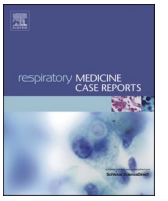
Respiratory Medicine Case Reports 53 (2025) 102161

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr



Case Report

Primary malignant melanoma of the lung; a case report and literature review

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ARTICLE INFO

Handling Editor: DR AC Amit Chopra

Keywords:
Malignant melanoma
Lung
HMB
Cancer

ABSTRACT

Primary pulmonary malignant melanoma is an extremely rare non-epithelial malignancy. Literature is merely limited to a few anecdotal case reports. Herein we present a case of a 74-year-old female who was diagnosed with primary malignant melanoma of the lung. To fully appraise the available evidence, we have sought to perform narrative review of the existing literature.

1. Introduction

Malignant melanoma (MM) is a primary cutaneous malignancy, where pulmonary involvement can potentially occur in form metastatic disease. Epidemiological studies suggest that more than three hundred thousand cases of malignant melanoma are annually reported globally [1]. Primarily the tumor is seen in the skin, but involvement of organs of the gastrointestinal or respiratory system as primary lesion has also been reported. Primary malignant melanoma of the lung is extremely rare with evidence merely limited to a few anecdotal case reports [2]. Here we report a unique case of primary malignant melanoma of the lung. We have also sought to perform review of the existing literature.

2. Case presentation

A 74-year-old woman with history of diabetes, hypertension, and hyperlipidemia with no prior history of skin cancer or melanotic tumors presented to the hospital with dyspnea at rest. It was associated with loss of appetite, twenty pounds of unintentional weight

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https://doi.org/10.1016/j.rmcr.2024.102161
Received 16 November 2024; Accepted 25 December 2024
Available online 28 December 2024

loss and expectoration of black colored sputum. Chest X-ray performed at the primary care provider's clinic revealed a large mass in the right lower zone of the lung. She was subsequently evaluated with computed tomography of the chest which revealed a 14 × 12 cm right lower lobe lung mass (Fig. 1). The mass was hypermetabolic on evaluation with positron emission tomography with standard uptake value (SUV) of 10.5. A bronchoscopy was then performed for further evaluation. Transbronchial biopsy was performed of the right lower lobe lung mass under fluoroscopy guidance. Endobronchial ultrasound (EBUS) revealed enlarged pre-bronchial (station 10R) and subcarinal (station 7) lymph nodes. Transbronchial needle aspiration was performed from the stations 7 and 10R lymph nodes. Histopathology revealed melanin pigments inside the malignant cells (Fig. 2). Immunohistochemical staining with SOX-10 revealed intranuclear melanin deposits (Fig. 3). Melanotic deposits in the cytoplasm of malignant cells was seen on MART-1 staining (Fig. 4). She was diagnosed with primary malignant melanoma of the lung. The patient was then treated with right pneumonectomy. Molecular profiling of the resected specimen revealed tumor mutation burden of ≥10 muts/Mb. Based on the molecular profile, she was started on immunotherapy with Pembrolizumab. Per the informed decision with the patient and the family she was randomized in a phase I clinical trial; SX-682 treatment in subjects with metastatic melanoma concurrently treated with pembrolizumab, ClinicalTrials.gov Identifier: NCT0316143 During the trial she will receive the highest safe dose level of SX- 682, in combination with pembrolizumab, during a two-year study duration. She continues to follow up in oncology and pulmonary medicine clinic for the last two years since the initial diagnosis.

3. Discussion

Primary malignant melanoma of the lung (PMML) is an extremely rare malignancy. We performed an extensive literature search We performed literature search in MEDLINE via PubMed, EMBASE, and Scopus. We identified 75 cases of PMML reported from 1963 to 2024 summarized in Table 1. Mean age at the time of diagnosis of PMML was 58 years. Average survival after the diagnosis was 14 months which suggests the extremely aggressive nature of the tumor.

Two theories have been postulated on the origin of primary melanoma in the lung. It is suggested that melanocytes are found throughout the respiratory tract the part as part of the neuroendocrine system, and malignant transformation occurs in the pre-existing melanocytes which are natural residents of the respiratory tract [64]. The other hypothesis suggests an embryogenic phenomenon where melanocytes drift towards the respiratory system and become cancerous cells [64]. Given the rarity of the tumor studies on the biological plausibility is limited highlighting the need of larger and more comprehensive research efforts.

