Case Report

Primary Malignant Melanoma of the Lung; Case Report of a Rare Entity

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Abstract

Primary pulmonary malignant melanoma is an exceptionally rare non-epithelial neoplasm, constituting around 0.01% of all primary lung malignancies. We report a case of a 57-year-old male with no comorbidities, in whom two nodules were incidentally detected in the middle and lower lobes of the right lung, later diagnosed as primary malignant melanoma of the lung. The prognosis for primary pulmonary malignant melanoma is dismal and many patients have rapid progression and a brief life span, despite intervention. The 5-year survival rate is less than 20%. The survival may range anywhere from a month to 7 years, but averages around 18-20 months according to literature. Our case, however, continues to remain clinically stable till date, presumably due to early detection while the patient was being investigated for an unrelated cause, and timely intervention.

Keywords: malignant melanoma; lung; neoplasm; case report

Introduction

Malignant melanoma accounts for approximately 300,000 new cancer cases worldwide annually.[1] Primary cutaneous Melanoma is frequently encountered, particularly in the peri-equatorial zones owing to increased ultraviolet radiation exposure. Nonetheless, other mucosal sites may also be involved, including the sinonasal tract, upper aerodigestive tract, vagina, anorectal region, and leptomeninges.[2] Primary malignant melanoma has additionally been documented in visceral organs such as uvea, lungs and liver.[2, 3] The pathology is exceedingly rare, accounting for 0.01% of all primary pulmonary malignancies.[1] After extensive literature review, merely 75 cases of PMML have been reported from 1963 to 2024.[3] Metastasis is extremely common and prognosis is dismal, with average survival being less than 18 months.[2]

Case Report

A 57-year-old male with no significant comorbidities presented with chest pain following a domestic fall one week prior. Initial evaluation of vital parameters revealed: pulse rate 74 bpm, respiratory rate 16/minute, Blood pressure 110/80 mm hg, oxygen saturation 99% on room air, and body temperature 98°F. Preliminary laboratory findings were essentially within normal limits.

The patient was of average build, with a GCS of 15/15. Systemic examination revealed no abnormalities, including no cutaneous or mucosal lesions. He denied tobacco intake, alcohol, recreational drug use, known allergies, dermatological or ocular surgeries, and no family history of cancer.

A PA-view chest radiograph demonstrated a nodular opacity at right lung hilum. A chest computerized tomography (CT) scan done elsewhere revealed two solitary pulmonary nodules in the right lung middle lobe. Subsequent PET-CT imaging (Figure 1) identified two FDG-avid enhancing solid nodules; one in the anterior segment of right lung upper lobe adherent to transverse fissure (29 x 28 mm; SUVmax 11.0), and another in right lung lower lobe anterior segment peribronchial region (24 x 20 mm; SUVmax 10.9). 68Ga-DOTATOC PET-CT corroborated these findings. No definite evidence of active primary malignant disease was detected elsewhere in the body.

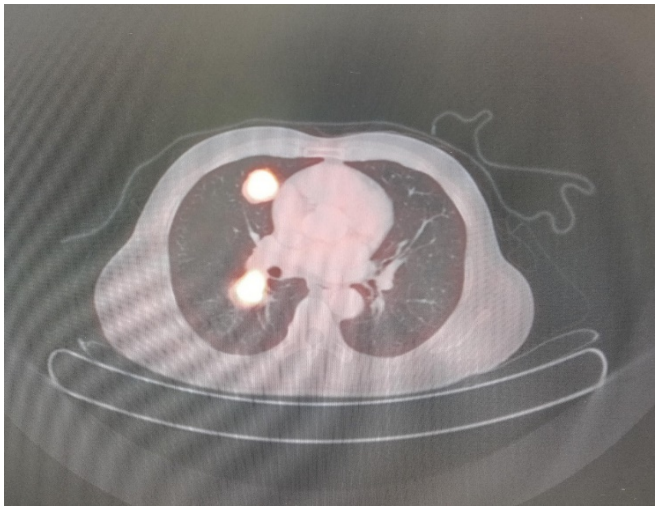

Figure 1: PET-CT (axial view) chest: shows two nodules in the right lung.

