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Case Report

Metastatic Malignant Melanoma to the Breast: Report of a Case and Review of the Literature

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Abstract

Melanoma is the most rapidly increasing cancer in the world. Associated morbidity and mortality are mainly related to metastatic potential. Metastases to the breast from malignant melanoma are rare and represent only 1.3%–2.7% of reported cases. The aim of this study was to present a rare case of metastatic malignant melanoma to the breast. A 51-year-old woman was admitted for management of a palpable mass of the left breast. The past medical history referred to a sizable nodular melanoma that was removed from her back. Classification of the breast lesion was BI-RADS 5. Core needle biopsy was compatible with the diagnosis of malignant melanoma. Immunohistochemical evaluation was positive for Mart1 and Ki67. Subsequent staging was indicative of multiple secondary foci in the liver and bones. The patient was administered a combination of PD L1 inhibitor nivolumab with the anti-CTLA4 inhibitor ipilimumab followed by additional targeted therapy with the BRAF inhibitor vemurafenib. Metastasis to the breast from malignant melanoma is extremely rare. Nevertheless, breast metastases must be suspected in patients with a history of malignant melanoma. Moreover, recent breakthroughs in the Braf and MEK inhibitors and immune checkpoint inhibition therapies have impressively improved prognosis in patients affected by melanoma.

Keywords

breast metastasis, clinical presentation, diagnostic modalities, malignant melanoma, therapeutic management

INTRODUCTION

Melanoma is a skin tumour of high malignancy characterized by the excessive proliferation of atypical melanocytes. Although melanoma is frequently diagnosed among people in the sixth to seventh decade, 5.9% of detected cases occur in patients aged 20–34 years. Melanoma is the most increasing cancer worldwide and up to 20% of cases develop metastatic disease.[1] Morbidity and mortality are mainly associated with its metastatic potential. In total, 90% of melanoma affected patients with secondary lesions succumb to disease within 1 year.[2] Metastases of melanoma are more frequently located in the lungs, central nervous system, liver, and bones.[3] Metastases to the breast from malignant melanoma are rare and represent only 1.3%–2.7% of reported cases. Although breast metastases are uncommon, melanoma is one of the most frequently determined primary sites in patients presenting with a metastatic breast lump.[4]

Invasive breast cancer is the most frequently diagnosed non-dermatologic malignancy in women. However, the breast is rarely the site of metastatic disease. Trevithick was the first to report a case of extra-mammary breast metastasis in 1903. Metastasis in the breast can be misdiagnosed

as a benign disease or primary malignancy and is usually a rare and unexpected diagnosis in a patient presenting with a breast mass.[5] The most commonly reported primary site of breast metastases is the contralateral breast. Other primary tumours that metastasize to the breast are hematologic malignancies, melanomas, and carcinomas of the lungs and ovaries. The aim of this study was to present a rare case of metastatic malignant melanoma to the breast. Clinical features, morphological and immunochemical findings are discussed, while the role of current diagnostic and therapeutic management of this uncommon entity is emphasized.

CASE REPORT

A 51-year-old woman was admitted to our institution for the management of a palpable mass of the left breast. Past medical history referred to a sizable nodular melanoma that was removed from her back seventeen years ago. Wide excision of melanoma was successful with free surgical margins. The lesion had been staged as Clark level 4; thus, administration of adjuvant therapy was not recommended. On clinical examination, an irregularly shaped, sizable mass measuring approximately 5 cm was palpable in the outer lower quadrant of the left breast. Subsequent digital mammography (craniocaudal and lateral views) was indicative of a nodular lobulated mass-like lesion in the outer lower quarter of the left breast, with a diameter of 5 cm and mild border irregularity. Additional benign calcifications, as well as an axial lymph node, were also detected ***(Fig. 1)****. Ultrasonography, also, confirmed the presence of a hypoechoic lobulated solid lesion with well-defined borders and parallel orientation in the left breast, located 0.5 cm from the nipple and 0.6 cm from the skin (Zone 1A). The lesion appeared with posterior acoustic enhancement, intense peripheral and central vascularization and heterogenous elastography findings measuring 5.3×3.5×5.5 cm. Overall classification was BI-RADS 5.*

