

Breast Metastases from Melanoma: Clinical, Radiological and Pathological Challenges Illustrated by Two Case Reports

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How to cite this paper: Mrida, M., Tshibola Nkashama, M., Basslam, O., Amine, W., Cherkaoui, M., Wajih, O., Bencherifi, Y., Benhessou, M., Ennachit, M. and El Karroumi, M. (2026) Breast Metastases from Melanoma: Clinical, Radiological and Pathological Challenges Illustrated by Two Case Reports. *Open Journal of Obstetrics and Gynecology*, **16**, 711-721. <https://doi.org/10.4236/ojog.2026.165069>

Received: March 1, 2026

Accepted: May 9, 2026

Published: May 12, 2026

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Abstract

Breast metastases from melanoma are an exceptional finding, accounting for only 0.4% to 6.6% of all malignant breast tumors. We report two clinical cases illustrating the diversity of presentations and the associated diagnostic challenges. The first patient, a 53-year-old woman, presented with unilateral breast lesions associated with axillary lymphadenopathy, while the second, a 34-year-old woman, presented with bilateral breast nodules in the context of disseminated metastatic disease. Imaging (mammography, ultrasound, and MRI) could not differentiate metastases from benign fibroadenomas. Diagnosis was based on histology complemented by immunohistochemistry (EMA, cytokeratin, S-100, HMB-45). Treatment varied according to disease extent: surgery with axillary lymph node dissection and adjuvant chemotherapy in the first case, and palliative chemotherapy in the second. These cases highlight the role of targeted therapies (vemurafenib) and immunotherapy (ipilimumab, pembrolizumab) in improving the prognosis of metastatic melanoma, although radiotherapy remains of limited benefit.

Keywords

Breast Metastasis, Melanoma, Breast Biopsy, Targeted Therapies, Pembrolizumab, BRAF, Secondary Breast Cancer

1. Introduction

The breast may be affected by a wide range of pathological conditions. Beyond

primary benign and malignant tumors arising from the breast parenchyma or overlying skin, it can also represent an uncommon site of metastasis from extramammary malignancies, including hematological cancers, lung carcinoma, ovarian carcinoma, and melanoma [1] [2].

Metastatic involvement of the breast is rare, accounting for approximately 0.4% to 6.6% of all malignant breast tumors, and often reflects advanced systemic disease [3]. Because of its rarity and non-specific clinical and radiological presentation, breast metastasis may be misdiagnosed as a primary breast neoplasm or a benign lesion, leading to delayed or inappropriate management.

Cutaneous melanoma is an aggressive malignancy with a rapidly rising incidence worldwide. Despite advances in early detection, melanoma is characterized by a strong metastatic potential, with common secondary sites including the lungs, liver, brain, and bones. Breast involvement remains exceptional and is most frequently observed in young women, often in the context of widespread metastatic dissemination [4] [5].

Radiological findings of breast metastases from melanoma are typically non-specific and may closely mimic benign entities such as fibroadenomas, particularly on mammography and ultrasound. Consequently, histopathological examination, supported by immunohistochemistry, remains essential for establishing the correct diagnosis and guiding appropriate therapeutic strategies.

We report two cases of breast metastases occurring several months after the diagnosis of primary cutaneous melanoma, illustrating the clinical, radiological, and pathological challenges associated with this rare entity and highlighting the importance of a multidisciplinary approach to management.

2. Case Report 1

A 53-year-old nulliparous patient with a history of excision of a nodular melanoma of the trunk in December 2022, with a Breslow thickness of 3.5 mm, ulceration present (pT4b according to the AJCC 8th edition), and clear surgical margins (R0 resection), presented with in-transit cutaneous metastases.

Clinical examination revealed three mobile nodules in the right breast: one 2 × 2 cm lesion at the junction of the outer quadrants, a second 2 × 2 cm lesion in the axillary tail, and a 1 × 1 cm lesion in the para-areolar region, along with a 2 × 2 cm mobile axillary lymph node. A 2 × 2 cm mobile para-areolar nodule was also palpated in the left breast.

Mammography revealed multiple retro-areolar opacities with well-defined regular margins and low density, corresponding on ultrasound to significant ductal ectasia filled with homogeneous, finely echogenic, avascular material on color Doppler and without detectable tissue components. The largest lesion measured 32.5 mm on the right and 19 mm on the left. A macrocalcification at the junction of the left outer quadrants with a clear center, suggestive of dystrophic changes, was also seen. Additional reniform opacities in the axillary tails, suggestive of lymph nodes, corresponded on ultrasound to bilateral axillary lymph nodes of preserved size and architecture (Figure 1).

