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Case report

# Thoracic metastasis of malignant melanoma of unknown primary: A case report and literature review

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ABSTRACT

*Introduction:* Metastatic melanoma of unknown primary (MUP) is an unusual entity found in distant sites without evident skin lesion. We report a case of 45-year-old woman who underwent monobloc resection of a metastatic thoracic malignant melanoma of unknown primary, and who is currently under immunotherapy without local or distant recurrence during a follow-up of 18 months. We demonstrate through this case that R0 resection of an MUP associated with immunotherapy improves the prognosis and survival in these patients.

*Case report:* This is a 45-year-old woman who underwent monobloc resection of a mass carrying the anterior arch of the second left rib associated with a wedge resection of a nodule at the left upper lobe. Histology confirmed that it was a malignant melanoma. Her history was negative for melanocytic lesions, physical examination and imaging had failed to identify a primary lesion. The patient is currently under nivolumab for Stage IV melanoma and does not present any complications or recurrence during the long term follow up.

*Discussion:* Metastatic melanoma of unknown primary (MUP) is a melanocytic lesion in distant sites in the absence of apparent skin involvement and is rare, accounting for 3, 2% of all incident melanomas as well as being yet poorly understood in terms of pathogenesis (Bae et al., 2015) [1]. MUP is clinically understudied, investigators to date have reported largely on the use of localized treatment for MUP (surgery or radiotherapy), while the efficacy of systemic therapy in MUP patients remains unexplored. Clinical trials of immunotherapy and targeted therapy in patients with advanced cutaneous melanoma have not explicitly reported response rates specific to MUP patient subgroups due to its low incidence and lack of annotation. MUP's response to these now FDA-approved therapies could add to the discussion of MUP's elusive biological characteristics, as well as aid in making clinical recommendations (Utter et al., 2017).

*Conclusion:* Metastatic MUP is an extremely rare entity which is still poorly understood, few cases are described in the literature, its treatment remains controversial and there are no specific treatment recommendations for patients with MUP. Several authors recommend local treatment when possible and tend to apply similar strategies for patients with paired stage primary known melanoma (PKM).

## 1. Introduction

Although more than 90% of melanomas have a cutaneous origin, occasionally it is discovered first as a secondary deposit, lymph node or visceral, without evident primary site. This entity of melanoma of unknown primary (MUP) was initially characterized by Das Gupta in 1963 who was the first to describe the criteria for MUP. [3] Metastatic melanoma of unknown primary is a melanocytic lesion in distant sites in the absence of apparent skin involvement and is rare, accounting for up to 3,2% of all incident melanomas as well as being yet poorly understood in terms of pathogenesis [4]. We report a case of 45-year-old woman who underwent monobloc resection of a metastatic thoracic malignant MUP, and who is currently under immunotherapy without local or distant recurrence during a follow-up of 18 months. The patient was diagnosed and managed in our institution; a tertiary referral university teaching hospital. This work has been reported in line with the SCARE 2020

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criteria [5].

## 2. Case report

A 45-years-old woman was admitted to our department of thoracic surgery with a 5-month history of left chest pain. The physical examination found a patient in good condition and normal vital signs. Computed tomography (CT) imaging of the chest showed a 3, 94 × 7, 34 cm calcified tissue mass of pleural appearance lysing the 2nd rib associated with a nodular lesion of the left upper lobe measuring 1.64 cm (Fig. 1 a, b). CT-guided biopsy of the mass objectified a malignant melanoma. She had no previous history of malignant melanoma or the presence of any melanocytic skin lesion. On examination, there were no melanocytic naevi on the skin and fundoscopy was normal. Blood count was within normal limits. A PET scan was performed showing a tissular mass of pleural appearance lysing the anterior arch of the 2nd rib and invading the ipsilateral pectoralis minor muscle of SUV max at 5.5 associated with a nodule of the apical segment of the left upper lobe of SUV max to 9 (Fig. 1, c d). After multidisciplinary concertation, the decision was the mass resection with adjuvant immunotherapy. Under general anesthesia and selective intubation, the patient underwent a mass resection enbloc with the second left rib and wedge resection of apical segment nodular of the upper left lobe. A 5 cm incision of the left second intercostal space was made and the exploration found a grayish mass of 7 cm expended to the second left rib. The rib resection was made using the costotome and the entire mass, then a wedge resection of the nodular lesion at the apical segment of the left upper lobe was performed using TA-55 with replacement of the rib by a prolene prosthesis to cover the defect and pleural drainage was left. No per-operative complications occurred. The post-operative was uneventful. The pleural drainage was removed on the second day and the patient was discharged from the Hospital. The histopathology of the specimen revealed a malignant melanoma expressing Melan A (clone A103) measuring 13x7x3cm and weighing 197 g with cartilaginous, bone and soft tissue limits R0, associated with the upper left lobe nodule measuring 3 × 2,2 × 2,1 cm and weighing 20 g of the same melanocytic neoplasm with R0 resection margins and no BRAFV600 mutation. (Fig. 2). A control PET scan performed after two months showed no recurrence or other secondary localization.(Fig. 3)She is currently in good general condition under nivolumab for Stage IV melanoma with a normal level of lactate dehydrogenase (LDH) when the treatment was started, and does not present any complications or recurrence during the long term follow up.

