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CASE REPORT

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Melanoma in the Breast: A Diagnostic Challenge

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Although rare, breast metastases can mimic primary tumors, both clinically, radiologically, and histopathologically. Melanoma is a highly metastasizing tumor, and it is known as a great mimicker of tumors. Metastatic melanoma in the breast can mimic primary breast cancer and pose a diagnostic challenge. In most cases, it is associated with disseminated disease and a poor prognosis, therefore, histologic, immunohistochemical and clinical correlation is crucial in diagnosing these cases. In this case report, we discuss a 63-year-old female who presented with clinical features of probable breast cancer, describe immunohistochemistry workup, and discuss pitfalls in interpretation.

INTRODUCTION

Presentation of breast lumps in postmenopausal women is often initially considered a possible primary malignancy due to the rarity of metastasis to breast from extramammary sites [1]. Metastatic spread of melanoma to the breast is a far less occurrence than primary breast cancer constituting 1.3-2.7% of all malignant breast tumors [1]. Among the primary tumors that metastasize to the breast, cutaneous melanoma is one of the most frequent and with the increase in its incidence, this observation is growing [2]. Metastatic melanoma in the breast can mimic primary breast cancer and pose a diagnostic challenge and, in most cases, it is associated with disseminated disease and a poor prognosis [1]; therefore, histologic, immunohistochemical and clinical correlation is crucial in diagnosing these cases. We report an unusual case of metastatic melanoma in a 63-year-old female who presented with clinical features of probable breast cancer and discuss pitfalls in interpretation of immunohistochemical stains.

CASE REPORT

A 63-year-old female patient presented with palpable lumps and discomfort in bilateral breasts for several months. She had no personal or family history of breast cancer and had an unremarkable mammogram several years ago. Physical exam was remarkable with palpable tender mass in the right breast at 9 o'clock position with no skin/nipple changes and large, palpable, and tender left axillary adenopathy. Diagnostic mammograms

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demonstrated a 2.5 cm oval mass in the right breast at 9 o'clock posterior depth and a 4.9 cm oval mass in the left axilla suspicious for malignancy. An ultrasound-guided core biopsy of both the right breast and left axillary masses was performed.

Hematoxylin and Eosin stained slides from both sites showed infiltration of fibrous tissue by solid nests of large epithelioid/plasmacytoid tumor cells with nuclear pleomorphism, hyperchromasia, prominent nucleoli, and mitosis, with foci of discohesiveness and prominent zones of tumor necrosis. There was evidence of background inflammatory infiltrates and stromal desmoplastic reaction. Ductal/lobular carcinoma in situ in the examined core biopsies was not identified. Ancillary studies on the tumor cells of the left axillary mass demonstrated positive immunostaining for markers SOX10, HMB45, MART1, and E-cadherin. Tumor cells were negative for cytokeratin AE1/AE3, myoepithelial markers p63, and smooth muscle myosin. Immunohistochemical stains on the tumor cells of the right breast mass demonstrated positive staining for SOX10, HMB45, MART1, and E-cadherin and negative staining for cytokeratin AE1/AE3, cytokeratin 7, cytokeratin 20, GATA3, estrogen receptor, and TTF-1 (Figures 1, 2, and 3). SOX10 is a transcription factor in the development of melanocytes and serves as an immunohistochemical marker for pinpointing melanocytic lesions, including melanoma. HMB45 is a monoclonal antibody reactive with melanosomes. MART1, integral in the regulation of melanin synthesis, is expressed in both melanocytes and melanoma cells. E-cadherin, identified as a cell adhesion molecule that may be expressed in melanoma. The morphology and immunohistochemical profiles in two masses were similar and supported the diagnosis of melanoma.

Molecular studies were performed on the tumor cells of the left axillary mass by Next Generation Sequencing (NGS) and Polymerase Chain Reaction (PCR), and detected BRAF V600E mutation. PET-CT scan demonstrated hypermetabolic activity in the right breast and left axillary masses compatible with diagnosed melanoma. There was a hypermetabolic mesenteric soft tissue mass suspicious for an additional site of metastatic cancer. There were no hypermetabolic skin lesions identified. MRI of the brain was negative.

Though not available at the time of the biopsy, a clinical history of melanoma was obtained after the diagnosis of metastatic disease. She was initially diagnosed with cutaneous melanoma over her left breast at age 38 that was treated with wide local excision. Later, she developed subsequent melanoma of skin over her back at age 50 and her left face at age 55 and both were treated with wide local excision. She never needed any adjuvant therapy. Though the melanoma in the right breast may represent a new primary, given the presence of metastatic disease in the left axilla and mesentery, a metastasis to the breast is most likely.

Due to multiple metastatic lesions, the patient was not a candidate for surgical resection; therefore, she was started on a systemic immunotherapy with nivolumab, a PD-1 inhibitor, to slow the progression of disease. Following treatment restaging CT scans showed interval decrease in size of right breast mass and stable left axillary and mesenteric masses suggesting response to treatment.