The primary clinical presentation involves constellation of respiratory symptoms with or without a pulmonary nodule or a mass on imaging. Diagnostic challenges associated with the rarity of the tumor may necessitate multidisciplinary care in diagnostic modalities and clinicians [6]. Melanoma in the lung could be primary tumor or metastatic disease. This entails comprehensive dermatological evaluation to rule out the presence of the skin and appendages. Radiologic characteristics of PMML can be like squamous cell carcinoma, and pigmented carcinoid tumor. Melanoma is typically avid on FDG PET scans (fluorodeoxyglucose positron emission tomography). Melanomas, especially advanced or metastatic ones, generally exhibit high metabolic activity, which FDG PET scans can detect due to the increased glucose uptake by cancer cells. PET scans can be used for staging, detecting metastasis, and monitoring treatment response in PMML like cutaneous melanomas. However, the sensitivity of FDG PET can vary depending on the size, location, and metabolic activity of the tumor. Small or less metabolically active melanomas might not show up as clearly on a PET scan [53]. Apart from the use of FDG PET other nuclear medicine based functional imaging modalities can be used for the diagnosis and staging of malignant melanomas. Some of the examples include, 18F-FLT PET (Fluorothymidine PET) to evaluate tumor proliferation and predict

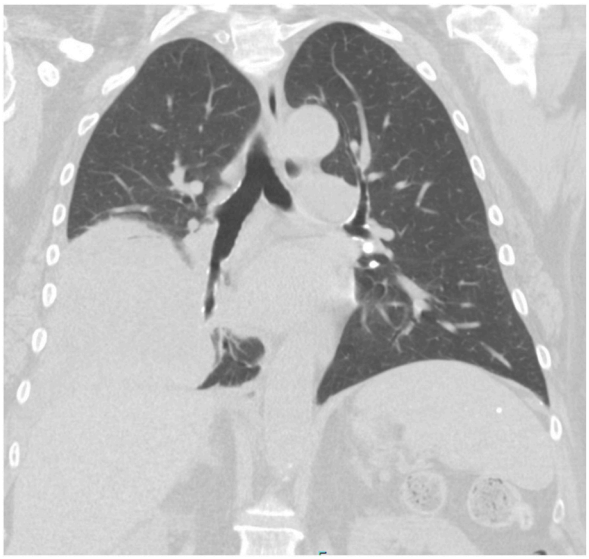

Fig. 1. Computed tomography of the chest showing 14 × 12 cm right lower lobe lung mass.

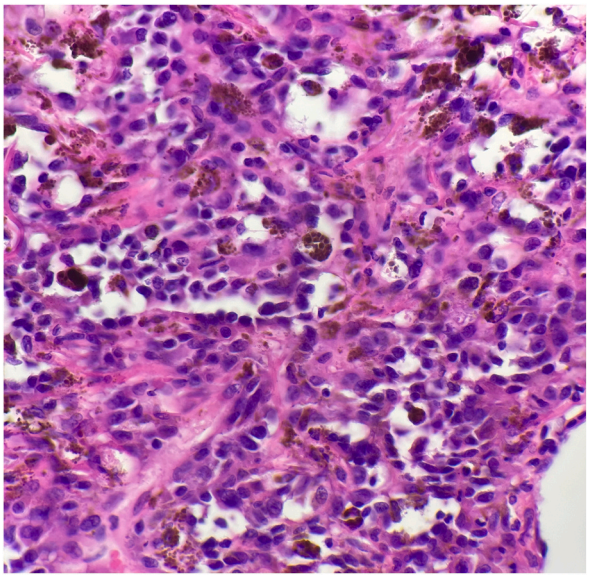

Fig. 2. Histopathology revealed melanin pigments inside the malignant cells.

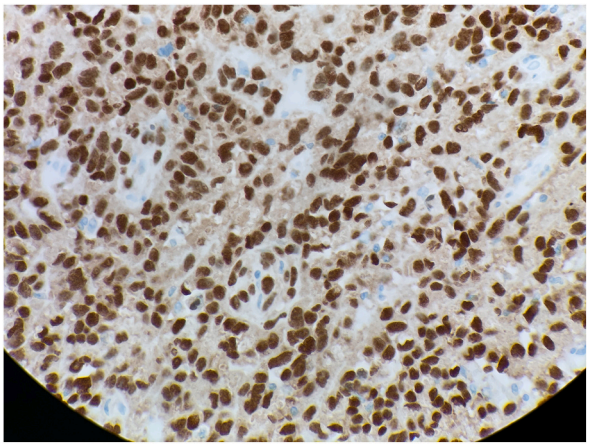

Fig. 3. Immunohistochemical staining with SOX-10 revealed intranuclear melanin deposits.