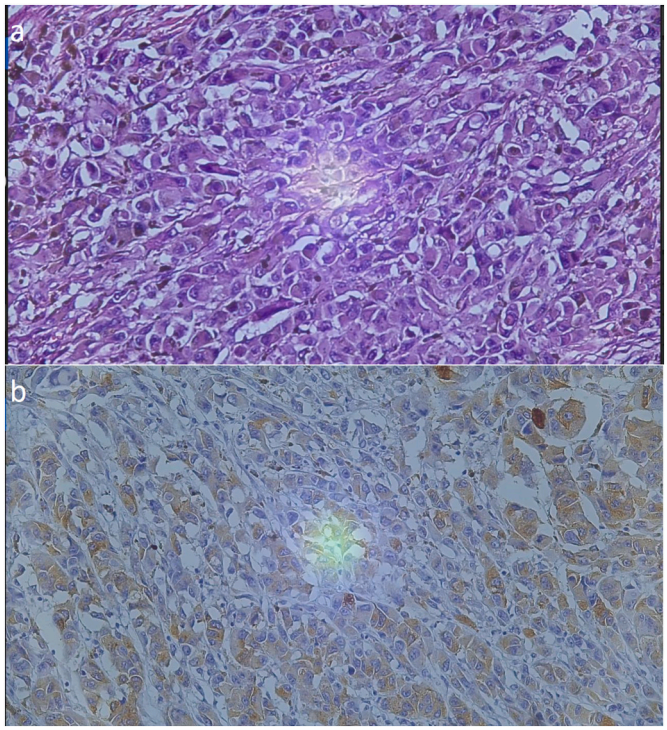


**Fig. 2.** (a, b); (a): melanocytic proliferation in massive and guts of a malignant melanoma (b):diffuse cytoplasmic expression of Melan A by tumor cells.

