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CASE REPORT PEER REVIEWED | OPEN ACCESS

Primary pulmonary malignant melanoma versus metastatic melanoma with indeterminate primary site

Harpreet Rai, Asghar H Naqvi, Waël C Hanna, Salem O Alowami

ABSTRACT

Introduction: Primary malignant melanoma of the lung is an extremely rare entity with a dismal prognosis.

Case Report: Herein, we present a case of primary malignant melanoma of the lung in a 67-year-old woman with a history of chest infection and a suspicious lesion on a chest X-ray. Computed tomography scan of the chest confirmed a nodule in the left lower lobe. Positron emission tomography showed a hypermetabolic tumor with no evidence of metastatic disease or mediastinal lymphadenopathy. The patient subsequently underwent surgery. Histopathological examination, supported by immunohistochemical analysis, was in accordance with malignant melanoma.

Conclusion: Since the published data focusing on cases of primary malignant melanoma of the lung are limited, the pathological features of these melanomas, their histogenesis, clinical behavior, and the possible therapeutic options are not well established.

Keywords: BRAF, Lung, Malignant melanoma

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INTRODUCTION

Malignant melanoma is primarily a cutaneous malignancy. Although rare, primary extracutaneous melanomas involving the ocular region, leptomeninges, and mucosal surfaces such as the oral cavity, anorectal region, genitourinary tract, and liver have been reported [1–4]. Primary malignant melanoma of lung (PMML) accounts for 0.01% of all primary lung malignancies and 0.4% of all malignant melanomas. Based on a literature search, there have been 76 cases of PMML identified [5].

CASE REPORT

A 67-year-old woman with no smoking history presented with symptoms of a chest infection. Her past medical history was significant for a right-sided stage II invasive ductal carcinoma grade II, estrogen receptor (ER)/progesterone receptor (PR) positive, and HER2 negative. She was treated with a partial mastectomy, radiation, and ongoing antiestrogen therapy with anastrozole. She had regular follow-up with her medical team. There was no prior history of skin, ocular, or gastrointestinal (GI) lesions. Her family history was significant for breast cancer and lung cancer. There was no family history of skin cancer(s).

Her chest X-ray demonstrated a lesion in the left lower lobe (LLL) measuring 1.6 × 1.2 cm. Subsequent CT scan of the chest further confirmed a centrally located nodule in

the lung. Her positron emission tomography (PET) scan showed hypermetabolic activity in the tumor. Computed tomography scan for staging showed no evidence of thoracic or intra-abdominal metastasis. Pulmonary function tests revealed an FEV1 of 102% predicted and diffusing capacity of carbon monoxide (DLCO) of 105% predicted. The patient underwent left lower lobe segmentectomy with thoracic lymphadenectomy with curative intent. A post-surgery CT scan of the chest revealed complete excision with no evidence of mediastinal or hilar lymphadenopathy.

The specimen was submitted for routine histopathological examination. Sections were stained with hematoxylin and eosin (H&E) and analyzed. Immunohistochemistry (IHC) and molecular analyses were also performed. Tumor cells were pleomorphic with high nuclear/cytoplasmic ratio, dispersed chromatin, and some with prominent nucleoli (Figures 1 and 2). Tumor cells were positive for S100, HMB45, melanoma cocktail, and vimentin (Figures 3 and 4), while cytokeratin, ER, PR, BRST-2, mammoglobin, GATA3, TTF-1, and Napsin-A were all negative. Histopathological analysis supported by IHC led to a diagnosis of malignant melanoma with negative resection margins. There was no lymph-vascular invasion and no nodal metastasis. Molecular analysis was negative for BRAF mutations.

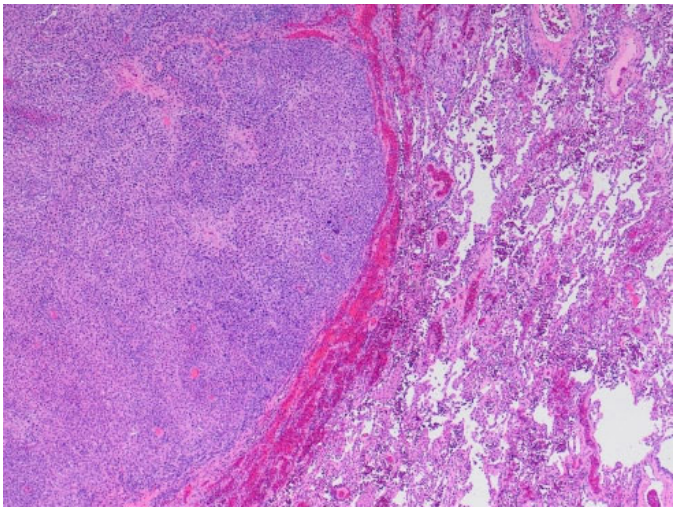

Figure 1: H&E shows malignant melanoma on the left and section of the lung on the right on power (40×).