DISCUSSION

Even though metastases from extramammary tumors to the breast are rare, melanomas and lymphomas are the most common origin of metastases to the breast. The interval to metastasis is also quite wide, but averages about 4 years, and relatively few patients present without prior melanoma history [1]. The tumor cells frequently present as a fast-growing solitary nodule most often in the upper outer quadrant of breast and can be uncomfortable or painful as seen in this case. The tumor generally averages 2 cm and is typically without superficial or deep fixation as seen in other cases [3]. It is only bilateral in 8% of cases, and changes in the nipple are rare [4]. Axillary lymph node involvement as seen in our patient has been reported in 25-80% of cases [5].

It can be challenging to recognize the metastatic origin of a breast tumor histologically. In the absence of a history of prior malignancy, unusual clinical features (such as contralateral axillary nodal involvement in the absence of ipsilateral involvement as in this case, or cutaneous involvement) may raise suspicion for metastatic disease. Histological features include unusual histology and lack of intraductal/lobular carcinoma in situ component, and the presence of prominent lymphovascular invasion [1,3]. For cells originating from malignant melanoma, melanin pigment, nuclear pseudoinclusions, prominent nucleoli, eccentric cytoplasm, and discohesiveness cells can often be seen in some of the neoplastic cells, but the diagnosis should be confirmed by immunohistochemistry. The working diagnosis was primary breast cancer (ie, high grade ductal carcinoma, pleomorphic lobular carcinoma, myoepithelial carcinoma given the plasmacytoid features). However, due the presence of contra-lateral axillary disease in the presence of clinically un-involved ipsilateral axilla, lack of an in situ component and plasmacytoid features, metastatic disease (melanoma, lung carcinoma) to breast parenchyma was considered.

An immunohistochemical panel comprising both epithelial (cytokeratins, EMA) and melanocytic (S100 protein, HMB-45 antigen, Melan A, SOX10, etc.) antigens with lineage specific markers when appropriate, is most helpful. A positive reaction to cytokeratins suggests carcinoma, while positivity for S100, HMB-45, and Melan

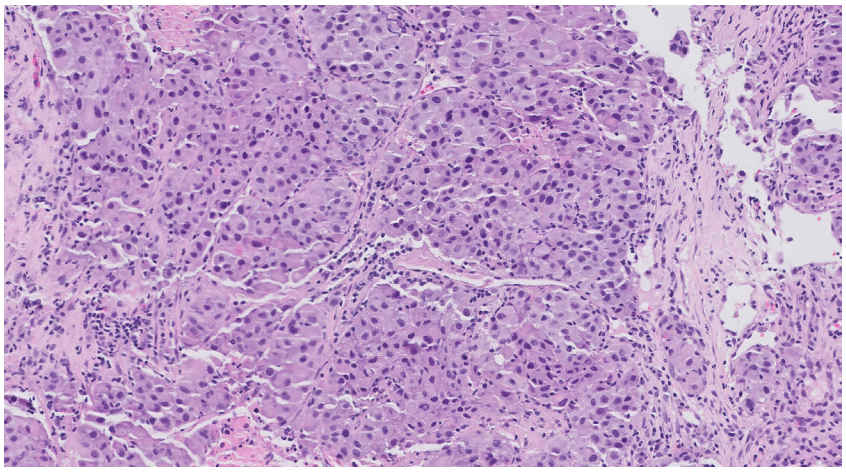

Figure 1. Hematoxylin & eosin-stained section of metastatic melanoma to breast parenchyma (100x).

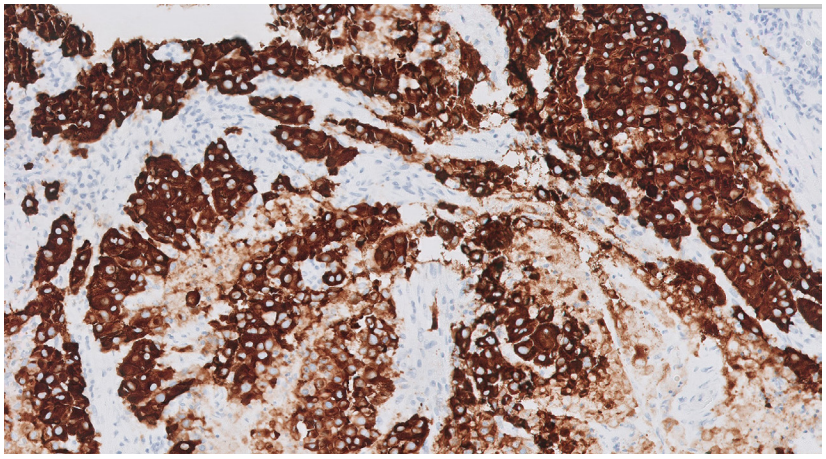

Figure 2. MART1 demonstrates cytoplasmic staining within malignant cells (100x).

