleural effusion cytology combined with thoracoscopy is an effective diagnostic method. The presence of melanocytes has improved the diagnosis of this condition.

Introduction

Malignant melanoma (MM) is the most aggressive form of skin tumor, originates from melanocytes, and displays a high degree of phenotypic plasticity. The disease primarily occurs in the skin, but is also found in the eyes, ears, oral cavity, digestive tract, genital mucosa, and leptomeninges ⁽¹⁾. It is the most deadly form of skin cancers with an increasing incidence over the past 30 years ⁽²⁾. Metastatic melanoma accounts for approximately 5% of all secondary lung malignancies and only 2% of the patients have manifested pleural effusions ⁽³⁾. This study reports a woman who presented with unilateral pleural effusion and finally diagnosed with metastatic melanoma using video-assisted thoracoscopic biopsy. We also considered 15 reported cases of metastatic melanoma that initially presented with pleural effusion and analyzed the clinical features of metastatic pleural melanoma.

Case Report

A 47-year-old woman was admitted to The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University with a 2-month history of dry cough and shortness of breath. She denied any other symptoms, including fever, chill, dysphagia—except for weight loss of 3 kg in the previous 2 months. The patient's surgical history was pertinent to the local excision of a melanoma lesion on the right heel 6 years prior, which was found to have infiltrated about 3.5 mm subcutaneously. On physical exam, she had a pulse of 87/min, blood pressure of 122/78 mmHg, temperature of 36.8°C, and respiration rate of 21/min. Chest examination showed dullness to percussion and diminished breath sound in the left lung. A surgical scar with a length of about 5 cm was observed on the right heel.

Laboratory tests, including routine blood, liver, and renal function tests were normal. The neuron-specific enolase was slightly elevated at 26.76 ng/ml, whereas other serum tumor markers for lung carcinoma, including squamous cell carcinoma, carcinoembryonic antigen, and cytokeratin 19 fragments were within

normal levels. However, the tuberculin purified protein derivative (PPD) skin test showed a 19*20 mm size induration. Spirometry was performed and it revealed severe mixed ventilation dysfunction and a decrease in the maximum ventilation per minute. The chest radiograph at admission revealed left pleural effusion with pleural thickening, collapsing of the left lung, and calcified mediastinal lymph nodes. Thoracentesis was performed because of massive pleural effusion, with removal of 2L straw-colored fluid. The pleural fluid was an exudate containing; 711 IU/L lactate dehydrogenase (LDH), Serosal Mucin (Rivalta test) 1 + positive, and 270 cells/ μ L (59% macrophages and 11% lymphocytes). Further examination demonstrated normal levels of adenosine deaminase (ADA: 18.3 U/L), carcinoembryonic antigen (CEA: 0.62 ng/mL), and cytokeratin subunit 19 fragment (CYFRA21-1: 3.75 ng/mL). The pleural fluid cultures were negative for bacterial, fungal, and mycobacterium tuberculosis infections. The diagnosis was not evident, so the patient underwent a video-assisted thoracoscopic biopsy which revealed numerous pink lumps arising from the parietal pleura and viscera along the diaphragm surface (Fig. 1). Biopsies of multiple pleural-based lumps were performed and a tunneled indwelling pleural catheter was placed. A chest contrast-enhanced CT scan (Fig. 2) showed left pneumothorax following thoracoscopy, left side pleural thickening with multiple nodules, right lower lobe nodules which were suspected to be inflammation, and mediastinal lymph node calcification. Immunohistochemical staining was positive for S100, SOX10, and Melan-A, confirming the diagnosis of metastatic cutaneous melanoma (Fig. 3a,b,c,d). The patient was administered 200 mg intravenous D1 immunotherapy with Sindilimum and showed abdominal metastasis at a 6-month follow-up.

Discussion And Conclusions

Malignant melanoma (MM) is a malignant tumor of pigment-producing cells (melanocytes) which primarily occur in the skin, but is also noted in the eyes, ears, oral cavity, digestive tract, genital mucosa, and leptomeninges ⁽¹⁾. The yearly incidences in Japan and the European Union are 0.93 and 12.41 per 100,000 people respectively ⁽⁴⁾. Secondary metastatic pleural melanoma is rare and usually occurs in pulmonary metastasis. Only 2% of melanoma patients with intrathoracic metastasis develop malignant pleural effusion ⁽³⁾.

There are few reports of recurrent malignant melanoma mainly presenting with pleural effusions in the literature ⁽⁵⁻¹⁸⁾ (Table 1); all were confirmed by pathology.

