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(CASE REPORT)

Malignant melanoma masquerading as primary breast carcinoma, a diagnostic dilemma in metastatic disease: Case report and a brief review of the literature

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Abstract

Metastatic melanoma to the breast is a rare but diagnostically challenging entity, frequently mimicking primary breast carcinoma due to overlapping clinical and radiological features. We present the case of a 59-year-old postmenopausal woman who presented with a progressively enlarging left breast mass and axillary lymphadenopathy, highly suggestive of invasive ductal carcinoma (IDC) on imaging. Initial histopathological examination provisionally favored poorly differentiated ductal carcinoma. However, a comprehensive immunohistochemical (IHC) analysis, revealing negative breast-specific markers (ER, PR, HER2, GATA3, mammaglobin) and strong positivity for melanocytic markers (S100, SOX10, MART-1, HMB-45, Melan-A), which established the diagnosis of metastatic melanoma. Subsequent molecular analysis identified a BRAF V600E mutation, and a small rectal mass that ultimately identified as the primary site. The patient achieved a sustained partial response with anti-PD-1 immunotherapy. This case features the critical importance of a high index of suspicion and thorough IHC evaluation in atypical breast presentations, even in the presence of compelling clinical and radiological evidence for primary breast cancer. It highlights a significant diagnostic dilemma and the transformative impact of precision oncology in managing such rare metastatic melanoma to the breast.

Keywords: Metastatic Melanoma; Breast Invasive Ductal Carcinoma; Melanoma of Unknown Primary; Immunohistochemistry; Precision Oncology; Anti-PD-1 Immunotherapy

1. Introduction

Metastatic involvement of the breast from extramammary malignancies is an exceedingly rare clinical phenomenon, accounting for 1.3% to 2.7% of all malignant breast lesions. [1] Among these, malignant melanoma is one of the most frequent primary sources, yet its presentation as an isolated or initial breast mass remains a significant diagnostic challenge. [1] [2] Clinicians often encounter these lesions in the sixth or seventh decade of life, where they frequently mimic the clinical and radiographic features of primary breast carcinoma, such as IDC.

Diagnostic challenges arise due to standard imaging like mammography and ultrasound inability to differentiate metastatic melanoma from primary breast cancer, which may result in improper surgery or delayed systemic treatment. [3] Furthermore, when the primary site is occult, as in melanoma of unknown primary (MUP), the prognostic uncertainty and management complexity escalate. [4] This report describes a case of metastatic melanoma masquerading as a primary breast malignancy in a 59-year-old woman, eventually traced to a primary rectal mass. We

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report this case to highlight the critical necessity of maintaining a high index of suspicion and utilizing a comprehensive IHC panel and confirmatory molecular studies to avoid misdiagnosis in atypical breast presentations.

2. Case Presentation

2.1. Clinical Presentation and Initial Evaluation.

A 59-year-old postmenopausal woman presented to the breast surgery clinic with a six-week history of a painless, progressively enlarging left breast mass. She initially consulted her primary care physician, who ordered breast imaging and referred her urgently to oncology. The patient also noted a firm left axillary swelling for approximately four weeks. Her medical history included well-controlled hypertension on lisinopril, type 2 diabetes managed with metformin, and a cholecystectomy at age 51. Family history was significant for breast cancer in her mother (diagnosed at age 72, deceased) and prostate cancer in her father (treated successfully at age 66). She denied prior skin lesions, changes in existing moles, or previous melanoma. Physical examination revealed a firm, irregular, 3.5 cm mass in the upper outer quadrant (UOQ) of the left breast, approximately 4 cm from the nipple, with overlying skin dimpling, and a 2.8 cm firm, fixed left axillary lymphadenopathy. No skin lesions were noted on comprehensive dermatologic examination. Initial laboratory studies showed normal complete blood count, liver function tests, renal function, and tumor markers, including CA 15-3 and CEA.

2.2. Radiographic Studies and Differential Diagnosis

Bilateral mammography demonstrated an irregular, spiculated 3.4 cm mass in the left breast upper outer quadrant with associated architectural distortion and suspicious microcalcifications, classified as BI-RADS 5. Targeted ultrasound confirmed a hypoechoic, irregular mass measuring 3.6 × 2.8 × 3.1 cm with posterior acoustic shadowing, and increased vascularity on Doppler imaging. An abnormal left axillary lymph node measuring 2.9 cm with loss of normal fatty hilum and cortical thickening was noted. Breast MRI with contrast showed heterogeneous enhancement of the primary mass with irregular margins, moderate background parenchymal enhancement, and confirmation of the pathologic axillary lymphadenopathy without additional suspicious lesions in either breast. The radiologic differential diagnosis primarily favored IDC with regional nodal metastasis, given the imaging characteristics and strong family history. Alternative considerations included invasive lobular carcinoma, metaplastic carcinoma, or lymphoma, though these were considered less likely based on imaging features. No distant metastases were identified on the staging chest radiograph.

