

Multimodality Imaging Findings of Breast Metastases from Malignant Melanoma: A Case Series

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Abstract

Breast metastases stemming from extramammary malignancies are rare, occurring in approximately 1.3–2.7% of breast malignancies. The most prevalent are metastases belonging to the primary carcinoma of the contralateral breast, followed by lymphoma and malignant melanoma.

Breast metastasis is to be suspected in patients with previous history of malignant melanoma who present with a breast mass. Distinguishing metastasis from primary breast neoplasms is a challenging task. Accurate diagnosis is crucial because the prognosis and management differ significantly between primary and secondary malignancies of the breast. Imaging features are non-specific on mammography and ultrasound. There have been several reports on the magnetic resonance imaging (MRI) characteristics of breast metastasis originating from malignant melanoma; however, only few studies have described the diffusion weighted imaging (DWI) feature and the apparent diffusion coefficient (ADC) value.

In this study, we report the multimodality imaging features of three cases of breast metastases from malignant melanoma. We particularly focus on MRI findings, such as DWI feature and ADC value and compare them with the MRI features reported in the literature.

Keywords: Melanoma metastasis, Mammogram (MMG), Ultrasound (US), Computed tomography (CT), Magnetic resonance imaging (MRI)

Introduction

Malignant melanoma is a highly malignant tumour arising from

melanocytes and metastases commonly spread through haematogenous or lymphatic routes.

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The common metastatic sites are liver, lung, and brain. Breast metastasis stemming from either malignant melanoma or other extramammary tumours is rare. Specifically, it occurs in approximately 1.3-2.7% of all malignant breast neoplasms. Nevertheless, metastasis should be suspected in patients with a previous history of malignant melanoma presenting with a breast mass or multiple masses. It is a challenging task to distinguish metastasis from benign or malignant primary neoplasms of the breast. Accurate diagnosis is crucial since the prognosis and management differ significantly between primary and secondary malignancies of the breast.¹

Herein, we discuss the multimodality imaging findings of breast metastases from malignant melanoma, including magnetic resonance imaging (MRI), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) features in three patients and compare them with findings reported in the literature.

Case 1

A 40-year old woman presented with a 2-

month history of a painful right breast lump. She had a history of wide local excision of a malignant melanoma confined to a hyperpigmented mole on her right arm two years prior. There was no other significant medical or family history of breast cancer.

Physical examination revealed a solitary mobile lump in the mid-inner region of the right breast measuring approximately 5.0×5.0 cm. The nipple and the overlying skin were normal. Another larger mass was also palpable in the right axilla which measured approximately 8.0×8.0 cm.

Mammogram (MMG) showed an oval high-density mass with indistinct margin in the lower inner quadrant of the right breast with an enlarged right axillary lymph node (Figure 1a, b). No associated calcification was observed. Ultrasound (US) demonstrated an oval hypoechoic mass with indistinct margin at the right 3 o'clock position measuring 2.2×1.7×1.8 cm (Figure 2a). Internal vascularity was noted on colour Doppler. There was also another irregular microlobulated hypoechoic mass with internal vascularity at the left 2 o'clock position measuring 1.2×0.7×0.8 cm

