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Diagnostic Delays in Metastatic Amelanotic Melanoma Presenting as Breast Pain

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 58-year-old
Final Diagnosis: Metastatic amelanotic melanoma
Symptoms: Breast mass • breast pain
Medication: —
Clinical Procedure: Mastectomy
Specialty: Dermatology • Oncology

Objective: Rare disease

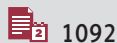
Background: Breast metastases from melanoma are rare. Amelanotic melanoma is difficult to diagnose, as primary lesions not only lack the pigment typical of melanoma, but also lack other features associated with these tumors, including asymmetry, irregular borders, and color variegation.

Case Report: A 58-year-old woman presented with an enlarging mass on her left breast, a finding confirmed by physical examination. Mammography showed a 10-cm breast mass of category 4 according to the Breast Imaging Reporting and Data System (BI-RADS). Staging computed tomography (CT) showed widely scattered metastatic sites in the brain, lungs, mediastinum, and adrenal glands. A biopsy of the mass in her left breast was non-diagnostic due to extensive necrosis. Because of severe pain, simple left breast mastectomy was performed. Tissue from the mastectomy revealed a diagnosis of amelanotic malignant melanoma.

Conclusions: Diagnosing amelanotic melanoma is difficult without tissue biopsy as these tumors lack the typical features of melanoma and can mimic other dermatologic diseases. This frequently results in a significant delay in diagnosing amelanotic melanoma, with patients often presenting with advanced stage disease having poor prognosis.

MeSH Keywords: Breast Neoplasms • Melanoma • Melanoma, Amelanotic

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Background

Metastases to the breast of extra-mammary tumors are rare, with an incidence of 1–2% [1,2]. Tumors that more frequently spread to the breast include malignant melanomas, pulmonary carcinomas, and lymphomas [3]. Malignant melanoma is one of the most prevalent and most aggressive forms of skin cancer worldwide [4]. These tumors most frequently metastasize to the liver, lungs, and brain, although they can metastasize to any organ including the breast, which is an uncommon site [5]. It may be difficult to distinguish metastases from primary breast tumors, especially when tumors present as an isolated mass with no evidence of systemic disease. Furthermore, metastatic amelanotic melanoma (AM) from an unknown primary is rare, with an incidence of 2.2% [6,7]. The poor prognosis of patients with AM is due in part to difficulties encountered in making an early accurate diagnosis. This report describes the challenges encountered in diagnosing metastatic AM in a woman who presented with an enlarging mass on her left breast and the associated poor prognosis of this patient.

Case Report

A 58 year-old post-menopausal Hispanic woman with no significant past medical history presented to the emergency room with an enlarged left breast of 6 months' duration, along with pain for the previous 1 month. Physical examination showed that her left breast was double the size of her right breast, along with erythema and warmth encompassing the lateral aspect. A firm, palpable, and tender 7-cm mass was observed on her left breast, accompanied by nipple retraction and dimpling, but no discharge. Ultrasound revealed a large oval mass with microlobulated margins and necrotic center occupying almost the entire left breast, with diffusely increased vascularity in the surrounding tissue. Mammography showed a 10 cm by 10 cm mass in her left breast classified as category 4 according to the Breast Imaging Reporting and Data System (BI-RADS) (Figure 1). An ultrasound-guided biopsy of the mass yielded a specimen unsatisfactory for diagnostic evaluation due to extensive necrosis. The sample was negative for all specific breast markers. Differential diagnoses included metastatic breast carcinoma, stromal component of malignant phyllodes tumor, and sarcoma not otherwise specified. Computed tomography (CT) scans of her head, chest, abdomen and pelvis revealed multiple enhancing lesions in the brain, mediastinal lymphadenopathy, pulmonary nodules with invasion into the pericardium, axillary nodules, and bilateral adrenal masses suggesting metastases (Figure 2). Although it was unclear whether this mass was a primary or secondary tumor site, its large size and associated pain prompted urgent palliative simple mastectomy of her left breast. Because the CT scans showed widespread disease, sentinel lymph node biopsy was