Bronchoscopic cryobiopsy from the right lower lobe mass was submitted for histopathological examination. Microscopy revealed endobronchial mucosa infiltrated by sheets, nests and cords of round to oval cells with mildly pleomorphic nuclei, conspicuous nucleoli and moderate pale to eosinophilic cytoplasm, along with necrosis and mitotic count of 6-7/2 mm² (calculated using a microscope with field number 20, objective lens 40X, field diameter 0.5 mm). Positive immunostaining in the neoplastic cells (Figure 2) was obtained for Vimentin (Clone: V9, Vendor: Roche), S100 (Clone: 4C4.9, Vendor: Roche) and MELAN-A (Clone: A103, Vendor: Roche), whereas a negative immunostaining for TTF1 (Clone: 8G7G3/1, Vendor: Roche) excluded primary lung adenocarcinoma, lack of Pan-Cytokeratin (CK) (Clone: AE1/AE3, Vendor: Diagnostic Biosystems) and epithelial Membrane Antigen (EMA) (Clone: E29, Vendor: Roche) ruled out metastatic carcinomas, absence of Synaptophysin (Clone: SP11, Vendor: Roche) and Chromogranin (Clone: LK2H10, Vendor: Roche) excluded NET. A provisional diagnosis of Amelanotic Melanoma was suggested based on the Immunohistochemistry findings.

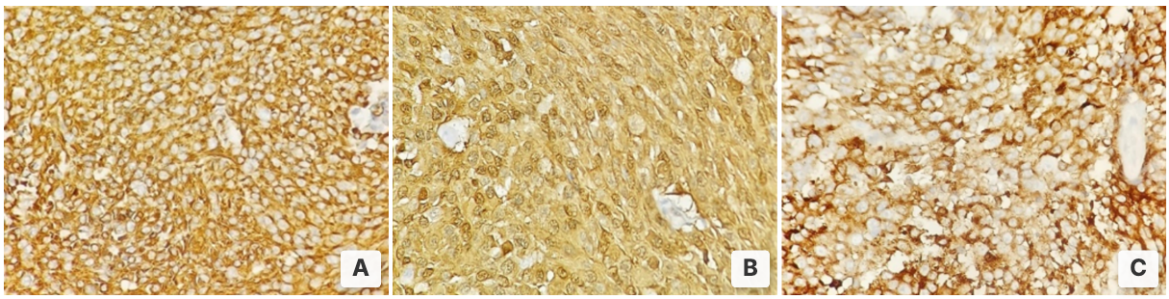

Figure 2: Immunohistochemistry: A. Melanoma cells showing positive cytoplasmic staining with Vimentin (400X), B. Melanoma cells showing strong and diffuse nuclear and cytoplasmic positivity with S100 (400X), C. Melanoma cells showing strong cytoplasmic positivity with MELAN-A (400X).

The patient underwent a right posterolateral thoracotomy with right lung upper and lower lobectomy, and mediastinal lymph node dissection. Grossly, two well-circumscribed tumours were identified in the two lobes (Figure 3). Histological examination showed infiltration of lung parenchyma by sheets, nests and lobules of epithelioid to spindle-shaped cells with

vesicular nuclei, prominent nucleoli and moderate cytoplasm interspersed by lymphocytic infiltrates (Figure 4). Mitosis and foci of necrosis were noted. No lympho-vascular or perineural invasion was observed. Resection margins and pleural surfaces were devoid of tumour. The mediastinal lymph nodes examined showed no tumour metastasis. Subsequent extended immunohistochemistry panel substantiated the provisional diagnosis. Negative immunostaining for CD45 (Clone: RP2/18, Vendor: Roche), CD34 (Clone: QBEnd/10, Vendor: Roche), SMA (Clone: 1A4, Vendor: Diagnostic Biosystems), Desmin (Clone: DE-R-11, Vendor: Roche), CD117 (Clone: EP10, Vendor: Roche) and CD138 (Clone: B-A38, Vendor: Roche) invalidated other possible differentials. The Ki-67 (Clone: 30-9, Vendor: Roche) index was 30%. All immunostaining was performed on the VENTANA Benchmark ULTRA automated IHC slide staining system, with optimally diluted Ready-To-Use (RTU) antibodies.

