

Case Report

The Curious Incident Of 3 Melanomas And Their Possible Origins: A Case Report and Review of Literature

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Abstract

Background: We describe an unusual case of 2 intra-parenchymal breast melanomas with a concomitant subcutaneous melanoma in the ipsilateral upper limb and no definite primary lesion.

Case Report: Our patient is a 40-year-old Chinese female who presented with a breast lump in her left breast for which excision biopsy showed melanoma. A PET-CT revealed a second lesion in her breast. A left upper arm nodule with no overlying skin changes was also noted. She underwent a mastectomy and excision biopsy of the upper arm nodule. Histology showed that the second breast lesion was also a melanoma, while the arm nodule contained melanoma cells within a fibrous capsule.

Conclusion: The presence of a melanoma in the breast should prompt a close and meticulous search for a primary lesion and potential signs of metastasis. Encapsulated subcutaneous nodules can be attributed to replaced lymph nodes or subcutaneous melanoma which can be either primary dermal melanoma or metastasis from an unknown primary.

Keywords: melanoma; breast; cancer; intra-dermal; melanoma-in-transit

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Introduction

Metastatic malignancies to the breast are uncommon. One of the more common tumors that metastasize to the breast is malignant melanoma. Primary dermal melanoma is a term used to describe melanoma confined to the dermis or subcutaneous tissue without an epidermal component. In this report, we describe an unusual case of 2 intra-parenchymal breast melanomas with a concomitant subcutaneous melanoma in the ipsilateral upper limb with no definite primary lesion.

Case Study

Mrs T is a 40 year-old Chinese female who presented to us in June 2013 with a left breast lump in the upper inner quadrant of one month's duration. Physical examination showed a mobile, well-defined palpable nodule in her left breast. She did not have other nodules or pigmented lesions. A mammogram and ultrasound showed a 15 mm benign-looking left breast nodule which was ovoid and well-defined. This was observed as the nodule appeared benign. However, there was a slow increase in the size of the nodule and the follow-up mammogram and ultrasound in August 2014, 14 months later, showed that it had increased in size to 24mm, was lobulated, and associated with increased vascularity. She presented to our center in September 2014 for treatment. As it remained well-defined and mobile, our impression was that of a likely fibroadenoma, and an excision biopsy was performed. Intra-operative findings showed a 2.5cm nodule in the upper inner quadrant of the left breast, which was encapsulated and well-defined. Gross examination revealed a homogenous yellowish-tan cut surface without any hemorrhage or necrosis (Figure 1). Histology revealed a lobulated proliferation of sheets of epithelioid cells featuring enlarged vesicular nuclei, conspicuous nucleoli and ample eosinophilic cytoplasm, accompanied by scattered intra-cytoplasmic brownish pigment (Figures 2A and B). Focally the tumor cells display eccentric nuclei with hyaline cytoplasmic inclusions (Figure 2C), giving rise to a rhabdoid morphology. The tumor cells showed strong and diffuse staining for S100 and melan-A with focal positivity for HMB45 (Figures 2D to F), establishing their melanocytic lineage. Multiple keratin markers were all negative. A diagnosis of melanoma with rhabdoid features was made. The tumor was negative for EWSR1 translocation on fluorescence in situ hybridization (FISH), hence a clear cell sarcoma was excluded.

In view of this histology, a PET-CT scan was done which showed another 7 mm nodule in the upper left breast with minimal FDG avidity that was indeterminate. There was no disease elsewhere. A repeat ultrasound in our institution confirmed the presence of this nodule. A vacuum-assisted biopsy was done with histology showing melanoma with an identical histomorphology (Figure 3A) and immuno-histochemical profile as the initial excision biopsy specimen. This case was further discussed at the sarcoma tumor board and as the impression was a primary multi-centric melanoma of the breast, a mastectomy with a sentinel lymph node biopsy was recommended.

Prior to surgery, a comprehensive physical examination was done to look for a primary cutaneous lesion and no abnormal-looking naevi was noted. A benign-looking scalp nodule and neck nodule were noted; both were excised and histology returned as intradermal melanocytic naevus and spongiotic dermatitis, respectively. In addition, esophagogastroduodenoscopy, colonoscopy and colposcopy were done to rule out mucosal melanoma and all were normal.