Metastatic pleural effusion is more frequent in males, with a ratio of approximately 11:4 with most of the patients being > 40 years old (Table 2). According to a previous study, the age of patients with metastatic melanoma to the thorax varies from 16 to 79 years (mean, 51 .9) and the male-to-female incidence ratio is approximately 1.6:1 ⁽³⁾. Most malignant melanomas originated from skin areas such as trunk and limbs but can also be mucosal such as the oral, cilioretinal, and choroidal.

The duration from diagnosis of the primary cancer to thoracic metastasis averages 32 months. However, the range is wide and pulmonary metastasis occurred 12 and 15 years after the initial diagnosis for two patients ⁽¹⁹⁾. There is no study done on the period of malignant melanoma metastasis to the pleura. In

our review, the time-lapse from the primary tumor to the detection of pleural metastasis is from 8 months to 16 years (mean, 4.9 years). Two patients were diagnosed with pleural metastatic melanoma using pleural biopsy histopathologic findings having denied having a medical history of malignant melanoma. Choroidal and oral malignant melanoma were also later discovered ^(11, 12). It may be postulated that concealment of the primary lesion caused delayed diagnosis. The longest recorded time from the primary tumor to pleural metastasis is 16⁽¹³⁾ years. The patient presented with left-sided massive pleural effusion; thoracoscopic pleural biopsy revealed metastatic malignant melanoma. The patient had malignant melanoma of the scalp 16 years prior ⁽¹³⁾ and later acknowledged a history of right heel surgery for cutaneous melanoma.

The clinical presentation of the disease is nonspecific, including; shortness of breath, chest pain, cough, and weight loss (Table 2). Therefore search for primary lesions is essential. It is known that primary cutaneous amelanotic melanoma may disappear during an advanced course ⁽²⁰⁾. Abdominal pain is a rare sign of malignant melanoma that was discussed by Mytinger AK. *et al.* ⁽¹⁵⁾ (Table 3). Anand, K. *et al.* ⁽¹³⁾ reported an unusual patient with chronic lymphocytic leukemia (CLL) with recurrent pleural effusions, indicating that T-cell dysregulation and dysfunction in CLL may increase the risk of recurrence or secondary malignancies. A 63-year-old man who presented with black-colored pus (pyopneumothorax) resulting from an infected pleural effusion (positive for *Pseudomonas*) and related to metastatic malignant melanoma of the skin was discussed by Patel, G. *et al.* ⁽¹⁴⁾.

Unilateral pleural effusion with or without pleural nodules, pleural thickening, pulmonary nodules, mediastinal lymphadenopathy, or calcification is the most common finding on imaging (Table 2, 3). W. Richard *et al.* reported ⁽¹⁹⁾ that 10 of 65 malignant melanoma patients that had thoracic metastasis presented with pleural effusion and 80% of them were unilateral pleural effusion. For our patient, the left pleura was significantly thickened and calcified so that the puncture needle had significant resistance to entry. Pleural thickening can indicate several diseases, such as malignant mesothelioma, tuberculous pleuritis, primary or secondary pleural lymphoma, metastatic lung cancer, ectopic thymoma, and sarcomatoid carcinoma ⁽²¹⁾. The differential diagnosis included mesothelioma, adenocarcinoma, primary pleural sarcoma, thymic epithelial tumors, lymphoma, and other metastatic tumors ⁽⁷⁾. Tuberculosis (TB) remains a significant public health concern in China, with one million new cases every year ⁽²²⁾. The patient was first suspected to have tuberculous pleuritis from the clinical manifestations of elevated T-SPOT with positive laboratory findings of Tuberculin purified protein derivative (PPD) skin test. However, the low ADA level indicated that the diagnosis was unlikely and she was finally diagnosed with metastatic pleural melanoma using thoracoscopy.

Pleural effusion is expected to be helpful for the diagnosis of metastatic pleural melanoma with the color being bloody, yellow, or black (Table 2). Bloody pleural effusion (BPEs) is the most common with approximately half being secondary to tumors. However, only 11% of the malignant effusions were BPEs. Other common causes of BPEs include parapneumonic and posttraumatic ⁽²³⁾. Melanin pigment is an indicator of malignant melanoma which can distinguish this disease from other morphologically similar

tumors, such as lung adenocarcinoma and malignant mesothelioma ⁽²¹⁾. However, malignant melanoma does not always present with melanin in pleural fluids which increases the difficulty of diagnosis. A combination of immunohistochemistry and immunocytochemical staining techniques are powerful tools for definitive diagnosis in cases of amelanotic or hypomelanotic melanoma ⁽²¹⁾.