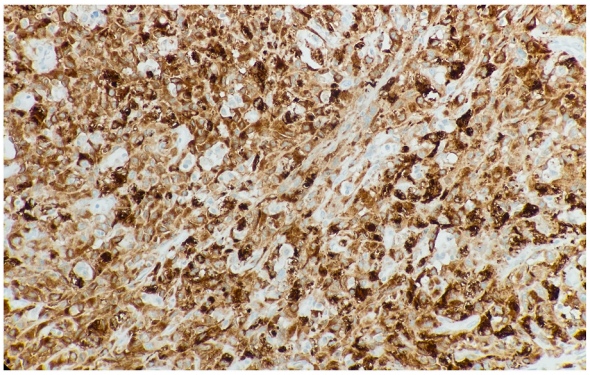

Fig. 4. Melanotic deposits in the cytoplasm of malignant cells was seen on MART-1 staining.

Table 1
Summary and clinical characteristics of reported cases of primary pulmonary malignant melanoma.

Case Number	Author	Publication	Gender	Age	Location of tumor	Survival in months from the time of diagnosis
1	Salm [3]	1963	M	45	LLL	7
2	Reed III [4]	1964	M	71	LLL	NA
3	Reid [5]	1966	F	60	RLL	NA
4	Jensen [6]	1967	F	61	LUL	7
5	Allen [7]	1968	F	40	RLL	NA
6	Taboada [8]	1972	M	56	LLL	14
7	Taboada [8]	1972	M	40	LUL	NA
8	Adebonojo [9]	1979	F	55	RUL	NA
9	Weshler [10]	1980	F	62	Left main bronchus	4
10	Robertson [11]	1980	F	70	RML bronchus to carina	2
11	Gephardt [12]	1981	M	47	Left mainstem bronchus	0
12	Carstens [13]	1984	F	29	RUL	1
13	Cagle [14]	1984	M	80	Minor fissure	5
14	Demeter [15]	1987	M	56	RUL	1
15	Alghanem [16]	1987	F	42	LLL	NA
16	Santos [17]	1987	M	58	RLL	2
17	Bagwell [18]	1989	M	62	LUL	2
18	Bertola [19]	1989	F	30	LLL	0
19	Barzò [20]	1995	F	48	LUL	72
20	Barzò [20]	1995	F	81	Left mainstem bronchus	5
21	Farrell [21]	1996	F	66	LLL	54
22	Wilson [2]	1997	M	71	LLL	108
23	Wilson [2]	1997	M	45	LUL	4
24	Wilson [2]	1997	F	55	RUL	18
25	Wilson [2]	1997	M	52	LUL	32
26	Wilson [2]	1997	M	64	LUL	4
27	Wilson [2]	1997	M	48	LUL	14
28	Wilson [2]	1997	M	50	LUL	30
29	Ost [22]	1999	M	90	LUL	NA
30	Özdemira [23]	2001	M	41	LLL	46
31	Filosso [24]	2003	M	55	Bronchus intermedius	14
32	Dountsis [25]	2003	F	41	RUL	18
33	Kundranda [26]	2006	M	60	LUL	NA
34	Reddy [27]	2007	M	74	LLL	10
35	Maeda [28]	2009	M	68	LUL	6
36	Xu-dong [27]	2010	M	81	RLL	NA
37	Zuckermann [29]	2011	F	68	RUL	NA
38	Seitelman [30]	2011	M	89	LLL	NA
39	Neri [31]	2011	M	58	LLL	6
40	Neri [31]	2011	F	69	RUL	6
41	Gong [32]	2012	F	52	LUL, LLL	4
42	Gong [32]	2012	F	65	RLL	NA
43	Ouarssani [33]	2012	M	68	RLL	2
44	dos Santos [34]	2013	F	62	LUL	12
45	Kamaleshwaran [35]	2014	M	56	LLL	NA
46	Liu [36]	2014	F	49	LUL	3
47	Hwang [37]	2015	M	82	RLL	NA
48	Zhang [38]	2015	M	60	LLB	18
49	Gupta [39]	2015	F	58	LUL	2
50	Postrzech-Adamczyk [40]	2015	F	69	RUL	6
51	Filippini [41]	2015	M	55	RSL	3
52	Watanabe [42]	2015	M	66	RML	NA
53	Watanabe [42]	2015	F	46	LLL	NA
54	Baniaka [43]	2016	F	13	Right paratracheal region	NA
55	Yamamoto [44]	2017	F	61	S10	15
56	Kyriakopoulos [45]	2017	F	56	RUL	5
57	Yunce [46]	2017	M	22	RLL	NA
58	Peng [47]	2017	F	61	RML	6
59	Yabuki [48]	2018	M	74	RB	7
60	Azuma [49]	2018	F	47	LB	3
61	Al-Helou [50]	2018	M	69	NA	NA
62	Shi [51]	2018	M	46	RUL	21
63	Rodriguez [52]	2019	M	76	RSL	NA
64	Landgrafa [53]	2020	F	69	LLL	NA
65	Deng [54]	2020	M	57	RLL	1