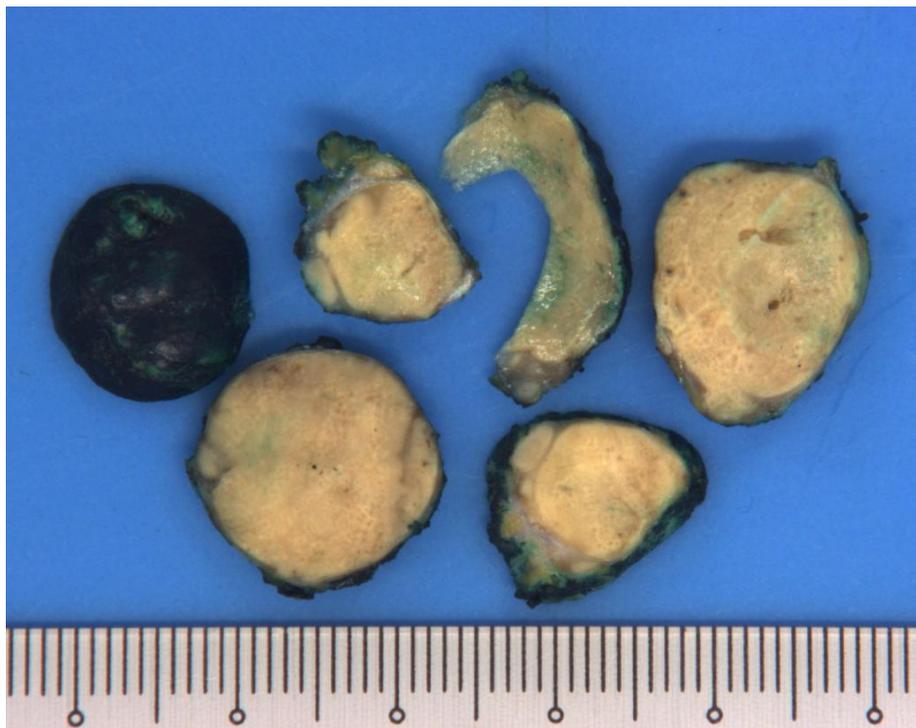


Figure 1 Cut sections of excision biopsy of left breast nodule showing a homogenous yellowish-tan appearance.

Just before the planned surgery, she reported a tiny stable subcutaneous nodule in her left upper anterior arm, which she had had for 8 months prior; it was well-defined and mobile. This nodule was excised during the mastectomy. At the same time, a sentinel lymph node biopsy and immediate breast reconstruction with a latissimus dorsi flap was done.

Histology of the breast showed a 1mm focus of residual melanoma at the biopsy site (Figure 3B). Resection margins were uninvolved by tumor, and all three sentinel lymph nodes were negative for malignancy.

However, histology for the upper arm nodule showed the presence of a melanoma surrounded by a fibrous capsule (Figures 3C and D), which raised the possibility of metastatic melanoma in a completely replaced lymph node. In all 3 nodules which tested positive for melanoma, no overlying skin was involved, and this precluded the usual melanoma staging by Clark's or Breslow's classification.

As there were no other detectable lesions, a collective decision was made with the patient for close clinical and radiologic surveillance.

Discussion

This patient presents with an interesting diagnostic conundrum that brings up certain pertinent aspects of melanoma.

When melanoma was first detected in the breast parenchyma in our patient, diagnostic considerations included that of a primary melanoma in the breast versus metastatic deposits from an extra-mammary primary melanoma. Primary breast melanoma with no overlying skin changes is unreported in literature, and to have two concomitant primary lesions was highly unlikely. However, extensive search failed to

identify a primary cutaneous melanoma. Since primary multi-centric breast melanoma was still a viable etiology, a mastectomy and sentinel lymph node biopsy was recommended.