The diagnostic approach involves a variety of methods such as thoracentesis, skin biopsy, lymph node biopsy, thorascopic pleural biopsy, and surgical operations. Thoracentesis is the most effective initial diagnostic procedure. Diagnosis was made for six patients using pleural fluid cytology, 8 by thorascopic pleural biopsy, and 1 through a resected specimen. It is reported that the diagnostic sensitivity of cytologic analysis ranged from 40–90% (mean; 65%) with a specificity of > 99%, since the highest reported false positive rate is 0.78% ⁽²⁴⁾. Multiple examination of pleural effusion provides a better diagnosis. Medical thoracoscopy is routinely used for the assessment of undiagnosed exudative pleural effusions. Combining these methods will facilitate diagnosis in > 90% of patients that present with pleural effusion ⁽²⁴⁾.

The prognosis of melanomas is dismal. Survival after radiographic detection of thoracic metastasis averaged 7 months and was not longer for patients with slow metastasizing primary malignancy ⁽¹⁹⁾. The typical survival time of secondary metastatic melanoma ranges between 4 and 5 months, after the diagnosis ⁽²⁵⁾. Mishe'el, S. *et al.* ⁽¹²⁾ described a patient who presented with diffuse melanosis cutis (DMC), black pleural effusion, black urine, and died 2 weeks after admission; DMC is an extremely rare manifestation of metastatic melanoma with a poor prognosis (mean survival of ~ 4 months) ⁽²⁶⁾ and was reported in approximately 0.22–0.27% of the cases ⁽²⁷⁾. However, Wang, T. S. *et al.* reported a case of complete spontaneous regression of the metastatic lesions. Of the 15 reported metastatic pleural melanoma cases, 5 died within 6 months of diagnosis, indicating the aggressive course of the tumor. Talc and bleomycin are usually used as sclerosing agents in malignant effusion ⁽²⁸⁾. Palliative treatment using pleurodesis was done in 4 of the 15 cases in our review.

In conclusion, we report a left-sided pleural effusion as a rare presentation of metastatic malignant melanoma. We also reviewed 15 reported cases of metastatic melanoma who initially presented with pleural effusion, and discussed the clinical features of metastatic pleural melanoma. A limited number of studies have been reported, although metastatic pleural melanoma is rare, and has nonspecific clinical manifestations. Pleural effusion cytology combined with thoracoscopy is an effective diagnostic method for metastatic pleural melanoma. The presence of melanocytes has improved diagnosis.

Abbreviations

MM

Malignant melanoma

LDH

lactate dehydrogenase

BPEs
Bloody pleural effusion
CLL
chronic lymphocytic leukemia
PPD
Tuberculin purified protein derivative
TB
Tuberculosis
ADA
adenosine deaminase

Declarations

Acknowledgments

Not applicable

Authors' contributions

Lihua Yu and Duoduo Quan designed the study and wrote the manuscript. Zhang Wei Qiu collected tissue and data; Hui Xu performed radiological evaluation; Jianbo He conducted thoracoscopy evaluation; Duoduo Quan conducted histological evaluation; Yuanrong Dai wrote and edited the manuscript. All authors critically reviewed the manuscript and gave final approval for publication.

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Availability of data and materials

The datasets generated during and analyzed during the current study are available in the corresponding author repository.

Ethics approval and consent to participate

Ethical approval for this investigation was obtained from the Research Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China.

Consent for publication

Written informed consent for publication of this case report and any accompanying images was obtained from the patient. A copy of the written consent is available for review.

Competing interests

The authors declare that they have no competing interests.

Author details

1. Division of Pulmonary Medicine, The Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China.
2. Division of Pathology Medicine, The Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, China.

These authors contributed equally to this work and should be considered co-first authors.

* Correspondence: daiyr@126.com

1. Division of Pulmonary Medicine, The Second Affiliated Hospital, and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, 325000, China.

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Tables

Due to technical limitations, Tables 1-3 are only available as a download in the supplemental files section

Figures

Figure 1

Thoracoscopic view. Numerous pink lumps arising from the parietal pleura and visceral along with the diaphragmatic surface.

Figure 2

Contrast enhanced CT of the chest after thoracoscopic biopsy showing a left pneumothorax and left-sided pleural thickening with multiple nodules of the parietal pleura.

Figure 3

a. HE stainin of pleural biopsy (*40 magnification). Immunohistochemical staining showing that the neoplastic cells were positive for Melan-A(b), S-100(c), SOX-10(d). b-d*100

Supplementary Files

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