2.3. Multidisciplinary Tumor Board Discussion and Pathologic Evaluation

A multidisciplinary tumor board convened with breast surgery, medical oncology, radiation oncology, radiology, and pathology. Discussion centered on optimal tissue acquisition strategy given the clinical presentation, highly suggestive of primary breast carcinoma with nodal involvement. The consensus recommendation was ultrasound-guided core needle biopsies of both the breast mass and axillary lymph node to confirm diagnosis, establish receptor status, and guide neoadjuvant versus surgical management. 14-gauge core biopsies were obtained from both sites under local anesthesia.

Histopathologic examination revealed poorly differentiated malignant neoplasm in both specimens, characterized by sheets and nests of pleomorphic epithelioid cells with high nuclear-to-cytoplasmic ratios, prominent nucleoli, abundant mitotic figures (>20 per 10 high-power fields), and areas of necrosis. (Figure 1 A, B, C, D, E, F) The provisional diagnosis favored poorly differentiated ductal carcinoma of the breast. IHC was initiated with a breast carcinoma panel including estrogen receptor, progesterone receptor, HER2, GATA3, and mammaglobin, all of which were negative. Further immunohistochemical analysis showed strong positive results for S100 protein, SOX10, HMB-45, and Melan-A, along with maintained expression of PRAME (Preferentially Expressed Antigen in Melanoma). These findings were diagnostic of melanoma rather than primary breast carcinoma.

Molecular analysis using next-generation sequencing detected a BRAF V600E mutation, along with additional genomic alterations, including a TERT promoter mutation and CDKN2A loss, confirming the diagnosis of metastatic melanoma. The tumor board reconvened to discuss these unexpected findings and to coordinate a comprehensive staging workup to identify the primary site and the extent of disease.

2.4. Additional Staging Studies and Treatment

Given the diagnosis of metastatic melanoma with unknown primary, comprehensive staging included whole-body PET-CT scan, which revealed hypermetabolic activity in the known left breast mass (SUV 8.4) and axillary lymph node (SUV 9.2), along with multiple previously unidentified metastatic sites: bilateral pulmonary nodules (largest 1.8 cm in right

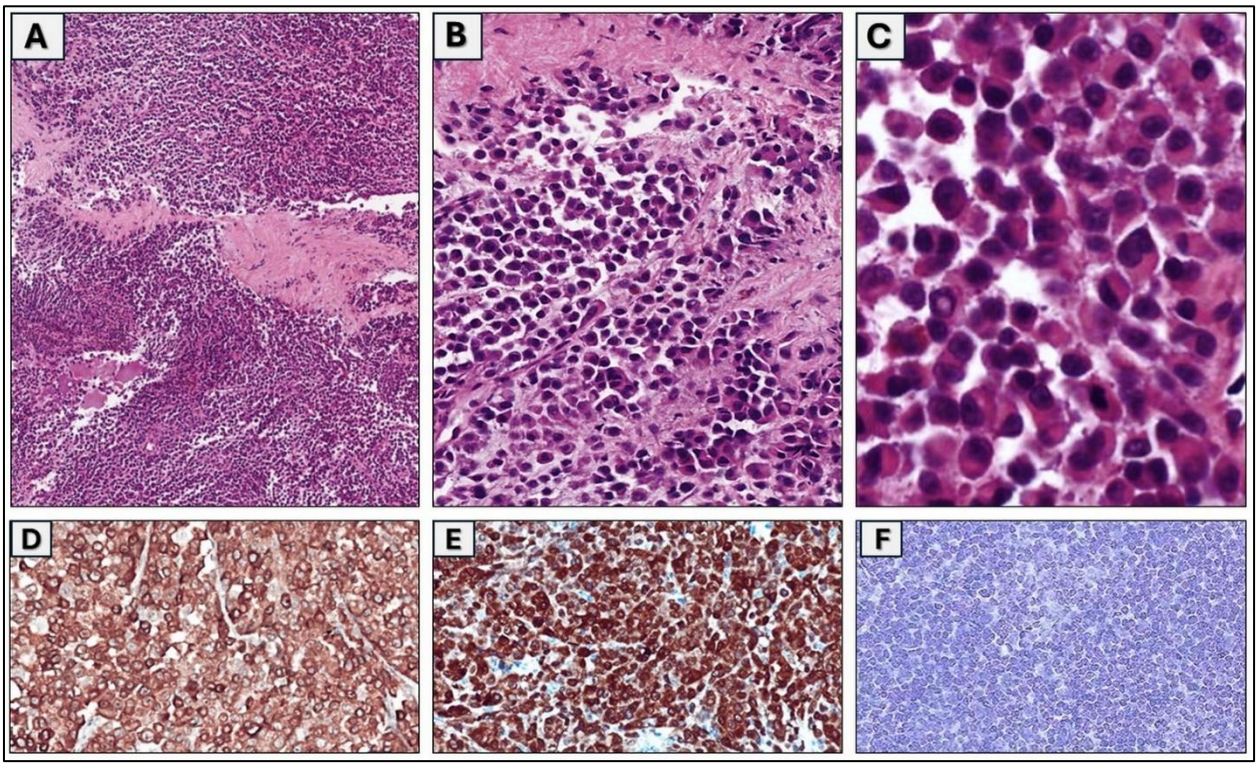
upper lobe), two hepatic lesions (segments VI and VIII, measuring 2.1 cm and 1.4 cm), and bone involvement in the thoracic spine (T7) and left iliac wing. Brain MRI with contrast showed no intracranial metastases. Dermatology performed a comprehensive skin examination, including dermoscopy, with no primary melanoma identified. Ophthalmologic examination excluded ocular melanoma. A 1.2 cm rectal mass was identified as melanoma, which was determined to be the primary tumor site.