Core needle biopsy of the breast was performed, and four specimens were harvested. Microscopic examination described the presence of a solid appearing, poorly differentiated neoplasm with a diffuse architectural pattern composed of medium and large epithelioid cells with oval shaped, basophilic nuclei containing intranuclear cytoplasmic inclusions and small eosinophilic cytoplasm. Differential diagnosis included pleomorphic invasive lobular carcinoma and melanoma due to previous history of malignant melanoma. The immunohistochemical evaluation was negative for estrogen and progesterone receptors, as well as for HER-2. Positivity for Mart1 (100%) and Ki67 (80%) was apparent, therefore compatible with the diagnosis of malignant melanoma ***(Fig. 2)****. Moreover, HMB-45, another highly sensitive marker for melanoma cells, was positive as well* ***(Fig. 3)****. Subsequent staging process with CT scan of lungs, abdomen and brain was indicative of multiple secondary foci in the liver parenchyma and*

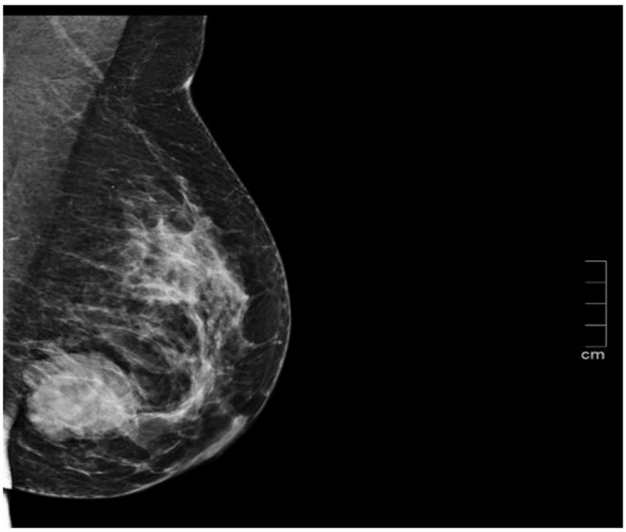

Figure 1. Digital mammography indicative of a nodular lobulated mass-like lesion in the outer lower quarter of the left breast, with a diameter of 5 cm and mild border irregularity.

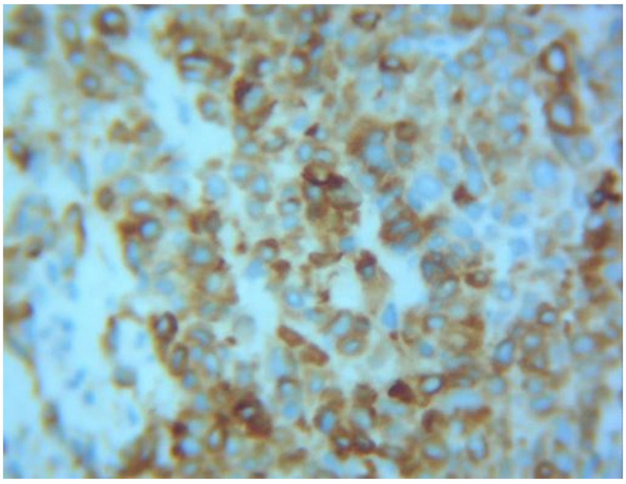

Figure 2. Mart1 positive immunohistochemical stain indicative of metastatic malignant melanoma of the breast.