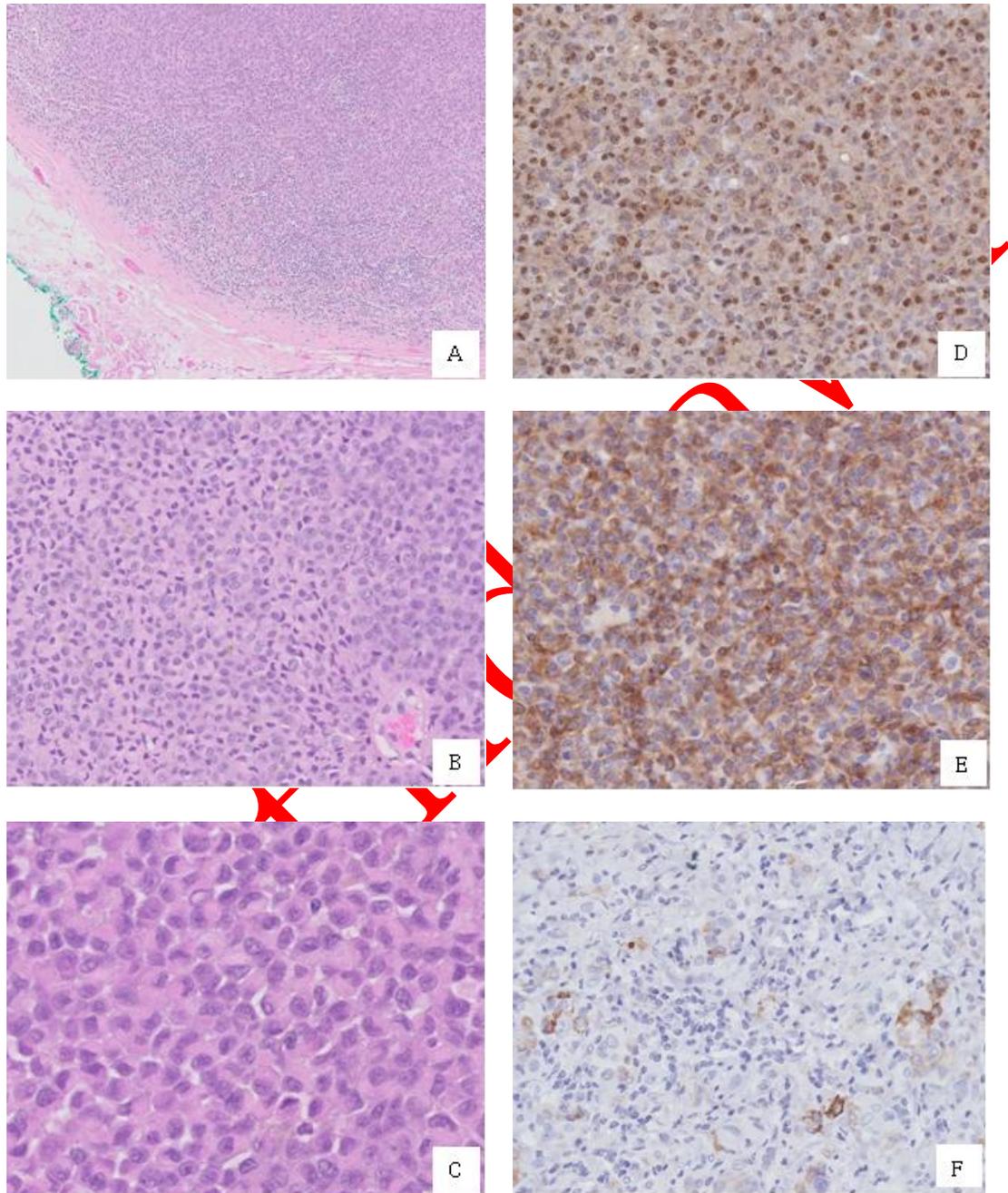


Figure 2 Hematoxylin and eosin stained sections of excision biopsy specimen of the left breast nodule showing a lobulated proliferation of sheets of epithelioid cells featuring enlarged vesicular nuclei with conspicuous nucleoli and ample eosinophilic cytoplasm (x5) (A), accompanied by scattered intracytoplasmic brownish pigment (X20) (B). Focally the tumor cells display eccentric nuclei with hyaline cytoplasmic inclusions (x40) (C). Immunohistochemistry showed strong and diffuse staining for S100 (D) and melan-A (E). Focal positivity for

HMB45 was noted (F).