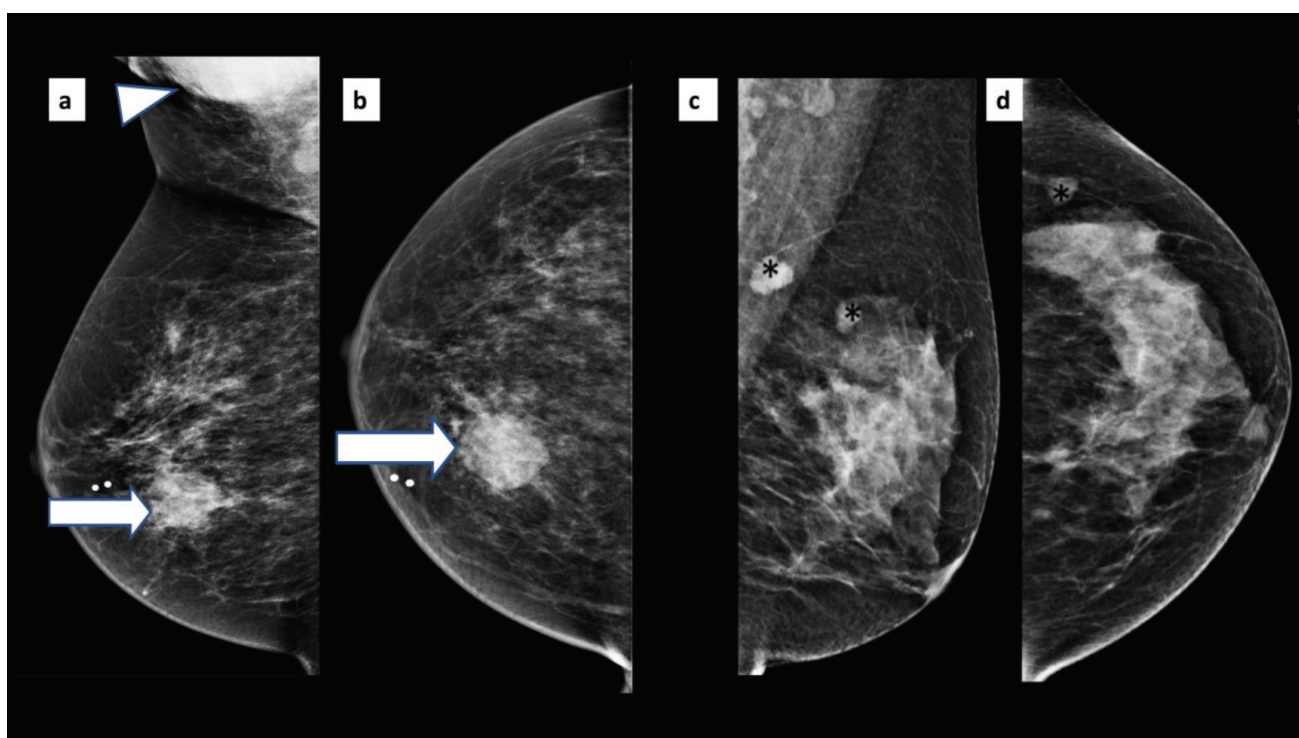


Figure 1. Mammography features: (a-b) Case 1 - Mediolateral oblique (MLO) and craniocaudal (CC) views of the right mammogram demonstrating an irregular high-density mass in lower inner quadrant (arrows) with an enlarged high density axillary lymph node (arrowhead). (c-d) Case 2 - MLO and CC views of left DBT showing two lobulated high density masses (*) in the upper quadrant. No associated calcification or architectural distortion.

(Figure 2b). Enlarged matted lymph nodes measuring 6.8×4.6 cm were also seen in the right axilla (Figure 2c). The MMG and US findings were categorized as highly suspicious of malignancy, BI-RADS 5, in accordance with American College of Radiology Breast Imaging-Reporting and Data System. US guided biopsies were subsequently performed and histopathology was consistent with metastatic malignant melanoma for the right breast mass and fibroadenoma for the left breast mass (Figure 3).

On MRI, the right breast 3 o'clock lesion appeared as an irregular heterogeneous mass which was hyperintense on T1/T2/STIR, showing restricted diffusion on DWI/ADC sequence ($b=1000\text{sec}/\text{mm}^2$) and early enhancement with rapid washout post-contrast, consistent with type 3 curve. The mean ADC value was $1.2 \times 10^{-3} \text{mm}^2/\text{s}$. There existed an associated skin thickening in the right upper inner quadrant (Figure 4a-f). On the left, the 2 o'clock lesion appeared as an oval circumscribed homogenous progressively

enhancing (type 1 curve) mass with no restricted diffusion on the DWI/ADC sequence. The mean ADC value was $1.8 \times 10^{-3} \text{mm}^2/\text{s}$. The large matted right axillary lymph nodes appeared heterogeneous and lobulated, hyperintense on T1/T2/STIR, showing restricted diffusion on DWI/ADC sequence ($b=1000 \text{sec}/\text{mm}^2$) and early enhancement with rapid washout post-contrast, consistent with type 3 curve. The mean ADC value was $1.1 \times 10^{-3} \text{mm}^2/\text{s}$ (Figure 5a-e).

Staging computed tomography (CT) revealed an irregular heterogeneously enhancing mass in the mid-inner quadrant of the right breast with surrounding fat stranding and overlying skin thickening. Several enlarged necrotic right axillary lymph nodes were observed with the largest measuring 6.1×8.7×7.8 cm (Figure 6 a,b). Multiple lung and pleural-based nodules were further detected.

The patient was diagnosed with stage IV malignant melanoma of the right arm with metastases to the lungs, breast, and right axilla.