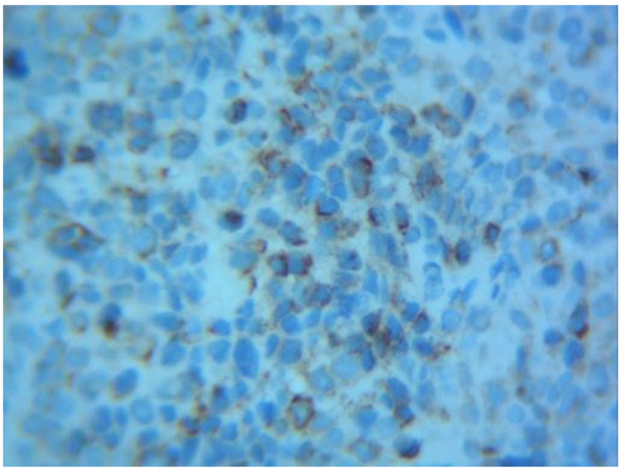

Figure 3. Characteristic immunohistochemical positive HMB-45, a highly sensitive marker for melanoma cells.

bones. The patient was administered a combination of PD-L1 inhibitor nivolumab with the anti-CTLA4 inhibitor ipilimumab. As the patient experienced disease recurrence under treatment and BRAF V600 mutation was documented, additional targeted therapy with the BRAF inhibitor vemurafenib was implemented with stabilisation of her condition.

DISCUSSION

Melanoma is the deadliest form of skin cancer and strikes thousands of people around the world each year.[1] Luckily, recent breakthroughs in the BRAF and MEK inhibitors and immune checkpoint inhibition therapies have impressively improved prognosis as well as long-term survival in melanoma affected patients.[2] Even though metastasis of melanoma remains a significant issue, a detailed mechanistic understanding of how this metastasis occurs is lacking. The favoured route of melanoma metastasis to distant organs is via the lymphatic vasculature of the skin, but the main sites of entry of the melanoma cells into the blood stream are not well detected.[1] Therefore, melanoma usually metastasizes to lungs, central nervous system, liver, and bones.[3] Metastases to the breast from malignant melanoma are extremely rare. However, breast involvement often presents as the first sign of a primary extra-mammary tumour. For this reason, breast metastases must be suspected in patients with a history of malignant melanoma and the detection of breast lesions always requires further diagnostic and instrumental procedures for their characterization.[6] A case of breast metastasis by melanoma to a ruptured implant capsule has also been described. We herein present an unusual and remarkably interesting case of metastatic malignant melanoma to the breast.

It is essential to underline that a melanoma metastasis to the breast presents with the same clinical features and imaging signs as any other breast tumour and is characterized with similar BI-RADS classification. Clinical examination and imaging techniques, such as digital mammogram, ultrasonography and magnetic resonance imaging (MRI), are often not specific. After core biopsy is performed, cytological and pathological examinations play a pivotal role in making the diagnosis. The history of melanoma remains of great diagnostic significance and should pose the clinical suspicion for the origin of the mass. Nevertheless, some metastatic lesions in the breast possess unusual and potentially confusing appearances on imaging. On mammograms, they tend to be well defined, presenting with single or multiple different nodules, while on ultrasonography, they can be lobulated with clear margins and low echogenicity.[6] In our case, standard imaging proved non-diagnostic and subsequent fine needle biopsy along with pathological staining examinations was implemented to establish the diagnosis of metastatic melanoma of the breast.

Metastatic melanoma to the breast has the same pathological profile with primary malignant melanoma. The histologic appearance of melanoma is highly heterogeneous with numerous morphological variants. A typical melanoma presents with pigmented epithelioid tumour cells, nucleic and cytoplasmic atypia.[7] In our case, oval shaped, basophilic nuclei, cytoplasmic inclusions, and small eosinophilic cytoplasm were observed. In contrast, breast cancer presents with a totally different pathological profile that depends on whether the tumour arises from the ducts or lobules, is in situ or invasive.[8] The immunohistochemistry of malignant melanoma includes S 100 positivity that remains the most sensitive parameter for melanocytic lesions, while markers such as HMB 45, Mart 1/Melan A, tyrosinase, and MITF demonstrate relative specificity but not as good sensitivity as S 100. Ki67 remains the most useful adjunct in distinguishing benign from malignant melanocytic tumours.[6] Our patient presented with positive MART 1 and Ki67 markers. Therefore, pathological and immunohistological examination is crucial to set the diagnosis.