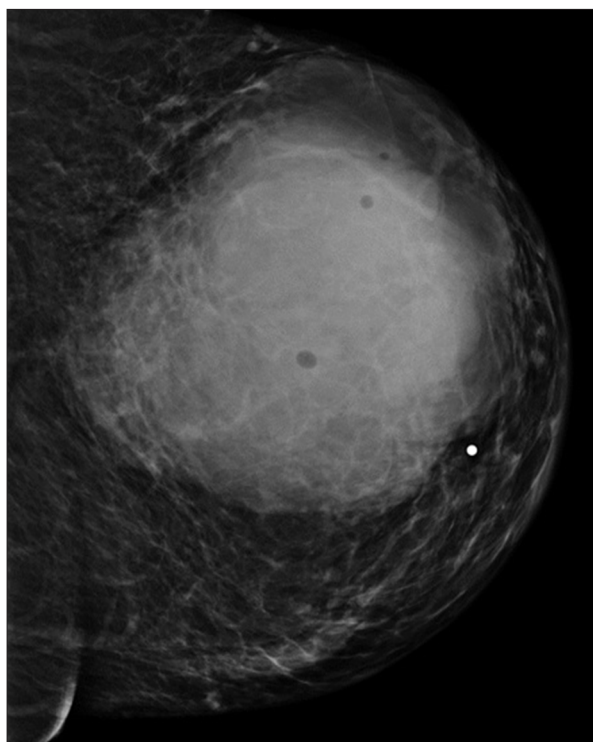


Figure 1. Mammogram showing a 10x10 cm mass in the left breast classified as BI-RADS category 4.



Figure 2. CT of the chest with contrast, showing pulmonary metastases.

not performed. Immunohistochemistry showed that the mass was positive for vimentin, S-100, and MiTF-1 and negative for MART, HMB-45, epithelial breast markers, and BRAF mutation, suggesting a malignant AM (Figures 3, 4). Although treatment with nivolumab and ipilimumab was planned, the patient's functional status deteriorated. She was enrolled in a hospice and died shortly thereafter.

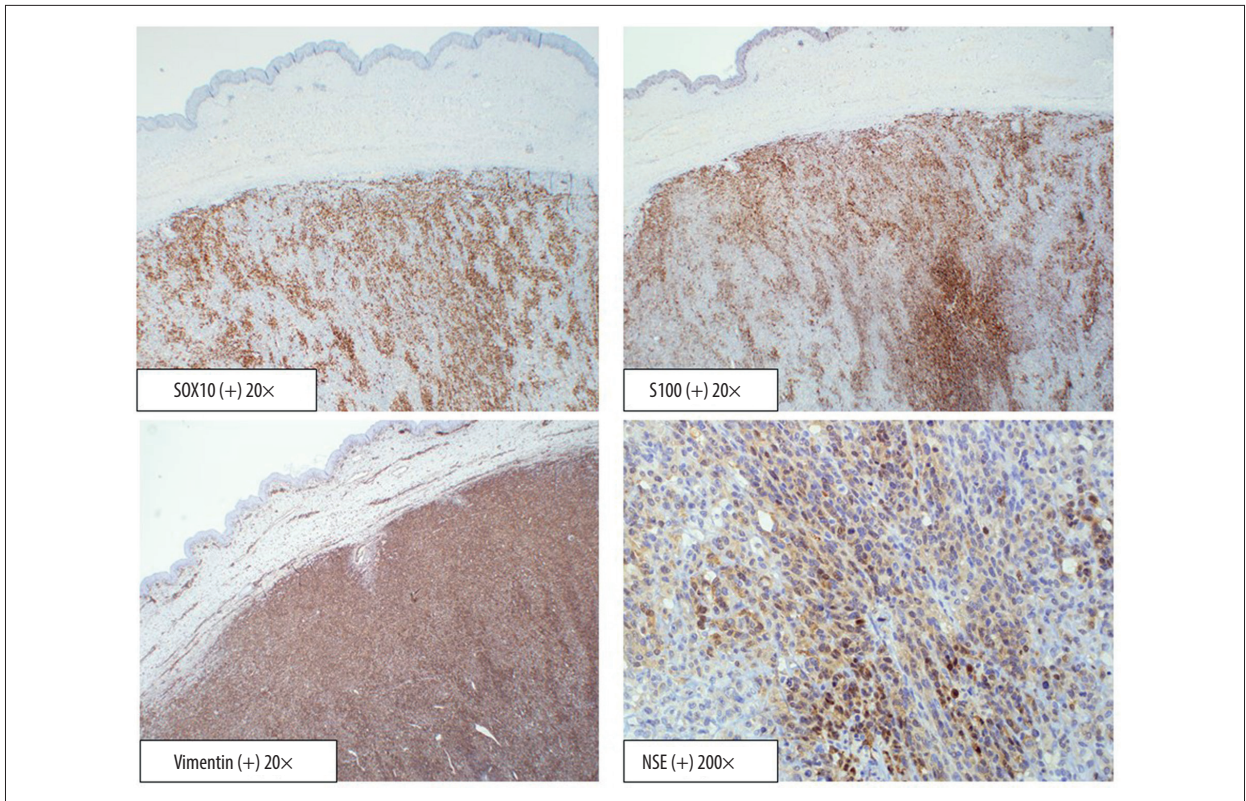


Figure 3. Immunohistochemical markers positive in a biopsy of the left breast.