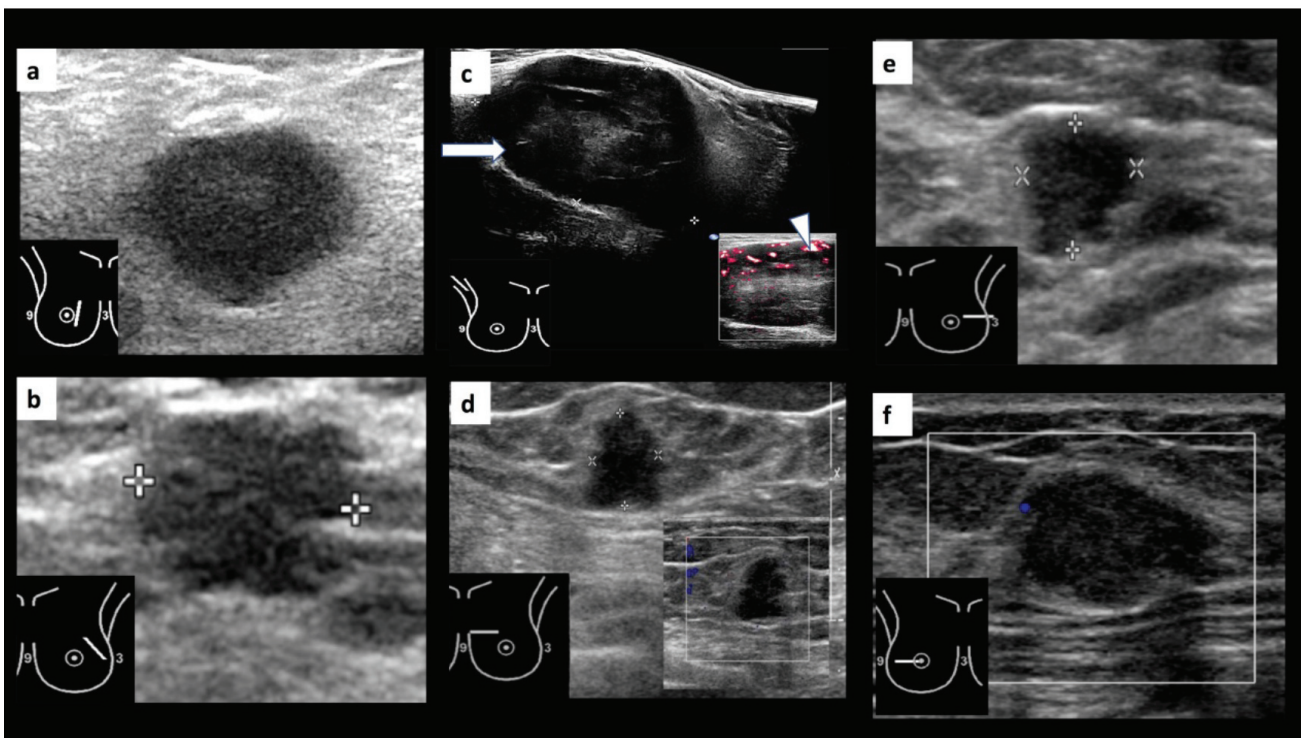


Figure 2. Ultrasound features: (a-c) Case 1 - (a) The right 3 o'clock breast metastasis appeared as a round indistinct hypoechoic mass with no posterior feature; (b) The left 2 o'clock fibroadenoma appeared as an irregular microlobulated hypoechoic mass; (c) the enlarged matted right axillary lymph nodes (arrow) appeared as a well-circumscribed oval heterogeneous mass with increased internal vascularity on colour Doppler (insert, arrowhead). (d-e) Case 2 - US of the left breast revealed taller-than-wide irregular spiculated hypoechoic masses at (d) 11 o'clock and (e) 2 o'clock with no posterior feature or internal vascularity (f) Case 3 - US showed an oval hypoechoic right 9 o'clock mass with partly indistinct margin and peripheral vascularity (US: Ultrasound).

The patient had completed six cycles of chemotherapy (Dacarbazine) to date.

Case 2

A 39-year-old woman presented with a mildly tender left breast lump of 3-week history. The patient had no associated nipple discharge, skin changes, axillary swelling, or known family history of breast carcinoma. The patient had a history of surgical excision of malignant melanoma from an unhealed left foot ulcer.

Physical examination revealed two palpable solid lumps in the upper outer and upper inner quadrant of the left breast measuring 1cm each. The overlying skin, nipple, and both axillae were normal.

Digital breast tomosynthesis (DBT) showed two oval microlobulated high density masses in the left upper region (Figure 1c, d). No associated calcifications or architectural distortion was found. Corresponding US showed two taller-than-wide irregular microlobulated hypoechoic masses at

the left 11 and 2 o'clock positions, which measured 1.1×1.1×1.2 cm and 0.7×1.0×0.9 cm, respectively (Figure 2d, e). No increased vascularity was observed on colour Doppler. DBT and US findings were categorized as BI-RADS 4c. Histopathology from US guided biopsy of both masses confirmed the diagnosis of metastatic melanoma.

Staging CT revealed multiple enhancing subcutaneous nodules in the right shoulder, chest and anterior abdominal wall, and retroperitoneal nodules adjacent to inferior pole of both kidneys (Figure 6c-f).

The patient was diagnosed with stage IV malignant melanoma of the left foot with breast, inguinal lymph nodes, retroperitoneal, and subcutaneous metastases. She was referred for chemotherapy with vemurafenib (a BRAF inhibitor) and ipilimumab (an anti-cytotoxic T-lymphocyte antigen 4 antibody). She had refused all treatment alternatives.