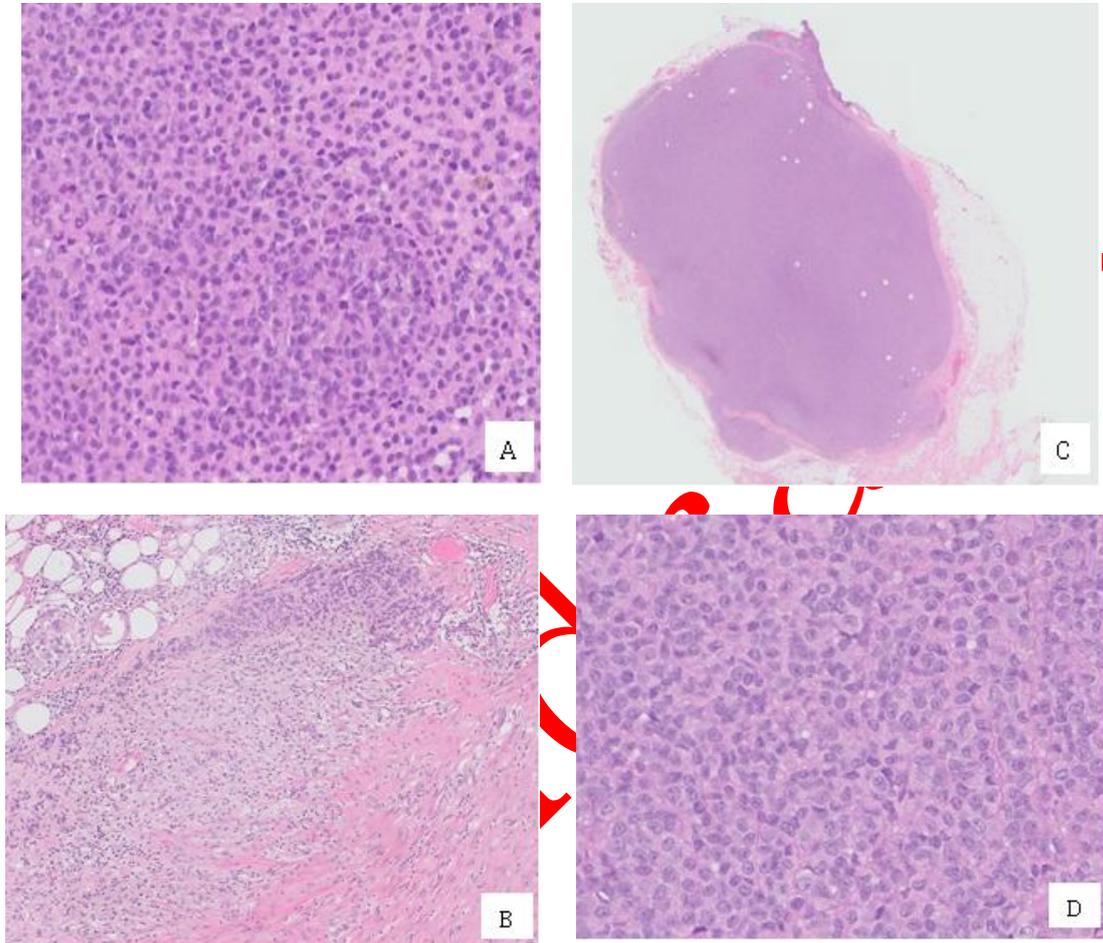


Figure 3 Hematoxylin and eosin stained sections showing a proliferation of tumor cells from follow up biopsy of small left breast nodule (x20) (A) and a residual focus of tumor in the left completion mastectomy specimen (x5) (B). The excision biopsy of the left arm lump showed an encapsulated tumor nodule (x5, hematoxylin and eosin) (C), composed of a sheet-like proliferation of tumor cells (x20, hematoxylin and eosin) (D). All of them showed a similar appearance to that of the initial excision biopsy.