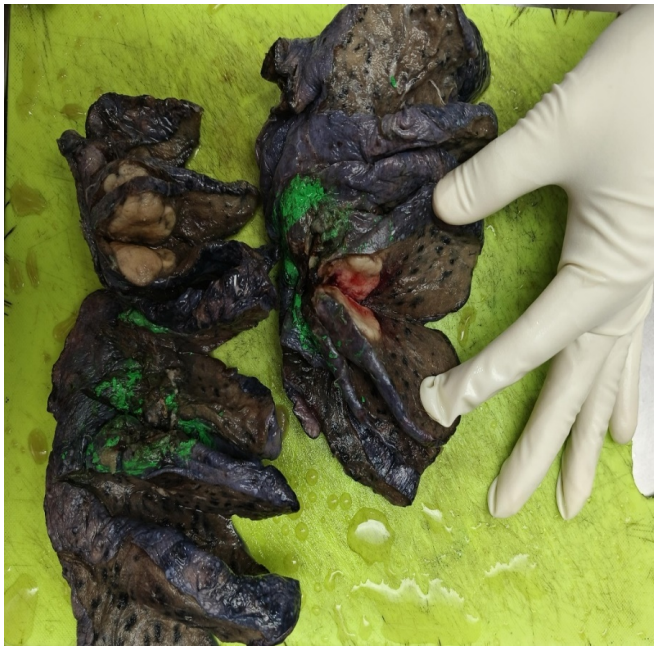

Figure 3: Gross: Right lung upper and lower lobectomy, reveals two discrete nodules one in the upper lobe adhered to transverse fissure, and the other in the lower lobe anterior segment peri-bronchial region.

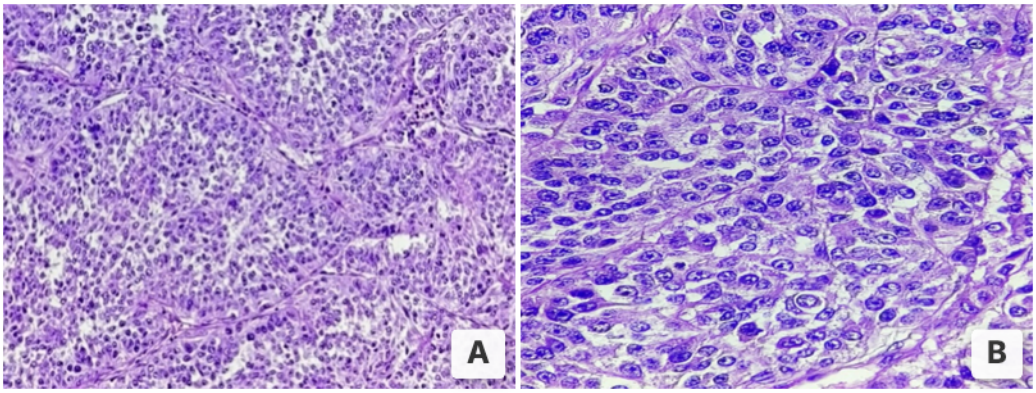

Figure 4: Microscopy: A. Stained sections show tumour tissue comprising of sheets, nests and lobules of epithelioid to spindle shaped cells interspersed by lymphocytic cell infiltrates (HEx100). B. Tumour cells show vesicular nuclei, conspicuous nucleoli and moderate cytoplasm. Conspicuous mitosis noted. (H&E x 400).

The patient was initiated on adjuvant immunotherapy with Pembrolizumab, to be continued for 17 cycles over one year. He remains clinically stable and under regular follow-up in oncology and pulmonary medicine clinics over the last two months since diagnosis.

Discussion

PMML is an extremely rare malignancy. [2, 3] A 2017 literature review reported a mean diagnostic age of 59 years, and a slight male preponderance.[2] Metastasis was seen in 47.5% of the cases, and death occurred in 65% within 18 months of detection. [2] The epidemiological profile in our case aligns with existing data. [2, 3]

The etiopathogenesis being unclear, two theories have been hypothesized regarding the origin of PMML. One theory suggests the malignant transformation of pre-existing resident melanocytes of the respiratory or esophageal mucosa. [4, 5] The other

hypothesis postulates an embryogenic phenomenon involving migration of malignant melanocytes towards the respiratory system from a possible antecedent and unrecognized skin lesion, and its subsequent spontaneous regression. [4, 5] The first theory may be the probable etiopathogenesis in our case, since the patient has no prior history of malignancy nor any detectable lesions elsewhere.