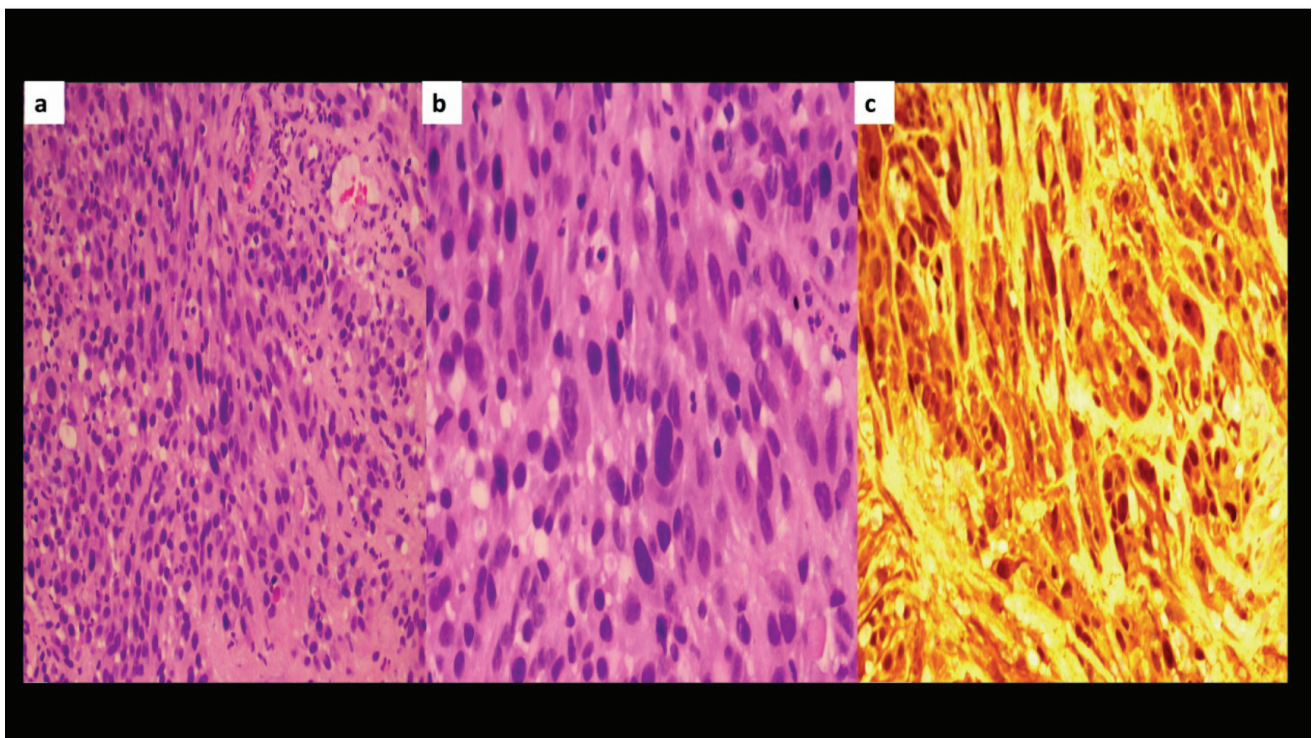


Figure 3. Histopathological findings: Haematoxylin and eosin (H&E) stain photographs under magnification 200× (a) and magnification 400× (b) showing diffuse infiltrate of malignant cells with pleomorphic nuclei. Mitoses are frequently observed. The stroma is densely infiltrated by neutrophils, histiocytes and lymphocytes. Marked fibroblastic proliferation was also seen. S-100 protein immunohistochemical stain photograph at magnification 200× (c) showed the cells were positive for S-100 protein. The overall features support the diagnosis of metastatic melanoma.

Case 3

A 47-year-old woman with a 2-year history of malignant melanoma of the right calf with recurrence in the right groin presented with right breast lump, which had been increasing in size over a few months. The patient had no known family history of breast cancer.

Physical examination revealed a solitary mobile lump in the mid-outer region of the right breast, which measured approximately 1.4×1.7 cm. The overlying skin, nipple, and both axillae were normal.

MMG demonstrated a focal asymmetry in the upper outer quadrant of the right breast corresponding to the clinically palpable mass. No suspicious mass or associated microcalcifications were observed (Figure 7). US showed an oval hypoechoic mass with partly indistinct margin at the right 9 o'clock position measuring 1.9×1.2 cm. Internal vascularity was noted on colour doppler (Figure 2f).

Staging CT showed several subcentimeter nodules throughout the lungs. The patient was

Table 1. Frequencies of primary tumour sources for breast metastases

Primary tumour	Frequencies (%)
Lymphoma	17
Melanoma	15
Rhabdomyosarcoma	12
Lung tumours	8
Ovarian tumours	8
Renal cell tumours	5
Leukaemia	4
Thyroid/cervical tumours	4
Intestinal carcinoid	3
Epidermoid carcinoma head and neck	3
Leiomyosarcoma	2
Others	19

diagnosed with stage IV metastatic malignant melanoma with breast, lymph nodes, and lung metastases. She was referred for systemic chemotherapy.

Discussion

Breast metastases from extramammary malignancies are rare, occurring in approximately