Therapeutic approach, on the other hand, can pose a dilemma. The only curative approach is surgical removal of the metastatic lesion. In patients with isolated metastatic disease limited to the breast, wide local excision with free margins should be accomplished. In clinically negative lymph nodes, sentinel lymph node biopsy might be attempted as a staging procedure even though it has no proven therapeutic value and carries a 5% morbidity risk. If axillary node involvement is verified, axillary lymph node dissection should also be performed. Nevertheless, in most cases this is not possible, due to the diffuse metastatic disease and the presence of multiple metastatic lesions in other sites. Systemic treatment in patients with metastatic melanoma is of paramount importance due to the aggressive nature of the disease.[8] Therefore, systemic therapy targets the palliation of symptoms as well as the prolongation and improvement of quality of life.[9]

Many factors influence the therapeutic decision and the type of systemic treatment.[10,11] First, clinical parameters such as performance status, extent of the disease and sites of metastases and comorbidities are taken into consideration. Secondly, biological factors, such as mutations in the BRAF gene, codon V600 and, less commonly, the c-kit gene which are frequently found, are important.[12] Based on these factors, one could initially choose treatment with immunotherapy with one of the PD L1 inhibitors (nivolumab or pembrolizumab) or the combination of nivolumab with the anti-CTLA4 inhibitor ipilimumab.[13] An equal option in patients with BRAF V600 mutations is the targeted therapy with a BRAF inhibitor (vemurafenib, dabrafenib, encorafenib) alone or in combination with a MEK inhibitor (cobimetinib, trametinib or binimetinib, respectively).[14,15] When quick response is needed, targeted therapy, where indicated, is preferred. Immunotherapy, on the other hand, is often associated with delayed and prolonged responses. In our patient, the initial unsuccessful administration of the combination of nivolumab with ipilimumab was followed by additional targeted therapy with the BRAF inhibitor vemurafenib, contributing to the stabilization of her metastatic disease for several months.

In conclusion, the timely diagnosis of a melanoma metastasis to the breast is of utmost importance. The clinician should accurately distinguish cases with a solitary breast metastasis that can be successfully treated surgically from cases with diffuse metastatic disease that are only eligible for systemic therapies.

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Метастатическая злокачественная меланома груди: отчёт о случае и обзор литературы

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Резюме

Меланома является самым быстрорастущим видом рака в мире. Сопутствующая заболеваемость и смертность в основном связаны с метастатическим потенциалом. Метастазы злокачественной меланомы в грудь встречаются редко и составляют всего 1.3–2.7 % зарегистрированных случаев. Целью данного исследования было представить редкий случай метастазирования злокачественной меланомы в молочную железу. 51-летняя женщина поступила для лечения пальпируемого новообразования в левой молочной железе. В анамнезе указывалось, что крупная узловатая меланома была удалена из её спины. Классификация поражения молочной железы была BI-RADS 5. Биопсия центральной иглы была совместима с диагнозом злокачественной меланомы. Иммуногистохимическая оценка была положительной для Mart1 и Ki67. Последующая стадия указывала на множественные вторичные очаги в печени и костях. Пациентке была назначена комбинация ингибитора PD L1 ниволумаб с анти-CTLA4 ингибитором ипилимумаб с последующей таргетной терапией ингибитором BRAF вемурафенибом. Метастазы в молочную железу злокачественной меланомы крайне редки. Тем не менее метастазы в молочные железы следует подозревать у пациентов со злокачественной меланомой в анамнезе. Более того, недавние открытия в области ингибиторов Braf и MEK и терапии, подавляющей контрольные точки иммунного ответа, значительно улучшили прогноз у пациентов с меланомой.

Ключевые слова

метастазы молочной железы, клиника, методы диагностики, злокачественная меланома, терапевтическое лечение