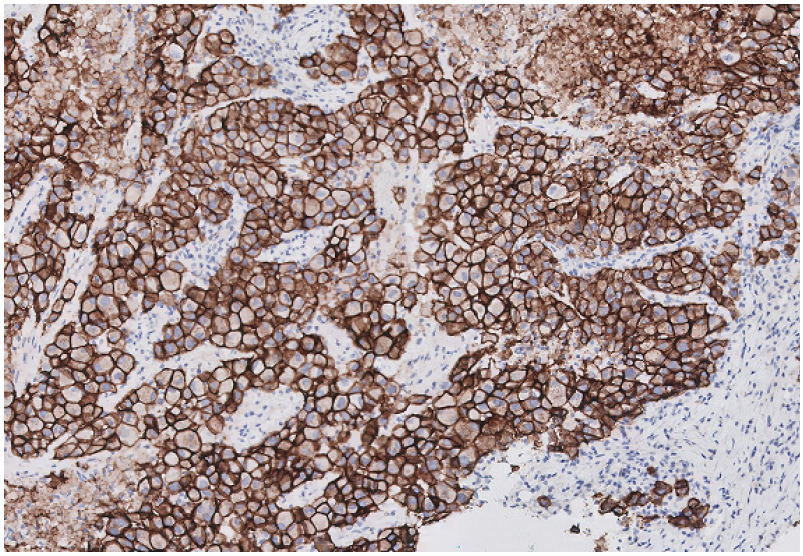

Figure 3. E-Cadherin stains the membranes of malignant cells (100x).

A indicates melanoma. S100 (expressed both in the cytoplasm and in the nucleus) is the most sensitive marker and is expressed in 95% of cases, however, S100 positivity may be seen in other carcinomas including breast, lung, ovarian, and pancreatic carcinoma [6]. In one study of 100 randomly selected invasive breast carcinomas, S100 positive tumor cells were seen in 48% of cases. Lobular and medullary carcinomas were more frequently positive (60% and 80% respectively) [7]. Rare variants of breast carcinoma such as acinic cell carcinoma and carcinoma arising from microglandular adenosis may be diffusely S100 positive. These are also typically triple negative but will be positive for cytokeratins. More recently, antibodies to SOX10, key nuclear transcription factor in the differentiation of neural crest progenitor cells to melanocytes, have been shown to be a sensitive and specific marker of malignant melanoma of multiple histologic types. However, some salivary-gland type carcinomas arising in the breast and nearly half of triple negative breast carcinoma may be SOX10 positive [8,9]. Small number of breast carcinoma have been reported to be HMB-45 positive (2/100) with positive staining observed in adjacent ducts and lobules [10]. Trichorhinophalangeal syndrome type 1 (TRPS1) has been recently identified as a specific marker for breast carcinoma and is a great diagnostic tool for triple negative breast carcinomas [10,11]. Of note, positivity for cytokeratins has been observed in melanomas, with a recent study reporting expression in up to 40% of cases, likely due to modern epitope retrieval techniques [12,13]. In this case, E-cadherin was performed to evaluate for pleomorphic lobular carcinoma, in which it is typically negative or attenuated. E-cadherin is typically expressed in carcinoma, however a recent tissue microarray study of 10,851 tissues demonstrated positive e-cadherin expression in 77% of melanomas with strong positive staining in 61% [14]. The role of e-cadherin in melanoma progression is being elucidated – expression of e-cadherin in normal melanocytes is largely reduced in the initial stages with different levels of e-cadherin found at advanced stages, raising the possibility that e-cadherin influences the invasive and metastatic potential of melanoma cells [15]. The reader is referred to comprehensive reviews of immunohistochemical markers in melanoma by Saliba et al. for further details on aberrant expression of muscle-specific, neuroendocrine, macrophage, vascular, and hematopoietic markers in melanoma [12].

As mentioned in the case, further studies on the tumor cells showed BRAF V600E mutation. The BRAF, an intracellular kinase, is frequently mutated in melanoma, thyroid and lung cancers among others. The BRAF V600E mutation is known to be oncogenic. The BRAF-targeted inhibitors encorafenib, dabrafenib, and vemurafenib alone or in combination with the MEK-targeted inhibitors binimetinib, trametinib, and cobimetinib, respectively, are FDA-approved for the treatment of patients with BRAF V600E/K mutant melanoma.

In conclusion, this case underscores the complexity of diagnosing metastatic melanoma mimicking primary breast cancer. Despite the rarity of breast metastases, the patient's clinical presentation, initially suggestive of primary malignancy, led to further investigations. Histopathological and immunohistochemical analyses confirmed metastatic melanoma, emphasizing the importance of precise diagnostic techniques. Notably, the identification of a BRAF V600E mutation through molecular studies provided crucial molecular insights into the nature of the malignancy, influencing subsequent treatment decisions. The staging CT further revealed hypermetabolic activity in the right breast and left axillary masses, solidifying the diagnosis and guiding the initiation of systemic immunotherapy. This case highlights the critical role of a multidisciplinary approach in unraveling the complexities of metastatic melanoma, where clinical, histopathological, and molecular aspects converge to inform accurate diagnosis and personalized therapeutic strategies. In summary, since metastatic melanoma can mimic primary tumor both clinically and radiologically, it is important to conduct a comprehensive work up to arrive at the correct diagnosis which will determine the appropriate lines of clinical management.

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