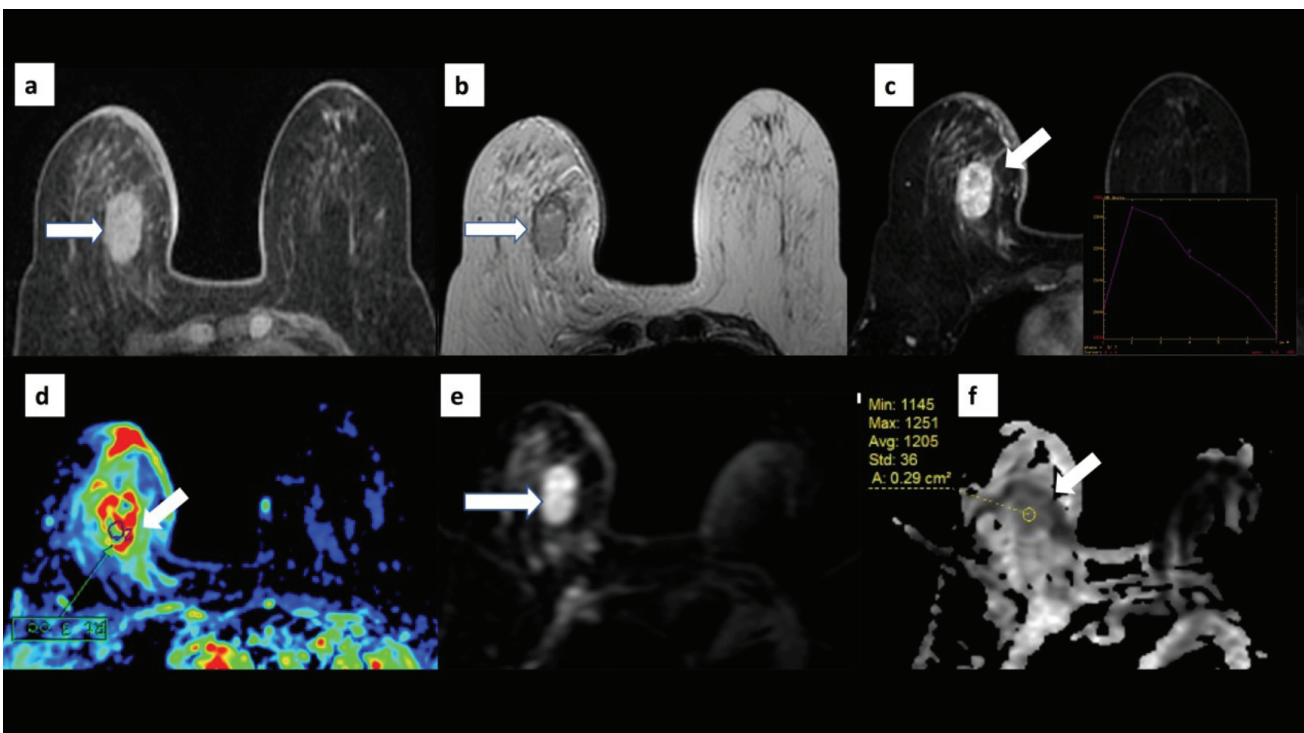


Figure 4. MRI features of melanoma metastasis: (a) Axial T1FatSat and (b) Axial T2 sequences showed a heterogenous mass with hyperintense signal on both T1FatSat and T2 sequences (arrow). (c) The subtracted phase 2 dynamic contrast-enhanced image showed a heterogeneously enhancing mass (arrow) with type 3 curve (insert). (d) The colour coded intensity map of the lesion, with red colour representing areas with the most intense enhancement. On DWI/ADC sequences, the mass (arrow) had high signals on DWI (e) and low signals on ADC (f) in keeping with restricted diffusion. (DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient).

1.3-2.7% of breast malignancy; metastases from a primary carcinoma of the contralateral breast is the most prevalent.¹ Other more common primary tumours for breast metastases are lymphomas, melanomas, rhabdomyosarcomas, lung and ovarian tumours.² Table 1 lists the frequencies of primary tumour sources for metastases to the breast.³

Up to 90% of the patients with melanoma have localized disease at initial diagnosis.⁴ The commonest form of recurrence is local regional recurrence (defined as the presence of a lesion within 5cm of the original scar or graft, a satellite lesion along the path of lymphatic drainage or metastases to regional lymph nodes). Upper trunk and extremities are the most prevalent primary sites of melanoma metastasizing to the breast. The primary lesion involving the lower extremities rarely metastasizes to the breast. In our case series, two patients had breast metastases from primary melanoma of the foot and calf, and one had primary melanoma in the right arm.

Metastatic malignant melanoma to the breast occurs predominantly in premenopausal women and most frequently metachronous.⁵ Breast metastases from melanoma usually occur through haematogenous spread; therefore, they are more commonly found in the upper outer quadrant due to the presence of more fibroglandular tissues and better vascularity.² Ironically, up to 66% of primary breast carcinomas also occur in the upper outer quadrant. The breast is not a favourable site for metastases following menopause due to the larger areas of fatty tissues and relatively poor blood supply.⁶ According to previous studies, solitary metastasis is more common than multiple metastases or bilateral involvement.⁴ All our patients were premenopausal women. Of the four metastatic lesions in our patients, only one was located in the upper outer quadrant. We observed solitary metastasis only in one patient.

Breast metastases can mimic primary breast carcinoma clinically and on imaging studies. They may be asymptomatic or present as a palpable