## 3. Discussion

At the start of 21st century, melanoma remains a potentially fatal

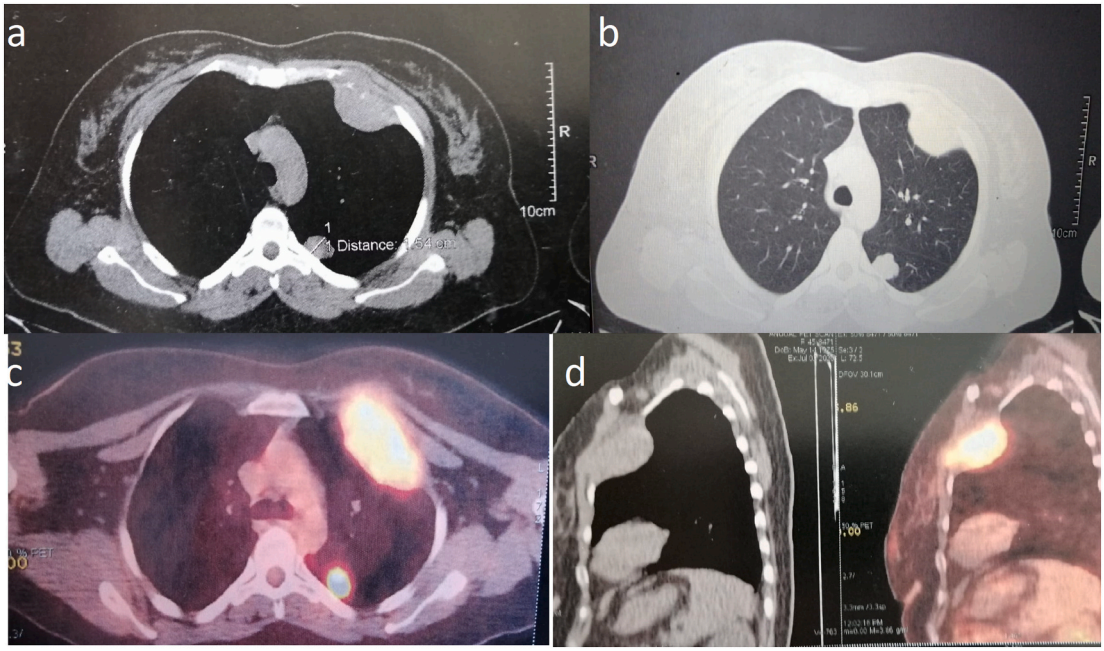


**Fig. 1.** (a, b, c, d): Computed tomography (CT) imaging and PET CT of the chest demonstrated a 3,94 × 7,34 cm Fusiform calcified tissue mass of pleural appearance lysing the 2nd rib associated with a nodular lesion of the left upper lobe measuring 1.64 cm.

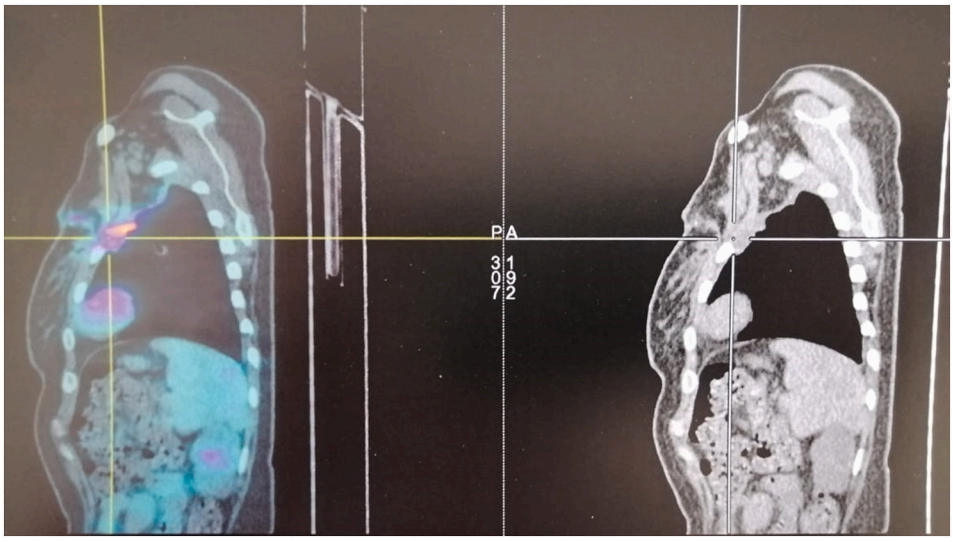


**Fig. 3.** A control PET CT performed after two months shows no recurrence or other secondary localization.

malignancy. At a time when the incidence of many tumor types is decreasing, melanoma incidence continues to increase. Although most patients have localized disease at the time of the diagnosis and are treated by surgical excision of the primary tumor, many patients develop metastases. The incidence of malignant melanoma has been increasing worldwide, resulting in an important socio-economic problem. From being a rare cancer one century ago, the average lifetime risk for melanoma has now reached 1 in 50 in many Western populations. Starting from 1960s, the incidence of this cancer has increased in Caucasian populations and, thus, melanoma has become one of the most frequent cancers in fair-skinned populations. Melanoma is now regarded as the fifth most common cancer in men and the sixth most common cancer in women in the United States. In Europe there is a gradient in incidence rates with the highest rates in Northern countries and the lowest ones in the Southern countries. This is probably due to increased protection against UV rays typical of highly pigmented skin (as the people who live in Southern European countries) but it is also due to the different pattern of sun (chronic rather than intermittent in Southern Europe). [6] Malignant melanoma is a very rare cancer in Morocco with an incidence of 0.42% and mortality of 0.32% [7].