(*continued on next page*)

Table 1 (*continued*)

Case Number	Author	Publication	Gender	Age	Location of tumor	Survival in months from the time of diagnosis
66	Luhuan Yang [42]	2020	F	39	RLL	NA
67	Xi [55]	2020	F	64	Lingular Bronchus	NA
68	Nigi [56]	2021	M	71	Lingular Bronchus	3
69	Fujita [57]	2022	M	90	RUL	NA
70	Balcı [58]	2022	F	48	RML	84
71	Kim [59]	2023	M	62	Lingular bronchus	9
72	Mada [60]	2023	M	63	RUL	2
73	Xiao [61]	2023	F	62	RUL	In remission till the publication of the case report in 2023
74	Chen [62]	2023	M	62	RLL	NA
75	Barisione [63]	2024	M	71	Left endobronchial mass	NA

RUL, RML, RLL; Right upper lobe, Right middle lobe, Right lower lobe.
LUL, LML, LLL, LB; Left upper lobe, Left middle lobe, Left lower lobe.

the response to therapy, MRI with Contrast (Using Gadolinium-based contrast agents) to evaluate intracranial spread of melanoma, and sentinel lymph node biopsy with lymphoscintigraphy to assess regional lymph node assessment in early stage melanoma, Melanin-Targeted Agents-radio-labeled or fluorescent agents designed to bind to melanin,18F-DOPA PET (Fluorodopa PET), 68Ga-DOTA-Peptide PET/CT (Gallium-68 labeled DOTA-peptides), and 18F-FP-RGD2 PET (Fluorine-18 labeled RGD PET) are largely in experimental stages [65].

Histopathological diagnosis of malignant melanoma is largely based on its immunohistochemical characteristics. The presence of positive staining for CKpan, P63 helps differentiate squamous cell cancer from PMML where the latter is negative for these stains and is instead positive for S-100 and HMB-45. Morphologically, primary carcinoid tumor and PMML are similar, and under electron microscopy primary carcinoid tumor stains positive for CK, CD56 and chromogranin-A on immunohistochemistry [66–70].

From a clinical perspective it can be challenging to distinguish PMML from metastatic melanoma. Previous case reports have suggested four clinical criteria to be satisfied for the diagnosis of PMML: invasion or destruction of the bronchial epithelium and intact bronchial mucosa; the above changes were proven to be a malignant melanoma by histology and immunohistochemistry; radiological manifestation of a solitary lung tumor; and no history or present clinical or laboratory findings of a cutaneous, mucosal, or ocular melanoma. Case reported herein fulfills all the four criteria [71–73].

The treatment of PMML entails surgical debulking of the tumor combined with radiotherapy, chemotherapy, along with immunotherapy. Given the risk of recurrence after surgical resection, treatment entails the combination of post operative adjuvant chemotherapy with agents like dacarbazine, interleukin 2, and interferon [74]. Radiotherapy can be used for locally advanced disease and for palliation in metastatic disease to brain and bones [75]. Immunotherapy, with immune checkpoint inhibitors, such as ipilimumab (anticytotoxic T-lymphocyte antigen-4 antibody) or nivolumab and pembrolizumab (anti-programmed cell death monoclonal antibodies), has been used for treatment in patients with advanced melanoma [76,77].

In a Phase I clinical trial published in 2013, Fifty-three patients received concurrent nivolumab/ipilimumab and 33 received sequenced treatment. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease $\geq$24 weeks) was observed in 65 % of patients. At the maximum tolerated dose (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 53 % of patients achieved an objective response, all with $\geq$80 % tumor reduction. Grade 3–4 related adverse events occurred in 53 % of concurrent-regimen patients but adverse events were qualitatively like historical monotherapy experience and were generally reversible [78].