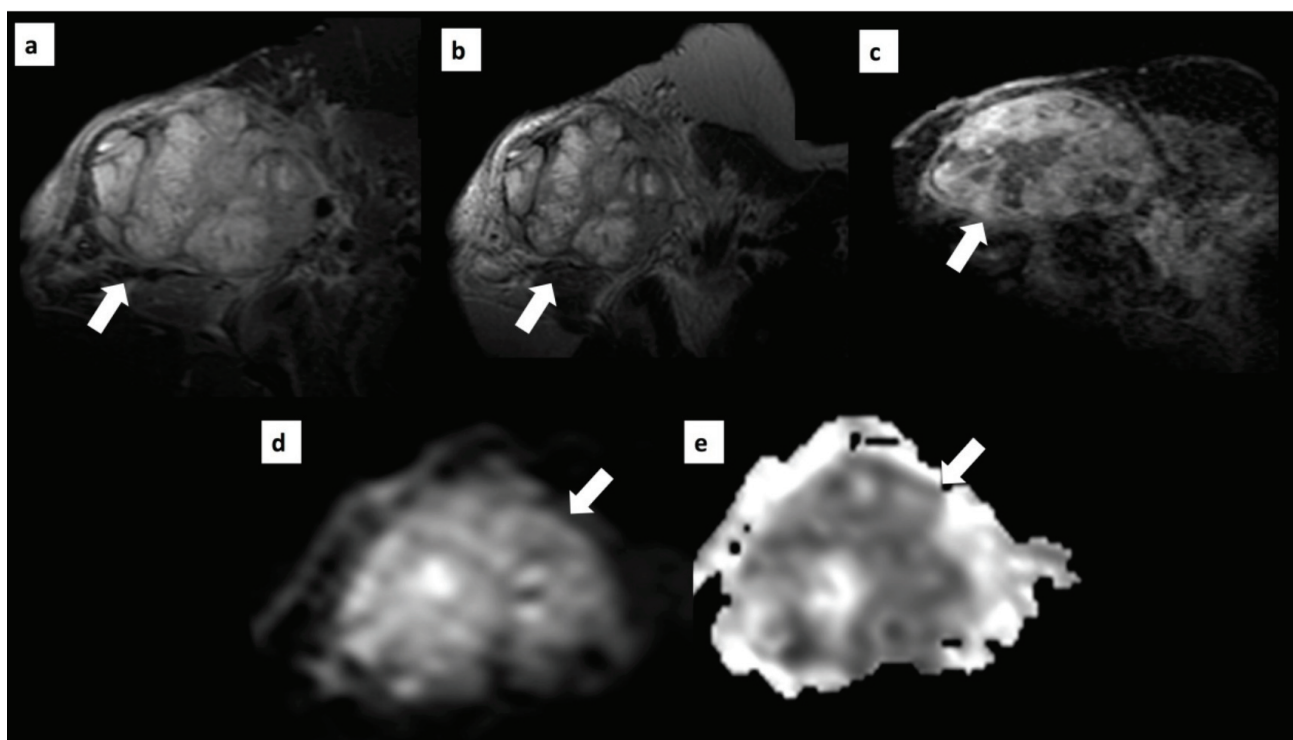


Figure 5. MRI features of axillary lymph nodes metastasis from melanoma: (a) Axial T1FatSat and (b) Axial T2 sequences showed a lobulated circumscribed heterogeneous mass (arrow) with hyperintense signals on both T1FatSat and T2 sequences (c) Post-contrast-enhanced image showed a heterogeneously enhancing mass with necrotic areas within. On DWI/ADC sequences, the mass (arrow) had high signals on DWI (d) and low signals on ADC (e) in keeping with restricted diffusion. (DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient).

lump rarely associated with skin or nipple changes. Nipple discharge is also rare due to extraductal location of metastases. On mammography, melanoma metastases usually appear as well-circumscribed nodular opacities with no associated spiculation, microcalcifications, architectural distortion and secondary skin or nipple changes. This indicates the lack of desmoplastic response,⁷ which is in contrast to primary breast cancer.⁴ In our patients, the metastases appeared as high density lesions, one with irregular and the other with lobulated margins. None were associated with spiculation, microcalcifications, or architectural distortion.

The typical sonographic features include rounded or oval hypoechoic masses with circumscribed or indistinct margins. These features differ from primary breast malignancy, which usually appear as irregular and heterogeneous with posterior acoustic shadowing. Most primary and metastatic malignancies in the breast are hypoechoic.⁸ All the metastatic melanomas in our patients, as well as the benign fibroadenoma

in the second case, were hypoechoic masses with irregular margins. The presence of non-specific and overlapping features render it difficult to differentiate benign from malignant lesions and metastasis from primary breast carcinoma based on sonographic imaging alone.

Breast MRI is a valuable method for evaluating multifocal and multicentric diseases in patients with dense breast parenchyma.⁶ Commonly, similar to other imaging modalities, it is difficult to differentiate metastatic lesions from primary breast neoplasm. Constellation of findings on MRI may raise the index of suspicion for malignancy. Typically, in metastatic melanoma, the paramagnetic effect of melanin shortens T1 and T2 relaxation times, resulting in high signals on T1 and low signals on T2-weighted images.^{6, 10} Therefore, metastatic melanoma or melanin-containing tumour should be diagnosed in lesions displaying these features on MRI. Marx HF et al.⁹ described four MRI signal patterns of melanoma in a study on 27 melanomas at various body areas. They characterized the typical pattern