The multidisciplinary tumor board reviewed the case, confirming stage IV melanoma (cTxN1cM1c) with BRAF V600E mutation. Given the extensive metastatic burden and presence of an actionable mutation, the patient was offered combination targeted therapy versus immune checkpoint inhibitor therapy. After a thorough discussion of risks and benefits, the patient elected to proceed with anti-PD-1 immunotherapy (pembrolizumab 200 mg intravenously every three weeks). She tolerated initial cycles well with manageable grade 1 fatigue and transient grade 2 thyroiditis requiring levothyroxine replacement. Restaging PET-CT after 4 cycles demonstrated a partial response, with significant reductions in metabolic activity and the size of all measurable lesions. Treatment continued for a total of two years.

2.5. Outcome and Long-term Follow-up

The patient achieved sustained partial response maintained throughout the two-year treatment period, with continued excellent tolerance aside from managed hypothyroidism and intermittent mild arthralgias. Surveillance imaging at regular intervals showed stable, small residual pulmonary nodules and no new sites of disease. Following completion of immunotherapy, she entered active surveillance, with clinical examinations every 3 months and imaging every 6 months. At three-year follow-up from initial diagnosis, she remains clinically well with stable disease and excellent performance status. She continued endocrinologic management for immune-related hypothyroidism and maintained regular oncologic surveillance. Quality of life remained excellent.

This case embodies the diagnostic challenges of melanoma presenting as an apparent primary breast malignancy. It highlights the critical importance of comprehensive IHC evaluation when histologic features are atypical, even in the setting of compelling clinical and radiologic features suggesting a specific primary diagnosis.



1A: Low power view showing solid tumor masses infiltrating the breast parenchyma (H&E X20).; 1B: Intermediate power view showing sheets and nests of pleomorphic epithelioid cells with no particular architecture (H&E X40).; 1C: High power view showing the melanoma cells with pleomorphic epithelioid-like cells with high nuclear-to-cytoplasmic ratios, eccentric nuclei prominent nucleoli, and occasional intranuclear inclusion. (H&E X60).; 1D: Tumor cells Positive for HMB-45; 1E: Tumor cells Positive for MART-1; 1F: Tumor cells negative for cytokeratin

Figure 1 Microscopic examination and immunohistochemistry of metastatic melanoma to the breast

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

The modern clinical characterization of malignant melanoma began with René Laennec in 1806, who coined the term "melanose." Historically, it has been recognized for its aggressive metastatic potential and unpredictable clinical course. [5] Epidemiologically, melanoma incidence has risen steadily over the past several decades, with a global incidence of approximately 3.4 per 100,000 person-years. [6] While it can affect all ages, the median age at diagnosis is 65, with a slight male predominance in cutaneous cases. Risk factors are multifactorial, encompassing genetic predispositions, such as CDKN2A mutations, and environmental triggers, primarily ultraviolet (UV) radiation exposure. However, mucosal melanomas, like the rectal primary identified in this case, are independent of UV exposure and carry a poorer prognosis. [7] [8] [9]

According to the World Health Organization (WHO) classification, melanoma is categorized by site of origin and cumulative sun exposure. [10] While primary breast melanomas are exceptionally rare (less than 5% of all melanomas), metastatic disease is more common but still represents a small fraction of breast malignancies. [7] The behavior is inherently malignant, characterized by rapid progression and widespread systemic dissemination. In cases of MUP, which accounts for 3% of all melanoma diagnoses, the primary tumor may have undergone spontaneous regression [4] [11] or originated from internal mucosal sites, like our case.