Another Phase 3 trial published in 2019 compared the effect of nivolumab plus ipilimumab or nivolumab alone for melanoma. At a minimum follow-up of 60 months, the median overall survival was more than 60.0 months (median not reached) in the nivolumab-plus-ipilimumab group and 36.9 months in the nivolumab group, as compared with 19.9 months in the ipilimumab group (hazard ratio for death with nivolumab plus ipilimumab vs. ipilimumab, 0.52; hazard ratio for death with nivolumab vs. ipilimumab, 0.63) [79]. In September 2024 the final 10-year follow up of the study was published. With a minimum follow-up of 10 years, median overall survival was 71.9 months with nivolumab plus ipilimumab, 36.9 months with nivolumab, and 19.9 months with ipilimumab. The hazard ratio for death was 0.53 (95 % confidence interval [CI], 0.44 to 0.65) for nivolumab plus ipilimumab as compared with ipilimumab and was 0.63 (95 % CI, 0.52 to 0.76) for nivolumab as compared with ipilimumab [80].

A Phase 3 clinical trial published in 2015 randomized 834 patients with advanced melanoma in a 1:1:1 ratio to receive pembrolizumab (at a dose of 10 mg per kilogram of body weight) every 2 weeks or every 3 weeks or four doses of ipilimumab (at 3 mg per kilogram) every 3 weeks. Primary end points were progression-free and overall survival [81]. The estimated 6-month progression-free-survival rates were 47.3 % for pembrolizumab every 2 weeks, 46.4 % for pembrolizumab every 3 weeks, and 26.5 % for ipilimumab (hazard ratio for disease progression, 0.58; $P < 0.001$ for both pembrolizumab regimens versus ipilimumab; 95 % confidence intervals [CIs], 0.46 to 0.72 and 0.47 to 0.72, respectively). Estimated 12-month survival rates were 74.1 %, 68.4 %, and 58.2 %, respectively (hazard ratio for death for pembrolizumab every 2 weeks, 0.63; 95 % CI, 0.47 to 0.83; $P = 0.0005$; hazard ratio for pembrolizumab every 3 weeks, 0.69; 95 % CI, 0.52 to 0.90; $P = 0.0036$) [82] This study suggested that, the anti–PD-1 antibody pembrolizumab prolonged progression-free survival and overall survival and had less high-grade toxicity than did ipilimumab in patients with advanced melanoma.

A recent phase 2 trial, randomly assigned patients with clinically detectable, measurable stage IIIB to IVC melanoma that was

amenable to surgical resection to three doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab (neoadjuvant–adjuvant group) or to surgery followed by pembrolizumab (200 mg intravenously every 3 weeks for a total of 18 doses) for approximately 1 year or until disease recurred or unacceptable toxic effects developed (adjuvant-only group). At a median follow-up of 14.7 months, the neoadjuvant–adjuvant group (154 patients) had significantly longer event-free survival than the adjuvant-only group (159 patients) (P = 0.004 by the log-rank test) [83]. The advent of immunotherapy has started a newer avenue of treatment of malignant melanoma improving clinical outcomes and overall survival.

4. Conclusion

Primary malignant melanoma of the lung is an extremely rare malignancy with a poor prognosis due to its tendency to metastasize early and rapidly. Treatment options include aggressive surgery combined with adjuvant chemotherapy and radiation. Recently, the advent of immunotherapy has introduced a new avenue for treatment.

CRediT authorship contribution statement

Yub Raj Sedhai: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Roshan Acharya:** Writing – original draft. **Priyanka Bhat:** Conceptualization, Investigation, Writing – original draft. **Subha Saeed:** Writing – original draft. **Hamza Sohail:** Writing – original draft. **Shreedhar Kunwar:** Writing – original draft. **Suman Kadariya:** Writing – original draft. **Muhammad Altaf Ahmed:** Writing – original draft, Writing – review & editing. **Irfan Waheed:** Writing – original draft, Writing – review & editing. **Rodney Steff:** Writing – original draft, Writing – review & editing. **Tahir Muhammad Abdullah Khan:** Writing – original draft, Writing – review & editing. **Nisar Kazimuddin:** Writing – original draft, Writing – review & editing. **Karan Singh:** Writing – original draft, Writing – review & editing.

Declaration and patient consent

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

Ethical approval

N/A.

Data availability

All data are available within the manuscript.

Sources of funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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