Allen and Drash established diagnostic criteria for PMML, which are : (i) lack of a previous melanoma; (ii) no perceptible melanoma at any other site intraoperatively; (iii) a solitary pulmonary mass; (iv) morphologically consistent with a primary tumour; (v) nesting of melanocytes underneath bronchial epithelium; (vi) the invasion and destruction of intact bronchial epithelium by melanocytes; (vii) immunohistochemical confirmation by S-100 and HMB-45 positivity; (viii) junctional activity evident on histopathology; and (ix) absence of primary melanoma elsewhere during autopsy.[6] Eight out of nine criteria are fulfilled by the case herein. Since the patient is alive till date, the ninth criterion is not applicable in this case.

The clinical presentation is variable; in some cases, the lesions may be discovered incidentally, similar to this case. On the other hand, respiratory symptoms with or without a pulmonary mass on imaging may be the initial presentation. PMML is typically endobronchial, manifesting cough, hemoptysis, dyspnoea, pleuritic pain, lobar collapse, pneumonia or other symptoms that corroborate with damage to the respiratory tract. [7] Melanoma in the lung could also metastasize to other organs, leading to organ-specific manifestations.

Metastatic melanoma being commoner than primary lung melanoma, a comprehensive dermatological evaluation is essential to rule out the presence of primary lesions on the skin. Other mucosal or visceral primaries should be excluded by endoscopic examination of the gastrointestinal tract and the sinonasal tract; gynecological examination in females; and positron emission tomographic (PET) scanning of the whole body. [8] Since there was no history of dermatological or ocular surgeries, no skin and mucosal lesions were evident, and radiology did not reveal any other lesions in the body, this case was diagnosed as PMML.

Melanoma is characteristically avid on FDG PET scans (fluorodeoxyglucose positron emission tomography), due to the increased glucose uptake by the metabolically hyperactive cancer cells. Apart from that, Melanin-Targeted radio-labelled or fluorescent agents like 18F-DOPA, 68Ga-DOTA-Peptide (Gallium-68 labelled DOTA-peptides), and 18F-FP-RGD2 (Fluorine-18 labelled RGD) can also be used in PET scans for more specific detection. [9]

The characteristic immunohistochemical findings are the cornerstone of histopathological diagnosis of malignant melanoma. Positive staining for pan-CK, P63 helps to differentiate squamous cell cancer from PMML. Morphological similarities between primary carcinoid tumour and PMML ordains Chromogranin-A to be performed on immunohistochemistry. The latter is negative for these stains and instead positive for S-100 and HMB-45. [10, 11, 12, 13].

PMML entails aggressive surgical debulking of the tumour combined with radiotherapy, chemotherapy, or immunotherapy. Keeping in mind the high recurrence rate, surgical resection is followed by post operative adjuvant chemotherapy with agents like dacarbazine, interleukin 2, and interferon [14]. Radiotherapy can be of use in locally advanced disease and for palliation in metastatic disease to brain and bones [15]. Immunotherapy is useful in patients with advanced melanoma with immune checkpoint inhibitors, such as ipilimumab (anticytotoxic T-lymphocyte antigen-4 antibody) or nivolumab and pembrolizumab (anti-programmed cell death monoclonal antibodies), to increase survival rates. [16]. Adjuvant Pembrolizumab post-R0 resection for PMML targets occult micrometastases. Following KEYNOTE-054/716 high risk protocols, initiation within 12 weeks post-surgery allows sufficient recovery as well as optimizes recurrence-free survival through T-cell-mediated surveillance, addressing the aggressive biological profile and systemic recurrence risk inherent to these rare mucosal-origin malignancies.

Despite aggressive management, most cases of PMML undergo rapid deterioration, with 5-year survival less than 20%. The survival period averages around 18-20 months. [2]

Conclusion

Primary malignant melanoma of the lung is an uncommon malignant entity with an aggressive biologic behavior, early and rapid metastatic potential and poor prognosis. Overall, this is the least common type of visceral melanoma and diagnosis requires fulfilment of definite criteria. It can present as either a localized pulmonary nodule or metastatic disseminated disease. This case emphasizes the significance of multidisciplinary investigations and clinicopathological correlation in early detection of diseases in their budding stage which may significantly improve the outcome. From a pathological perspective, this case underscores the need to account for morphological mimics and align the ancillary testing in accordance with the differentials before rendering the final diagnosis. Treatment options include complete surgical removal combined with adjuvant chemotherapy and radiation. Of late, the introduction of immunotherapy has introduced a new therapeutic avenue.

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Declaration and patient consent: A written informed consent was obtained from the patient prior to obtaining data for publication of the case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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