3.2. Pathogenesis, Pathophysiology

Melanoma arises from the malignant transformation of melanocytes, which are neural crest-derived cells. Pathogenesis involves a complex interplay of molecular alterations, most notably the BRAF V600E mutation found in this patient, which constitutively activates the MAPK/ERK signaling pathway, driving uncontrolled cellular proliferation and survival. [12] Additional mutations, such as TERT promoter alterations and CDKN2A loss, further promote immortalization and cell cycle dysregulation. These genetic drivers facilitate the tumor's aggressive mechanisms of growth and hematogenous spread, allowing cells to bypass normal apoptotic signals and colonize distant organs, such as the breast, lungs, and liver. [7] [9]

Pathophysiologically, the breast mass and axillary lymphadenopathy result from the infiltration of pleomorphic epithelioid cells, which create sheets and nests that displace normal architecture. The high nuclear-to-cytoplasmic ratio and frequent mitoses correlate with the rapid clinical enlargement observed. Symptoms like skin dimpling arise from the tumor's desmoplastic response or involvement of Cooper’s ligaments, mimicking primary carcinoma. [5] Histopathologically, the lack of GATA3 and mammaglobin expression, coupled with strong positivity for S100, SOX10, and HMB-45, confirms the melanocytic lineage. [13] These biomarkers and the BRAF mutation serve as critical targetable pathways for modern precision therapies, such as BRAF/MEK inhibitors or immune checkpoint blockade. [14]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical-radiology-pathology, lab, diagnosis, management and outcome):

Literature characterizes metastatic melanoma to the breast as a "great mimicker," frequently presenting clinical and radiographic features indistinguishable from primary breast carcinoma [15] Like our patient, most reported cases involve postmenopausal women presenting with a palpable, firm mass, often classified as BI-RADS 4 or 5 due to irregular margins and increased vascularity. [16] However, unlike primary breast cancer, metastatic melanoma typically lacks microcalcifications on mammography, [17] although our case was atypical in presenting with suspicious calcifications, further complicating the initial differential.

A review of the existing literature indicates that, while the lungs and skin are common primary sites, mucosal primaries, specifically anorectal melanoma, are rare, accounting for less than 1% of all melanomas [2] [13] [18]. The diagnostic workup in the literature emphasizes the role of core needle biopsy over fine-needle aspiration to provide sufficient tissue for IHC analysis. [5] Our case aligns with established findings that triple-negative breast markers (ER, PR, HER2) and GATA3 negativity should prompt an expanded IHC panel including SOX10 and S100. [19]

Clinical decision-making in literature has shifted significantly with the advent of targeted medicine and immunotherapy. [14] [20] Historically, metastatic melanoma to the breast carried a dismal prognosis with a median survival of less than one year. [5] Recent studies, however, demonstrate improved outcomes with BRAF-targeted therapies and PD-1 inhibitors like pembrolizumab. [20] Our patient's sustained partial response over three years mirrors the success seen in modern courts. [6] [14]

4. What Have We Learned from This Case

This case provides several critical diagnostic and clinical insights. First, it underscores the importance of "diagnostic humility"; even a classic presentation of a spiculated breast mass with axillary involvement can be a metastasis from an extramammary source. A key red flag for clinicians is the "triple-negative" IHC profile in a poorly differentiated neoplasm, which should immediately broaden the differential to include melanoma, especially if GATA3 is negative.

Management-wise, the identification of a BRAF V600E mutation and the subsequent success of pembrolizumab highlight the impact of precision oncology on survival, even in Stage IV disease. [7] Future practice should involve early integration of expanded IHC panels for atypical breast lesions to prevent unnecessary radical surgeries. This case shows that melanoma can mimic many cancers, therefore a comprehensive search for the primary site, including mucosal surfaces, is essential when metastasis is found.

Abbreviations

- Immunohistochemical (IHC);
- Invasive ductal carcinoma (IDC);
- Melanoma of unknown primary (MUP)

Conclusion

We present a compelling case of metastatic melanoma to the breast, initially misdiagnosed as primary breast carcinoma, highlighting a significant diagnostic challenge in oncology. This case is particularly noteworthy due to the unusual presentation with suspicious microcalcifications on mammography and the identification of a rectal primary, an uncommon site for melanoma. Successful management with anti-PD-1 immunotherapy, guided by molecular profiling, emphasizes the evolving landscape of precision oncology and its profound impact on patient outcomes in advanced metastatic disease. This report underscores the critical importance of maintaining a broad differential diagnosis for breast masses, especially in the context of atypical imaging or IHC findings, to ensure accurate diagnosis and appropriate, timely therapeutic intervention. Clinicians should be vigilant for melanoma mimics and integrate comprehensive pathological and molecular analyses to optimize patient cares

Compliance With Ethical Standards

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Disclosure of conflict of interest

All authors make the following declarations:

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

Consent for the publication of this Case was obtained from the patient.

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