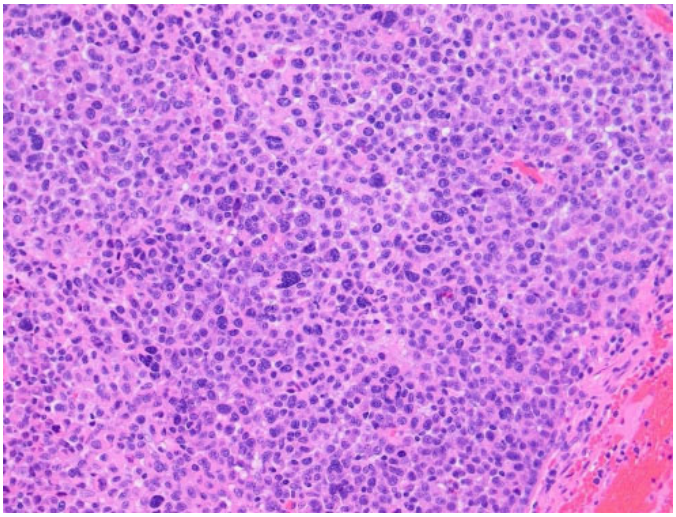

Figure 2: H&E section shows sheets of pleomorphic tumor cells with high nuclear/cytoplasmic ratio, dispersed chromatin, and some with prominent nucleoli (200×).

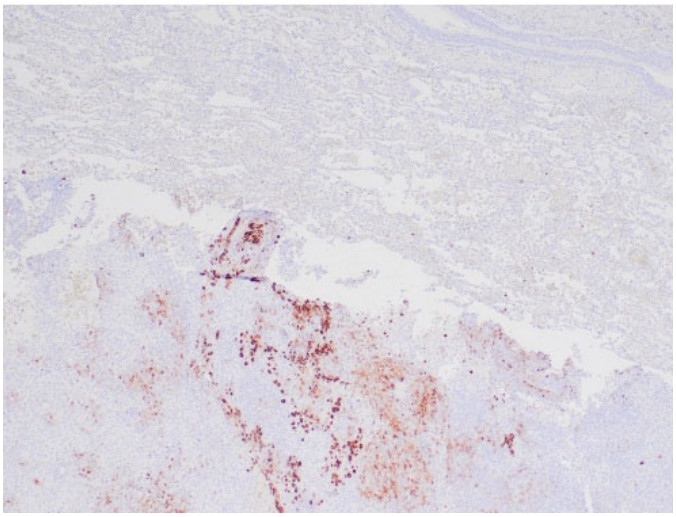

Figure 3: Tumor cells show focal positivity for HMB45 (40×).

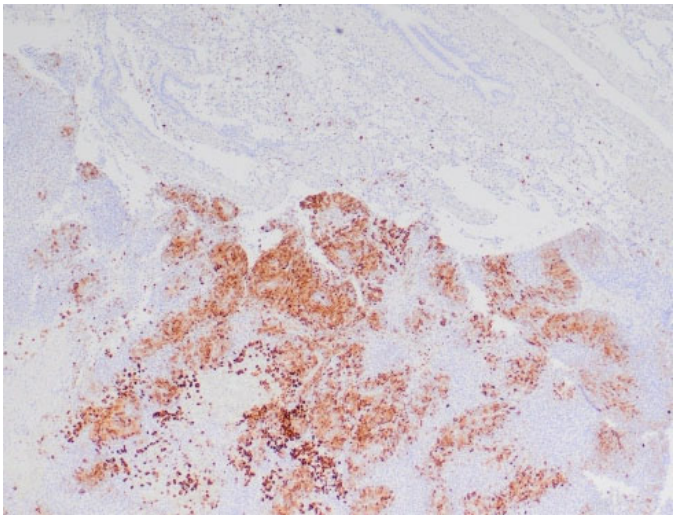

Figure 4: Tumor cells are positive for melanoma cocktail (40×).

After the diagnosis of malignant melanoma, the patient was examined thoroughly with no clinical evidence of cutaneous, ocular, or mucosal melanoma. She subsequently developed a solitary brain metastasis involving the frontal lobe and was transferred under palliative care. She passed away 11 months after the initial diagnosis of PMML.

DISCUSSION

Melanoma is a malignancy of melanocytes, pigment producing cells which originate from the neural crest and are present in the basal epidermis, hair follicles,

most squamous mucous membranes, and leptomeninges [6–8]. Cutaneous melanomas are unique in that they can spontaneously regress after metastasis; therefore, it is difficult to recognize the difference between a PMML and a metastatic lesion to the lung. Malignant melanomas involving the lung are nearly always metastatic until proven otherwise. Before establishing the diagnosis of PMML, other sites of origin such as skin, eyes, and mucosal surfaces must be ruled out.