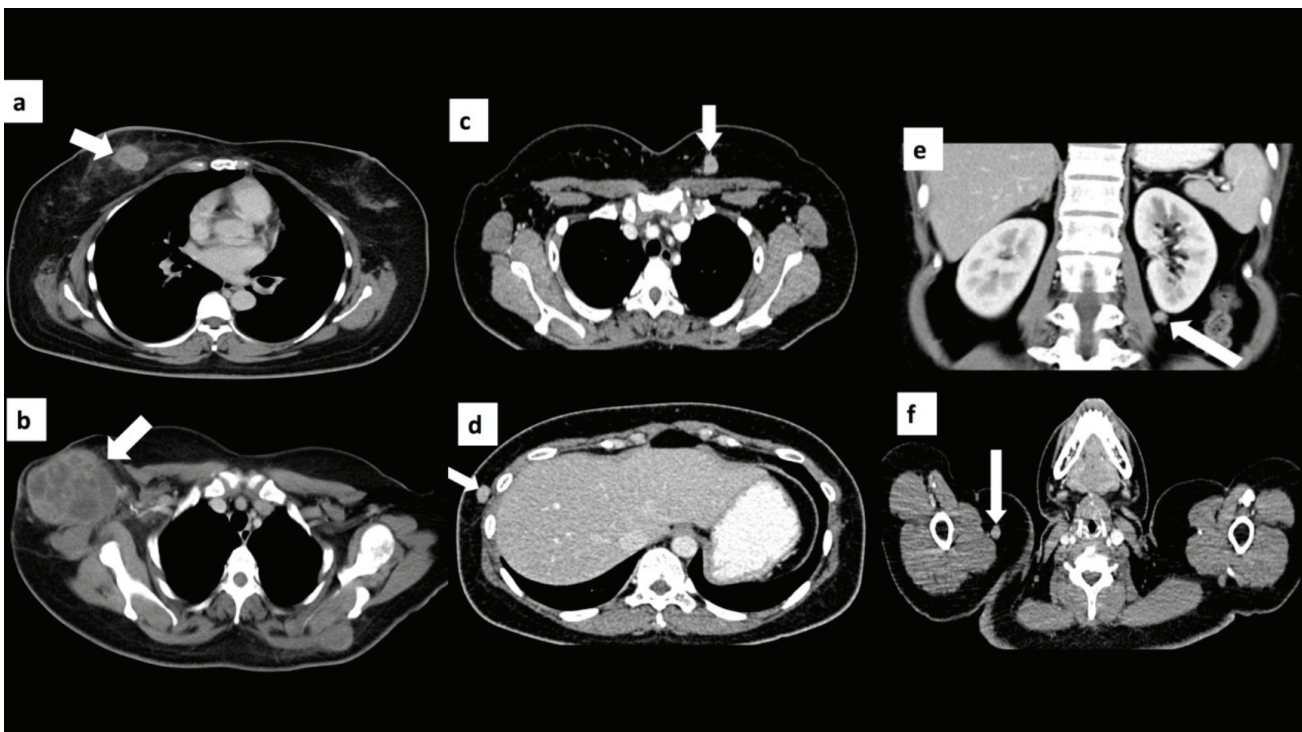


Figure 6. CT features: (a-b) Case 1- (a) CT demonstrated a hypodense heterogeneously enhancing irregular lesion in the right breast (arrow). (b) The enlarged matted lymph nodes with areas of necrosis within the right axilla (arrowhead). (c-f) Case 2 - (c) CT showed an irregular hypodense enhancing lesion in the upper inner quadrant of the left breast (arrow). Staging CT scan demonstrated other sites of metastases, (d) subcutaneous nodule in the right lateral chest wall (arrow), (e) retroperitoneal nodules (arrow) adjacent to the inferior pole of both kidneys, and (f) right shoulder (arrow). (CT: Computed tomography)

by high signals on T1 and low signals on T2-weighted images, indicating shortened T1 and T2. Other patterns included lesions demonstrating low signals on T1- and high signals on T2-weighted images, high signals on both T1- and T2-weighted images, and intermediate signals on either T1- or T2-weighted images.⁹ Characteristic MRI features may be masked by the presence of intralesional haemorrhage. This condition frequently occurs spontaneously in melanoma and in post-procedural haematoma, where the lesion is hyperintense on both T1 and T2-weighted imaging.¹⁰ We did not observe typical melanoma signal patterns on MRI in our patient. Our patient's mass, hyperintense on both T1 and T2-weighted imaging, fits one of the signal patterns described by Marx et al.⁹ Alternatively, this signal pattern may also be the result of the presence of hematoma, which developed secondary to the recent ultrasound guided biopsy.

Malignant lesions, including melanoma, typically demonstrate restricted diffusion, representing high cellularity on DWI.⁶ ADC values allow for the quantification of diffusion signal;

they are also able to facilitate the differentiation of benign and malignant breast tumours.¹¹ A meta-analysis by Partridge et al. revealed that mean ADC for malignant lesion ranged from $0.87 - 1.36 \times 10^{-3} \text{ mm}^2/\text{s}$. They also showed that breast cancers had significantly lower ADCs compared to benign breast lesions or normal breast tissues.¹¹ In our centre, we adopted $1.4 \times 10^{-3} \text{ mm}^2/\text{s}$ as the cut-off value for malignant lesion on ADC value. To date, there is no study describing the ADC value pertaining to metastatic melanoma of the breast. Diffusion restriction was evident in our patient; the ADC values of the melanoma metastases and the metastatic axillary lymph nodes were $1.2 \times 10^{-3} \text{ mm}^2/\text{s}$ and $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$, respectively, which is in keeping with malignant lesions.

The biopsy-proven fibroadenoma in the contralateral breast did not demonstrate restricted diffusion with mean ADC value of $1.8 \times 10^{-3} \text{ mm}^2/\text{s}$ in conformity with benignity.