Although more than 90% of melanomas have a cutaneous origin, occasionally it is discovered first as a secondary deposit, lymph node or visceral, without evident primary site. This entity of melanoma of unknown primary was initially characterized by Das Gupta in 1963 who was the first to describe the criteria for MUP [1,3]. Metastatic melanoma of unknown primary is a melanocytic lesion in distant sites in the absence of apparent skin involvement and is rare, accounting for up to 3,2% of all incident melanomas as well as being yet poorly understood in terms of pathogenesis. it is twice as common in males and the peak age of presentation is the 4th and 5th decades [8]. The pathogenesis of malignant melanoma of unknown primary origin is still not well understood, there are two probable explanations: it is either a melanoma occurring de novo in an area bearing a lymph node (cryptogenic melanoma) or it is spontaneous regression of a primary lesion. Considerable support for the latter hypothesis was presented in 1965 by Smith and Stehlin [9]. If the latter concept is true, then a chart analysis of patients with unknown malignant melanoma should reveal data similar to that obtained in patients whose primary lesion is known.

According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging criteria, patients presenting with melanoma metastases in the (sub)cutis, soft tissue, and/or lymph nodes, without a detectable primary tumor, are diagnosed with stage III disease; by contrast, patients presenting with distant metastases, including visceral metastases, are diagnosed with stage IV disease [10].

Molecularly, MUP tumors carry high somatic mutation rates consistent with melanoma of primary known melanoma ultraviolet signature, as well as comparable rates of BRAF and NRAS mutations. [11,12].

MUP is clinically poorly understood, investigators to date have reported largely on the use of localized treatment for MUP (surgery or radiotherapy), while the efficacy of systemic therapy in MUP patients remains unexplored. Clinical trials of immunotherapy and targeted therapy in patients with advanced cutaneous melanoma have not explicitly reported response rates specific to MUP patient subgroups due to its low incidence and lack of annotation. MUP's response to these now FDA-approved therapies could add to the discussion of MUP elusive biological characteristics, as well as aid in making clinical recommendations [2].

Currently, monotherapy with PD-1 blockade (pembrolizumab or nivolumab) or PD-1 blockade combined with CTLA-4 blockade (nivolumab and ipilimumab) are the preferred options for immunotherapy. The combination of BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib and cobimetinib) are the preferred options for targeted therapy. In clinical trials, these immunotherapy and targeted therapy approaches have reported median OS durations that exceed 30 months and 20 months, respectively. Although there are no specific treatment recommendations for patients with MUP, physicians tend to apply similar strategies for patients with stage-matched PKM. This approach is supported by the results of a large study into the molecular characterization of patients diagnosed with MUP, in which it was shown that the clinical behaviours and molecular patterns of BRAF/NRAS alterations were similar between patients with MUP and stage-matched PKM [13].

For nodal MUP, radical lymph node dissection of the affected region is generally undertaken. Patients who undergo surgery are less likely to have a recurrence of the malignancy and have improved survival compared to patients undertaking other treatments. Some patients with stage III MUP may benefit from adjuvant systemic and radiation therapy with identical criteria to patients with a primary known melanoma when undergoing the same treatment. An epidermal component is sometimes identified in the wide local excision specimen, establishing it as primary cutaneous melanoma rather than MUP. Patients with MUP may have a long survival than a primary known melanoma because there may be a more active tumor directed immune response against the malignant cells (supporting the idea that MUP may be a result of tumor regression) [14,15].

Favourable prognostic factors are: Low number of involved lymph nodes, female gender, absence of visceral metastases (stage IV melanoma), low serum lactate dehydrogenase (LDH) in those with stage IV melanoma and early surgical intervention. Factors associated with poor survival are: stage IV melanoma with a median survival of 12 months, older age at diagnosis, involvement of more than one organ, and presence of more than one metastasis. [16,17].

## 4. Conclusion

This case report highlights that MUP is a challenging malignancy which cause the problem of diagnosis and treatment and need more randomized and prospective research to better understand its pathogenesis and set the protocols of its management. The multidisciplinary team is required to improve the prognosis of patients with MUP.

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## Ethical approval

N/A

## Consent

Written informed consent was obtained from the patient for 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.

## Author contribution

N. ID EL HAJ: study design, and data analysis, and writing.
S. HAFIDI: study design, data collections, data analysis, and writing.
R.KARAM: data collections, data analysis.
M.KARKOURI: study design, data collections and analysis.
S.BOUBIA, M.KARKOURI, M.RIDAI: data analysis and reviewers.

## Research registration

N/A

## Guarantor

Dr. Sara HAFIDI.

## Declaration of competing interest

The authors disclose no conflicts.

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