Malignant tumors which metastasize to the breasts are rare and only account for 0.5-2% of all malignant lesions in the breast. Of these, melanomas, rhabdomyosarcomas, lymphomas remain the more common tumours [1-3]. In our patient, these nodules were very superficial and hence may have been subcutaneous, suggesting a greater likelihood of being metastases instead of primary lesions. The location of a lump in the breast does not help distinguish between a secondary deposit versus a breast primary [4]. Features of metastatic disease on breast imaging such as mammograms or ultrasounds are often subtle and indistinguishable from primary or benign breast lesions, as was the case in our patient, and hence confirmatory histological diagnosis is required [5]. MRI of the breasts has not been evaluated

as a tool in differentiating metastatic lesions from other lesions and hence was not considered in our patient. Furthermore, a negative breast sentinel lymph node biopsy with another lesion in the upper arm, possibly a lymph node, suggests a primary lesion in the upper limb with breast metastases. Thus far, there has been no strong predictive factor identified for the development of breast metastasis from an extra-mammary primary. However, in a review of 15 patients with melanoma metastases in the breast, *Amichetti et al.* did note that they were all premenopausal [6]. Similarly a review of 8 patients by *Loffeld et al.* found that at least half of their patients were premenopausal [7]. This suggests a possible predisposition to breast metastases in pre-menopausal melanoma patients. The prognosis for such patients is often poor with the median survival approximately 10 months [7,8].

Close analysis of the upper arm nodule revealed a completely contained lesion within a fibrous capsule, located within subcutaneous fat. Other than the capsule-like sheath, there was no residual lymph node histo-architecture to support a nodal origin. Whilst it was entirely possible that this was a completely replaced lymph node, the nodule's location in the upper anterior arm, at a distance away from the axilla, was an atypical location for a lymph node. Other alternatives considered include a possible melanoma-in-transit lesion, subcutaneous metastasis or a primary intradermal melanoma. An extensive search for a primary in the upper limb proved futile, indicating that this could be a melanoma of unknown primary.

A prospective study by *Lee et al.* of 1,571 patients showed significantly better 5-year overall survival for those with melanoma of unknown primary compared to melanoma of known primary (55% +/- 6% v 44% +/- 3%; P = .0021) in patients who had undergone regional lymphadenopathy for palpable nodal metastasis [9]. Age more than 60 years, increased number of tumor-involved nodes, and male sex were also associated with a poorer prognosis [9].

In our patient, a completion lymphadenectomy was not done for several reasons. Firstly, the diagnosis of the upper arm nodule was not histologically certain – it could have been a completely replaced lymph node or simply melanoma deposits with a fibrous response. In addition, the benefit of axillary dissection in a clinically negative axilla was unclear. PET scan also did not show any other suspicious lesions in the axilla. Furthermore, after the prior mastectomy, she had immediate breast reconstruction using the latissimus dorsi. Access to the axilla could compromise the blood supply to the flap. Hence, the decision was made for close clinical surveillance with subsequent PET scans for recurrent disease. At present, no viable adjuvant therapy has been shown to reduce the risk of recurrence and prolong survival in such patients [9].

The postulation that the upper arm lesion could be a melanoma with a surrounding fibrous response raises the possibility of this being either a primary intradermal melanoma, a very rare tumor indeed, or melanoma-in-transit (N2c) from a primary that has undergone regression, or a subcutaneous metastasis (M1a) from an unknown primary.

Since the extensive search for a primary in the upper limb was futile, a regressed primary lesion is a worthwhile consideration. Compared to other cancers, melanoma is more likely to undergo spontaneous regression. Partial regression of primary cutaneous melanoma has been documented in 10-35% of cases, with complete regression even rarer at a rate of 0.22-0.27% [10,11]. This incidence may be under-reported in literature as reported cases of melanoma of unknown origin (MUP) – report an incidence of 4-6% in literature – might also be explained by the phenomenon of primary tumor regression [12-14].