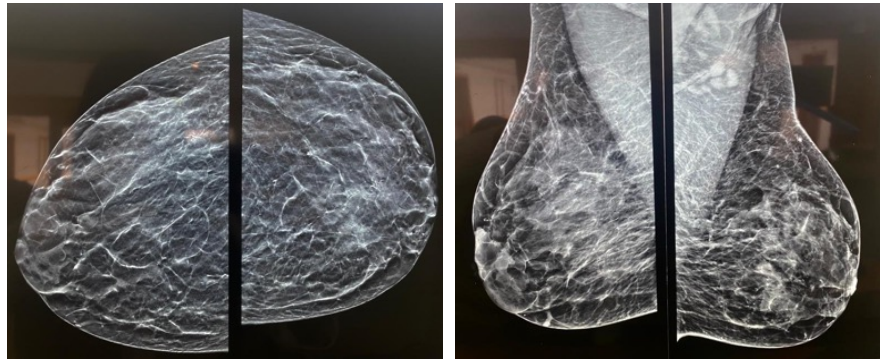


Figure 1. Mammography—craniocaudal and mediolateral oblique views.

Mammography and ultrasound findings were considered probably benign (BI-RADS 3) according to ACR criteria, mainly suggestive of ductal ectasia without identifiable solid components.

Mammography and ultrasound findings were non-specific and could not reliably distinguish between benign and malignant breast lesions. Therefore, breast MRI was performed to further characterize the lesions, assess locoregional extension, and evaluate axillary involvement in this high-risk oncologic context.

Breast MRI confirmed bilateral ductal ectasia classified as BI-RADS 3, but additionally revealed two suspicious right breast lesions located at the junction of the outer quadrants and in the axillary tail, as well as suspicious right axillary lymphadenopathy, leading to an overall assessment of BI-RADS 4 for the right breast (**Figure 2**).

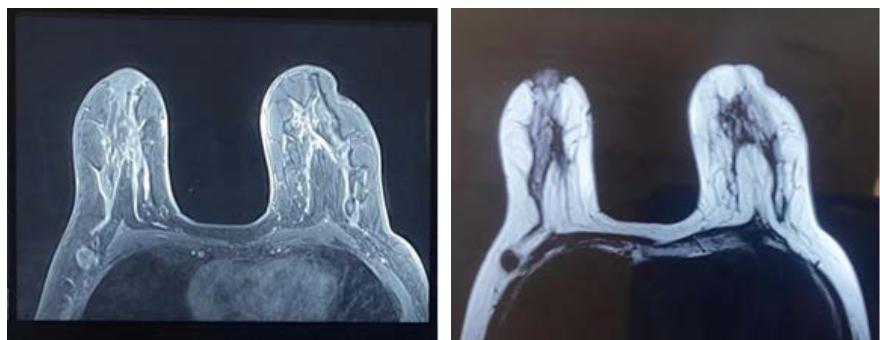


Figure 2. Breast MRI demonstrated bilateral ductal ectasia.

An ultrasound-guided core biopsy of the right breast lesions and axillary adenopathy confirmed metastatic localization of the previously diagnosed malignant melanoma.

A PET scan revealed a right breast tumor process with axillary lymph node involvement and low-metabolic remodeling in the right submammary region at the site of melanoma excision, with no other suspicious hypermetabolic foci in the lungs, bones, or viscera.

The case was discussed in a multidisciplinary tumor board. Given the presence of multiple lesions within the right breast, including involvement of the axillary

tail, and the difficulty in achieving clear margins with breast-conserving surgery, a right mastectomy with axillary lymph node dissection was preferred over a conservative approach. This strategy aimed to ensure complete local disease control in the context of oligometastatic disease.

Following surgery, systemic immunotherapy with pembrolizumab was initiated due to the presence of a BRAF mutation and the high risk of recurrence. The treatment was administered with a curative intent, aiming to achieve durable disease control.

Pathology of the surgical specimen confirmed a 6-cm right breast melanoma metastasis with vascular emboli and 3 positive axillary lymph nodes out of 13 harvested. BRAF mutation testing was positive, and the patient was started on pembrolizumab.

The patient was regularly followed up in oncology consultation. At 2 years of follow-up, she showed no evidence of local recurrence or distant metastatic progression under pembrolizumab therapy.

Clinical timeline: Primary nodular melanoma of the trunk was diagnosed and excised in December 2022. Eight months later, the patient presented with breast nodules. Imaging was inconclusive, and core needle biopsy confirmed metastatic melanoma. PET scan showed isolated breast and axillary involvement. The patient underwent right mastectomy with axillary lymph node dissection, followed by systemic immunotherapy with pembrolizumab. At 2 years of follow-up, no recurrence or disease progression was observed.