Most malignant and benign lesions may be enhanced following intravenous gadolinium-based contrast agent administration. Dynamic contrast

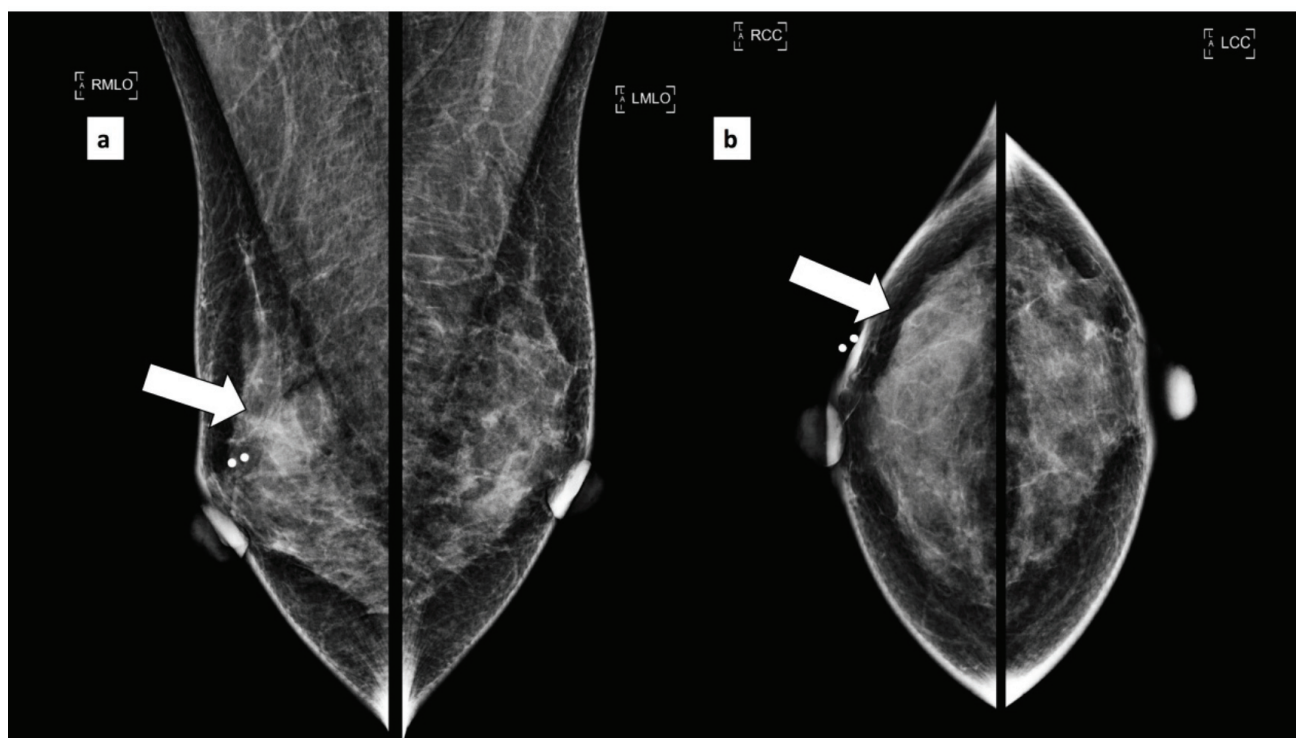


Figure 7. Mammography features: (a-b) Case 3 - Mediolateral oblique and craniocaudal mammogram views demonstrating focal asymmetry in the upper outer quadrant of the right breast (arrow) corresponding to the clinically palpable mass. No suspicious mass or associated microcalcifications.

enhancement curve or kinetic curve may facilitate the differentiation between malignant and benign lesions with type 3 curve, rapid contrast uptake with washout in the later phase, being more suspicious for malignancy.¹² Both the metastases and the metastatic axillary lymph nodes in our patient showed heterogeneous enhancement with type 3 enhancement curve. This is contrary to the benign fibroadenoma in the contralateral breast, which demonstrated benign type 1 curve.

The radiological findings of metastatic malignant melanoma are not always distinguishable from primary breast carcinoma; therefore, histopathological correlations are necessary for definitive diagnosis. Tumour cell immunoreactivity for S100, HMB-45, and MART-1 has been proven useful in differentiating malignant melanoma from other malignant tumours.¹³

At the time of breast metastasis diagnosis, the preponderance of patients commonly have other metastases. Accordingly, contrast-enhanced CT or PET-CT is recommended for staging. These studies will confirm the presence of other foci of metastases to the rest of the body. Melanomas are FDG avid on PET-CT.¹⁴ In all our patients, in addition to the metastases in the breast and axillary nodes, staging CT demonstrated multiple metastatic nodules in the lung, pleura, retroperitoneum, subcutaneous tissues, and other lymph nodes.

Presence of breast metastases in metastatic melanoma indicates a widespread disease, and aggressive surgical procedures are to be avoided due to the poor prognosis.¹⁵ Treatment alternatives include close observation, surgical resection of solitary breast metastases, systemic chemotherapy, and radiotherapy.⁵ In light of the disseminated metastatic disease in all our patients upon breast metastases diagnosis, all underwent systemic chemotherapy.

Conclusion

Metastases to the breast from malignant melanoma neoplasm are rare; however, they should be suspected in patients presented with a breast mass and a prior history of melanoma. The

clinical and imaging distinction between a primary breast carcinoma and melanoma metastases may not be straightforward. Although imaging findings are non-specific, MRI features with kinetic analysis, DWI sequence, and ADC value are useful in differentiating between benign and malignant lesions, as well as further characterizing the breast lesions. However, imaging findings do not obviate the need for histopathology evaluation for accurate diagnosis and subsequent management of the affected patients.

Informed Consent

Informed consent was obtained from all patients.

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Conflicts of Interest

None declared.

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