Diagnostic criteria have evolved with increased understanding of PMML [9]. According to the Armed Forced Institute of Pathology, the presence of an intraepithelial component within the bronchial epithelium (which is a part of the original criteria by Allen and Drash [10]) supports a primary pulmonary origin, should not be required or considered pathognomonic for the diagnosis of PMML. This is because of the known occurrence of intraepithelial growth of metastatic malignant melanoma to the lung. The selection criteria proposed by Armed Forces Institute of Pathology involves: (1) A solitary tumor; (2) A malignant melanoma confirmed by immunohistochemistry and/or electron microscopy; (3) No past history of excision or fulguration of a cutaneous, mucous membrane, or ocular lesion; (4) A central pulmonary lesion; (5) No demonstrable tumor elsewhere at the time of diagnosis [9]. The patient in our case study fulfilled the above criteria of PMML.

The exact histogenesis of PMML is not well understood. Several theories have been proposed but challenge remains: (1) Migration of benign melanocytes during embryogenesis. This theory is supported by the presence of melanocytes and melanocytic proliferation in the esophagus and larynx, which shares a common embryonic origin with the lung [10]. (2) Melanogenic metaplasia in the submucosal bronchial glands, which is speculated to occur in response to chronic irritation and squamous metaplasia. (3) Melanoma cells may be derived from pluripotent stem cells in the lower respiratory tract. There have been previous reports of melanocytic differentiation in neuroectodermal and neuroendocrine neoplasms [11]. (4) Some have speculated that these lung lesions are metastatic malignant melanoma with spontaneous regression of previous skin lesions [12].

Non-specific clinical features make a clinical diagnosis of PMML challenging. Primary malignant melanoma of lung may present as an incidental finding or with non-specific respiratory symptoms. The most common presenting symptoms are cough, hemoptysis, chest pain, dyspnea, and weight loss. In 30% of patients, there may be an incidental finding on imaging [13]. Primary malignant melanoma of lung mainly affects middle aged individuals as compared to lung cancer which affects older individuals. Based on the literature review by Paliogiannis et al., approximately half of PMML patients in whom data regarding smoking habits was available were non-smokers, which suggest that there might be a different etiopathogenesis for PMML than lung cancer.

As PMML is considered a non-UV related melanoma, it might exhibit few somatic mutations unlike sun-exposed cutaneous melanomas. Non-cutaneous melanomas have significantly lower numbers of mutations [14]. Molecular analysis with BRAF is important in management of cutaneous melanomas. From a literature search, one case of BRAF mutation [15] and one case of NRAS mutation [16] have been reported in PMML, which is not enough data to draw substantial conclusions. We performed genetic testing on our patient and no BRAF mutations were detected.

Given the rarity of PMML, there are no clear guidelines from the National Comprehensive Cancer Network (NCCN) regarding treatment. In practice, surgical resection of the tumor with an adequate margin and lymph node dissection represent the treatment regimen of choice. In patients with locally advanced or distant metastatic disease, chemotherapy with dacarbazine and immunotherapy with interleukin-2 or interferon are considered [17].

In recent years, discovery of BRAF mutations in cutaneous malignant melanoma (MM) patients has led to treatment with BRAF inhibitors, such as vemurafenib and dabrafenib, together with an MEK inhibitor such as trametinib [18,19]. Immunotherapy with programmed death-1 (PD-1) checkpoint inhibitors has shown promise in metastatic cutaneous MM [20]. Even though several new agents have been approved for the treatment of cutaneous MM, there is a paucity of published information regarding the efficacy and safety of these combinations in other melanoma subtypes. Further studies are required to establish a definitive role for these modalities in the treatment of PMML.

Overall, the 5-year survival rate of all patients with lung cancer, irrespective of stage, is 16%, compared to a 5-year survival rate of stage 4 melanoma metastatic to the lung of 7–9% [21]. For PMML, there is insufficient data due to the rarity of the disease to establish a 5-year survival rate. However, based on published case reports, the prognosis of PMML is poor with occasional long-term survivors [22].

CONCLUSION

Despite the absence of melanocytes in the lung, cases of PMML have been observed. The clinical differentiation between PMML and other lung cancers is challenging. Histopathological examination supported by IHC is the mainstay of diagnosis along with radiological and clinical criteria. Although rare, PMML should be considered in the differential diagnosis of primary tumors of the lung.

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Author Contributions

Harpreet Rai – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Asghar H Naqvi – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Waël C Hanna – Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Salem O Alowami - Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.