3. Case Report 2

A 34-year-old woman (G2P2) with a history of excision of a left palmar melanoma two years earlier, with a Breslow thickness of X mm, no ulceration (pT2a according to the AJCC 8th edition), and clear surgical margins (R0 resection), presented with self-detected bilateral breast nodules.

On clinical examination, multiple nodules were noted in all four quadrants of both breasts.

Mammography (**Figure 3**) revealed multiple well-circumscribed rounded and oval opacities larger than 1 cm in both breasts (about 9 on the right and more than 10 on the left), the largest located in the axillary tail. Ultrasound demonstrated multiple intraglandular, oval or round, heterogeneous hypoechoic nodules, most of which appeared necrotic with posterior enhancement. The largest lesion measured 19.5×11.5 mm in the right axillary tail and 17×9 mm in the left breast. A heterogeneous necrotic left axillary lymph node measuring 14×9 mm was also visualized (**Figure 4**). The examination was classified as BIRADS 4 bilaterally by ACR criteria.

Given the presence of multiple bilateral breast nodules with indeterminate features on mammography and ultrasound, breast MRI was indicated to better assess lesion multiplicity, bilaterality, and extent, particularly in a young patient with dense breast parenchyma.

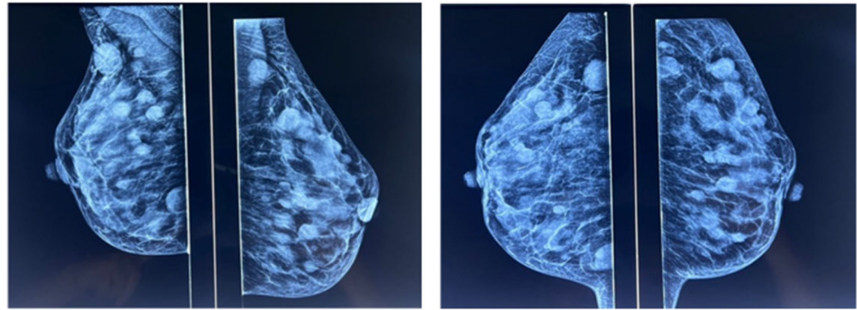


Figure 3. Mammography—craniocaudal and lateral views showing multiple well-circumscribed bilateral rounded opacities.

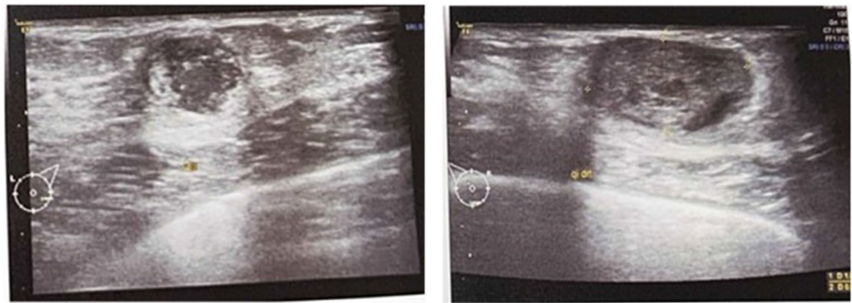


Figure 4. Breast ultrasound—multiple disseminated nodular lesions, oval or round, heterogeneous hypoechoic with necrotic appearance and posterior acoustic enhancement.

Breast MRI (**Figure 5**) revealed multiple bilateral breast lesions involving all quadrants, ranging from subcentimeter to centimeter size, rounded or oval, well circumscribed, with regular margins and occasional internal septations (type III enhancement curve for all lesions). Suspicious left axillary lymphadenopathy was also noted, and the examination was classified as BIRADS 4 bilaterally by ACR criteria.

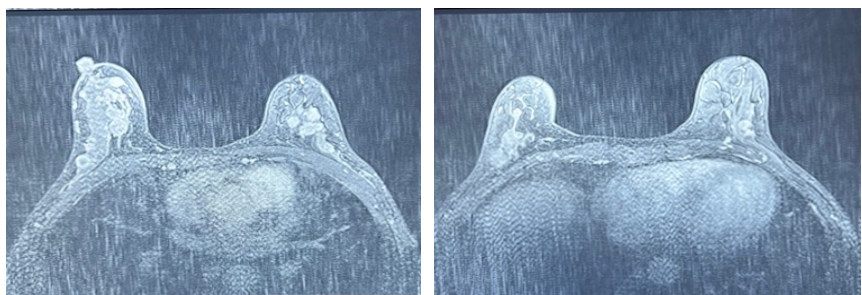


Figure 5. Breast MRI—multiple bilateral breast lesions, centimeter and sub-centimeter in size, round and oval, well-circumscribed with regular margins.