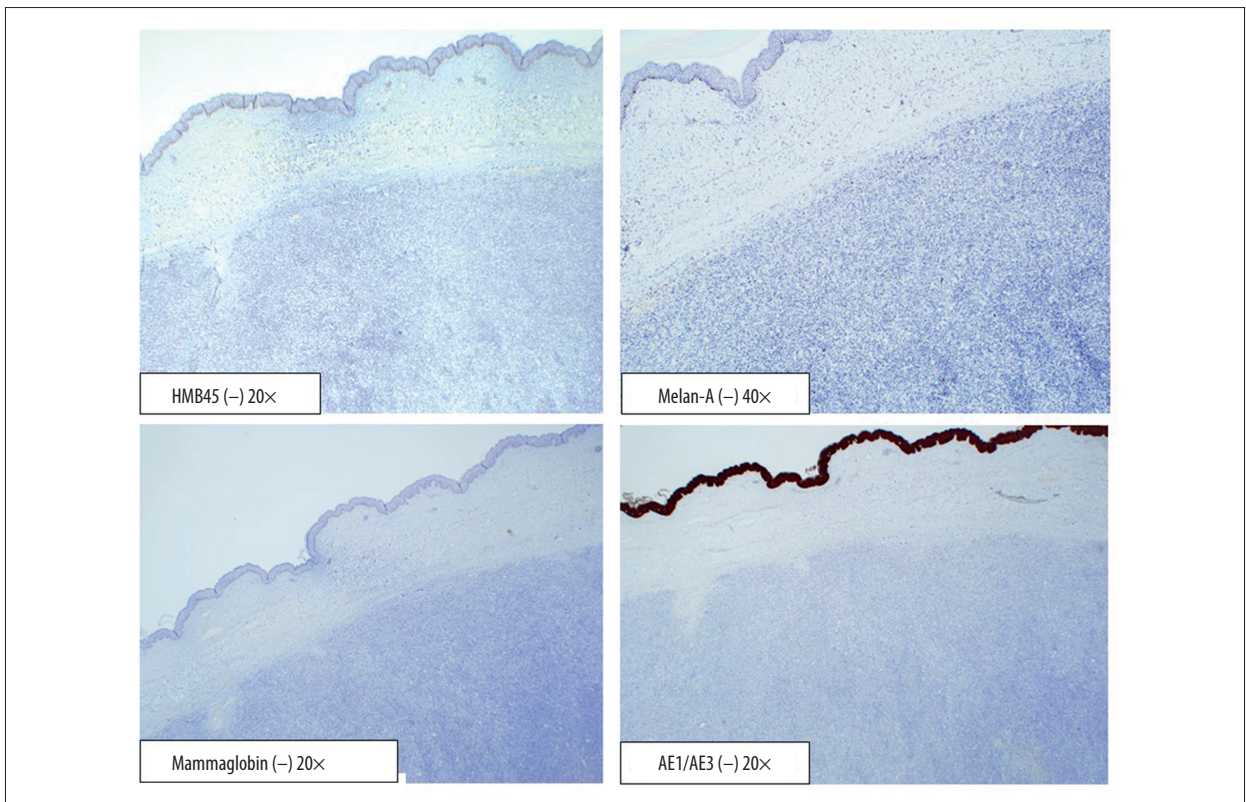


Figure 4. Immunohistochemical markers negative in a biopsy of the left breast.

Table 1. Review of patients with amelanotic melanoma involving the breast.