The prognostic significance of regressed melanomas is unclear. Studies have shown a correlation between regressed primary melanomas and nodal metastasis with the cause-and-effect relationship undefined as yet [15]. Some have theorized that nodal metastasis stimulated an immune response that

causes regression of the primary lesion. Lymphocytic infiltrates of histological specimens from partially regressed melanomas have lent credence to this theory with the presence of lymphocytes importance in supporting an enhance immune response [16,17]. It follows that nodal metastasis would portend a poorer prognosis for these patients. Some authors have found that regression is a negative prognostic factor [11]. However, the survival of such patients is highly variable with overall survival ranging from 6 week to 11 years [16]. Evidence to the contrary shows that regression may actually have little effect on the risk of metastasis, and that it is not regression itself per say, but rather the degree of regression that has an effect on propensity for metastasis. *Guitart et al.* have found that lesions with regression of >50-80% have a higher chance of metastasis [15]. Other proposed causes of tumor regression include operative trauma, infection, blood transfusions, vaccinations, and endocrine factors, all of which were absent in our patient [18].

If the arm nodule was melanoma-in-transit (N2c) from a regressed primary, prognosis would then be more guarded for the patient. Melanoma-in-transit are located in regional and sub-dermal lymphatics along the route of spread from a primary melanoma to their regional nodal basins. It has been shown to portend poorer outcomes with up to 75% eventually progressing to nodal or distal disease or both [19]. Treatment options would include surgical resection, isolation limb perfusion or infusion with melphalan, or systemic chemotherapy. Surgical resection if possible is the mainstay of treatment, with adjuvant therapy with interferon-alpha or participation in clinical trials [19]. In light of the absence of a primary lesion in our patient, the diagnosis of melanoma-in-transit could not be confidently made, and adjuvant treatment was held off as their benefits could not be ascertained.

While rare, primary dermal melanoma can occasionally simulate metastatic melanoma from an unknown primary. In a retrospective review of 1800 patients by Bowen et al., the prevalence of patients diagnosed with a presumed metastatic melanoma (ie stage IV) to the skin was 0.61% with 8-year survival of 83%. The survival rates for Bowen's population far exceed the commonly quoted 5-8% 5-year survival for stage IV melanoma patients [20]. This uncharacteristic prognostic data is further reinforced by various other case series which demonstrate 5 year survival rates in excess of 80% for cutaneous metastases in unknown primary melanoma patients [20,21]. The unprecedented survival data suggests that the natural history for such patients differs from patients with stage IV melanomas as currently staged by the AJCC criteria. These tumors may not represent metastatic melanomas, and the term 'primary dermal melanoma' was coined to refer to these melanomas as primary lesions that have arisen within the dermis or subcutaneous fat. It has been postulated that such lesions may arise from non-epidermal melanocytes, or from melanocytes associated with deeper appendageal structures [21]. However, the true origin of such tumors remains nebulous. Due to the vast difference in prognosis, it is important to make a distinction between primary dermal melanoma and metastatic melanoma when confronted with a melanoma within the subcutaneous tissue or dermis. Unfortunately, there have been no reliable histo-pathologic or immune-histochemical differences noted thus far, and such a diagnosis must always be considered when confronted with a melanoma confined to the dermis or subcutis [22].

For our patient, the prognosis is unclear – the outcome associated with melanoma of unknown primary or even possible primary dermal melanoma balances or even outweighs the negative prognostic significance of breast metastases remains to be seen.

In conclusion, the presence of a melanoma in the breast should prompt a close and meticulous search for a primary lesion and for potential signs of metastasis in nodal basins and common metastatic sites. This should be done via clinical examination as well as appropriate imaging studies such as PET-CT, CT scans or MRI scans.. Encapsulated subcutaneous nodules can be attributed to replaced lymph nodes or subcutaneous melanoma either secondary to metastasis from an unknown primary or as a primary

dermal melanoma. The various permutations should be considered, especially in patients with atypical presentations such as ours, such that a suitably appropriate management and follow-up plan can be tailored.

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