Core biopsies of the largest lesions from each breast and histopathological examination revealed a malignant proliferation composed of atypical cells arranged in sheets, with marked nuclear pleomorphism and prominent nucleoli.

Immunohistochemical analysis demonstrated that the tumor cells were positive for MELAN-A and HMB-45, confirming melanocytic differentiation, while being

negative for cytokeratin AE1/AE3 and GATA3, ruling out a primary epithelial breast tumor. These findings supported the diagnosis of breast metastasis from malignant melanoma.

A PET scan revealed diffuse involvement of the bone marrow, lungs, breasts, liver, spleen, adrenal glands, and cutaneous and muscular tissue.

The patient was started on dacarbazine pending BRAF mutation results after discussion in a multidisciplinary tumor board.

Given the extent of disseminated metastatic disease, the patient was managed with palliative systemic therapy. At 8 months of follow-up, she remained alive with persistent metastatic disease, including bone marrow, lungs, breasts, liver, spleen, adrenal glands, and cutaneous and muscular tissue, under ongoing palliative treatment.

Clinical timeline: Primary palmar melanoma was excised two years prior to presentation. The patient subsequently developed bilateral breast nodules. Imaging revealed multiple suspicious lesions, and biopsy confirmed metastatic melanoma. PET scan demonstrated widespread metastatic disease involving multiple organs. The patient was started on systemic chemotherapy (dacarbazine), pending molecular analysis. Given the extent of disease, management remained palliative. At 8 months of follow-up, the patient was alive with persistent metastatic disease under ongoing treatment.

4. Discussion

The breast is a rare site for metastases from extra-mammary malignancies. The most frequent primary tumors leading to breast metastases include lymphomas, melanomas, rhabdomyosarcomas, and lung or ovarian cancers [4] [5]. Approximately 20% of patients with malignant melanoma present with metastases, most commonly involving the liver, lungs, and brain. Breast involvement remains exceptional [3] [6].

Clinically, the most common presentation of breast metastases from cutaneous melanoma is a unilateral, isolated, and asymptomatic lesion, usually located in the upper outer quadrant. In our first case, two right breast lesions were detected, one at the junction of the outer quadrants and another in the axillary tail. Bilateral breast metastases are extremely rare in the literature and are almost always associated with widely disseminated disease, as in our second case [4] [7] [8].

In-transit metastases represent a distinct pattern of melanoma dissemination, defined as cutaneous or subcutaneous metastatic deposits occurring between the primary tumor site and the regional lymph node basin, reflecting lymphatic spread of tumor cells [9] [10]. Their presence is associated with an increased risk of regional nodal involvement and distant metastatic disease, and they are considered a marker of aggressive tumor biology [11].

After axillary lymph node involvement, melanoma cells may continue to spread along lymphatic pathways, raising the possibility that breast lesions—particularly those located in the axillary tail or upper outer quadrants—could represent in-

transit metastases rather than true hematogenous breast metastases. This hypothesis is supported by the anatomical lymphatic drainage of the trunk and upper limb, which converges toward the axillary basin and adjacent breast tissue [12] [13].

Differentiating in-transit metastases from parenchymal breast metastases remains challenging, as both entities share similar clinical, radiological, and histopathological features. However, lesion distribution along lymphatic drainage pathways, proximity to the axilla, and association with axillary lymph node involvement may suggest a lymphatic route of spread [14]. Recognizing this mechanism is clinically relevant, as in-transit metastases are associated with poorer prognosis and may influence staging, prognostic assessment, and therapeutic decision-making [10] [15].

Although breast metastases from extramammary malignancies are rare, melanoma is among the most frequent primary tumors to metastasize to the breast, particularly in young women [1]-[3]. Nevertheless, such cases remain exceptionally uncommon, and diagnosis can be challenging due to non-specific clinical and radiologic features that may mimic benign lesions or primary breast carcinoma.

The publication of these cases is important for several reasons. First, it raises diagnostic awareness, helping clinicians and radiologists consider breast metastases in patients with a history of melanoma and avoid misdiagnosis. Second, it illustrates the clinical diversity of breast metastases, with both unilateral and bilateral presentations. Third, it highlights therapeutic implications, including the role of surgery, systemic therapy, and targeted immunotherapy in disease management. Finally, these reports contribute to the limited existing literature, providing valuable insights into imaging characteristics, histopathology, disease course, and patient outcomes.