Article	Age, gender	Time to diagnosis	Method for diagnosis	Sites of involvement	Skin lesions	Receptors	Treatment outcome
Roy S. et al. (2008) [13]	40 yr, Female	3 months of symptoms. Diagnosed on presentation	Simple mastectomy	Right breast mass	None	(+) S100 (+) HMB-45	No treatment as patient was lost to follow up
Biswas A. et al. (2014) [14]	32 yr, Female	18 months of symptoms after a lumpectomy. Diagnosed on presentation	Fine needle aspiration	Left breast mass; left axillary node	None	(+) S100 (+) HMB-45	Wide local excision of the left breast mass; left axillary node dissection; post-operative radiation therapy to the entire left breast; adjuvant immunotherapy with interferon alpha-2b; complete remission nine months after immunotherapy
Sathiah P. et al. (2017) [15]	58 yr, Female	No timing of symptoms noted. Diagnosed at presentation	Core needle biopsy	Left breast mass; bilateral axillary nodes; bilateral cervical nodes; pericardial effusion	None	(+) S100 (+) HMB-45	No treatment as patient was lost to follow up
Kobayashi G. et al. (2000) [16]	47 yr, Female	3 weeks of symptoms. Diagnosed at presentation	Fine needle aspiration Skin biopsy	Right breast mass; right axillary node; back with nodular, pigmented ulcer	3×3 cm nodular hyperpigmented ulcer on the back	(+) S100 (+) HMB-45	No mention of treatment or follow up

Discussion

AM is an uncommon subtype of melanoma, being present in 2–8% of patients with malignant melanoma [8,9]. Diagnosing AM is challenging because the primary lesion lacks the typical pigment usually found in melanoma. Lesions may be amelanotic or hypomelanotic, which appear similar on clinical examination. These lesions can be distinguished by dermatoscopy, as discernible pigmentation is present only on hypomelanotic lesions [9]. Adding to the diagnostic challenge, AM rarely exhibits the classic features of melanomas, such as asymmetry, irregular borders, and color variegation [10]. AM lesions can have various shapes, borders, and colors, with these characteristics mimicking several other dermatologic diseases. For example, AM lesions can appear nodular or flat; have well- or poorly-defined borders; be pink-erythematous or light brown color; and have scaling or disruption of skin markings [9]. The atypical appearance of AM often results in a significant delay in diagnosis, with most patients presenting with advanced stage disease. The five year survival rates are 85% for patients with localized AM and 96% for patients with melanotic melanoma [11], compared with 26% in patients with

metastatic AM [11]. It is difficult to identify a primary skin lesion in patients with metastatic AM. For example, a primary skin lesion was detected in only one of four patients with AM of the breast, (Table 1).

Because of the atypical clinical presentation of these lesions, immunohistochemistry is required to confirm diagnosis, as in our patient, and to differentiate between benign and malignant melanocytotic tumors. All four additional patients with amelanotic melanoma of the breast identified in the literature, were positive for S-100 and HMB-45 (Table 1). Although our patient was also positive for S-100, she was negative for HMB-45. Many immunohistochemical markers, including S-100, HMB-45, MART-1/Melan-A, tyrosinase, and MITF, are highly specific for melanoma, with S-100 being the most sensitive. Because the histological features of melanoma vary considerably, no single histologic marker is diagnostic [10].

This case highlights the difficulties diagnosing metastatic AM of unknown primary origin. AM in this patient was finally diagnosed by IHC staining after mastectomy rather than by staining of an ultrasound guided biopsy sample, as the latter

sample was unsatisfactory. Diagnostic delay may have been reduced by obtaining a core needle biopsy sample, which is more sensitive than fine needle aspiration cytology in diagnosing primary breast cancers, although these two diagnostic methods have not been compared for melanomas of the breast [12]. Two of the four patients with metastatic AM were diagnosed by fine needle aspiration. Diagnostic inaccuracy in our patient not only delayed her diagnosis, but resulted in an unnecessary and invasive simple mastectomy in a patient with extensive metastatic disease. The findings in our patient also emphasize the importance of identifying a primary malignancy site before treatment, as management depends on the origin of the primary tumor. This patient died 56 days after her initial presentation. Of the four patients reviewed, only one received treatment, which included wide local excision, node dissection, whole breast irradiation, and adjuvant interferon alpha-2b, and resulted in complete remission (Table 1). Breast metastases from melanoma may indicate wide metastatic spread and poor patient prognosis, suggesting that aggressive surgical procedures may be ineffective.

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Conclusions

This report describes a patient who initially presented with metastases of AM to the breast and illustrates the poor prognosis of patients with this condition. Because of difficulties diagnosing metastatic AM, a multidisciplinary team is essential for further management, which may be palliative due to the advanced stage of the tumor and poor patient prognosis at presentation.

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Conflict of interest

None.