Radiologic findings are non-specific. Mammography typically shows a rounded, well-circumscribed mass without microcalcifications or overlying skin changes, more suggestive of a benign tumor such as a fibroadenoma. In both of our cases, the imaging characteristics were similar [3] [16]-[18]. Ultrasound often reveals non-specific, oval hypoechoic nodules with well-defined margins, posterior wall preservation, and no visible calcifications [19] [20]. The only discriminatory feature may be increased intralesional vascularity on Doppler ultrasound [21].

MRI can be particularly useful in young patients with dense breast parenchyma. In breast metastases from melanoma, MRI may demonstrate T1 hyperintensity and T2 hypointensity, reflecting melanin deposition [3].

Fine-needle aspiration is often the first-line diagnostic approach but has limitations in terms of sensitivity and specificity. Core needle biopsy provides more reliable histological assessment. Immunohistochemistry remains essential for the differential diagnosis, with EMA and cytokeratin positivity favoring carcinoma and S-100 and HMB-45 positivity supporting a melanocytic (melanoma) origin [22]. The diagnosis relied heavily on immunohistochemistry, with positivity for melanocytic markers (MELAN-A, HMB-45) and absence of epithelial markers (CK

AE1/AE3, GATA3), allowing exclusion of a primary triple-negative breast carcinoma.

Breast metastases from melanoma, particularly in bilateral presentations, require a full systemic evaluation, as they are most frequently associated with disseminated disease. Treatment options include wide surgical excision for isolated metastases, systemic chemotherapy, and radiotherapy. Response rates to dacarbazine and interleukin-2 remain poor. The introduction of targeted therapies such as BRAF inhibitors (vemurafenib) and immune checkpoint inhibitors such as anti-CTLA-4 (ipilimumab) and anti-PD-1 (pembrolizumab) has dramatically improved survival in metastatic melanoma. Radiotherapy plays a limited role due to the relative radioresistance of melanocytic cells [4] [23]-[25].

In our first case, treatment consisted of right mastectomy with axillary lymph node dissection followed by chemotherapy. In the second case, palliative chemotherapy was initiated due to the extent of metastatic disease.

Breast metastases from melanoma, particularly in bilateral presentations, require a comprehensive systemic evaluation, as they are most frequently associated with disseminated disease. Treatment strategies depend on disease extent and molecular profile and include surgery for isolated metastases, systemic chemotherapy, targeted therapy, and immunotherapy.

In the first case, the patient underwent right mastectomy with axillary lymph node dissection followed by systemic treatment. Given the presence of a BRAF mutation, immunotherapy with pembrolizumab was initiated, resulting in disease control during follow-up. At two years of follow-up, the patient remained alive without evidence of new metastatic progression.

In contrast, the second patient presented with widespread metastatic disease involving the bone marrow, lungs, breasts, and visceral organs. Palliative systemic chemotherapy was initiated due to the advanced stage of the disease. At eight months of follow-up, the patient was still alive, with persistent bone, pulmonary, and breast metastases under palliative treatment.

These two cases illustrate the prognostic heterogeneity of melanoma breast metastases, which largely depends on disease burden, metastatic distribution, and access to modern systemic therapies.

5. Limitations

This report has several limitations inherent to case reports. First, the radiological findings were non-specific and could not reliably distinguish breast metastases from benign lesions or primary breast tumors, limiting the generalizability of imaging-based conclusions. Second, it remains difficult to definitively differentiate between hematogenous and lymphatic (in-transit) spread based solely on clinical, radiological, and histopathological findings. Third, the outcomes observed in these two patients are strongly influenced by the overall metastatic burden, tumor biology, and access to modern systemic therapies, particularly immunotherapy and targeted treatments. Therefore, these cases cannot be used to establish stand-

ardized management guidelines but rather aim to highlight diagnostic challenges and support clinical awareness of this rare entity.

6. Conclusions

Breast metastases from melanoma are rare and usually indicate advanced disseminated disease, associated with poor prognosis. Their non-specific clinical and radiologic presentation makes histology and immunohistochemistry essential for diagnosis.

Therapeutic management must be individualized and discussed in a multidisciplinary setting. Surgery may be considered for isolated breast metastases, whereas disseminated disease requires systemic therapy. The advent of targeted therapies and immune checkpoint inhibitors has significantly improved overall survival in metastatic melanoma, although close clinical and imaging follow-up remains crucial.

Ethical Statement

Written informed consent was obtained from both patients for publication of this case report and any accompanying images. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki. Patient anonymity has been strictly preserved, and no identifying information is disclosed in this article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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