Primary Malignant Melanoma of the Breast: Case Report and Review of the Literature

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Abstract. Background: Melanoma of the breast is a rare disease and may present as a metastatic manifestation of primary cutaneous melanoma or as primary malignant melanoma of the breast (PMMB). Clinical presentations of PMMB vary and surgery is the mainstay of treatment. Case Report: We present the case of a 54-year-old woman with a primary malignant melanoma of the left breast. She was treated with mastectomy, axillary sentinel lymph node excision and primary reconstruction with a tissue expander. Final histology revealed a malignant melanoma with 10 cm in the largest diameter. Molecular characterization by DNA-sequencing showed B-RAF, N-RAS and c-kit wild types. Immunohistochemical characterization demonstrated weak expression of S100 and melan-A and strong expression of polyclonal S100. HMB45, tyrosine kinase and the cytokeratins AE1/AE3 and MNF 116 were not expressed. Lymphoma-specific markers (CD30, CD3, CD20) and sarcoma-specific markers (desmin, actin, CD34) were also negative. The tumor proliferation rate according to Mib1-staining was 90%. Staging of the abdomen, chest, head and bones showed no evidence of metastases. A dermatological examination showed no primary melanoma of the skin. Interferon-alpha was suggested as adjuvant therapy but declined by the patient. With a follow-up of 6 months, the patient is still alive with no evidence of disease. Conclusion: PMMB is rare and may be successfully treated with surgical excision. Locally advanced PMMB may occur without regional and distant metastases.

Melanomatous lesions of the breast may occur as a metastatic manifestation of primary cutaneous melanoma or as true primary malignant melanoma of the breast (PMMB) (1, 2). Of note, melanoma is the foremost cause of metastasis to the breast from extramammary solid neoplasms (2). PMMB, however, is a rare entity and accounts for 3-5% of all melanomas and for <0.5% of malignant breast tumors (1, 3). PMMB may derive from the breast skin or-less commonly-from the glandular parenchyma of the breast (4). One hundred and eighty-seven cases of PMMB are to date reported in the literature, based on a recent PUBMED search (search terms: breast, breast cancer, breast tumor, melanoma, malignant melanoma, melanotic, amelanotic; search date: 14-08-2014).

The largest series of women with PMMB dates back to the 1970s reporting 115 cutaneous melanomas of the breast, including 14 cases of PMMB of the nipple/areola complex (3, 4). The authors concluded that mastectomy offered no advantage over local excision of the primary lesion and recommended regional axillary lymph node dissection. A recent series from Italy included 39 cases of PMMB and noted a distribution pattern different from breast cancer with a predominance of the upper inner quadrant (5). Specifically, 22 lesions were located in the upper inner quadrant, 10 lesions in the upper outer quadrant and five lesions located between the inner and outer upper quadrants. One lesion was in the lower outer quadrant and one in the areolar zone. Lesions were equally distributed in the right and left breasts. These data suggest an etiological role of sun exposure in PMMB because the inner quadrants are typically more exposed to sunlight than the outer quadrants.

A smaller series of 12 PMMB cases was published by Lee et al. in 1977 (6). This and the above stated publications reported no case of lymph node metastasis in internal mammary nodes suggesting that regional dissection of the internal mammary chain is not necessary in PMMB (3-6). Kurul et al. reported survival rates of a series of 9 women with PMMB with 6 of them developing distant metastases and/or locoregional recurrence within a follow-up period of up to 60
The histopathological diagnosis of PMMB is complex and based on a combination of morphological and immunohistochemical features. Melanoma cells have a diverse appearance ranging from epithelioid to spindled cells and include different cytoplasmatic morphologies, such as signet ring shapes and clear cells. In addition, their growth pattern results in a large architectural variation with trabeculae, rosettes, glands and papillaries (14). Due to this variability, immunohistochemistry is required to distinguish melanomas from epithelial, hematological, mesenchymal and neural tumors and from metastases of extramammarian malignancies, such as melanomas and carcinomas of the lung, ovary, prostate, kidney and stomach (15). S100 is the most sensitive marker for melanoma with a sensitivity of 97-100% (16). Other established sensitive and specific markers for melanoma are melan-A, tyrosinase and HMB-45 (17, 18). Usually, an additional panel of epithelial, mesenchymal, lymphoma- and sarcoma-specific markers is assessed to exclude metastatic disease. Finally, Ki-67 or Mib-1 staining may be used to distinguish between benign and malignant tumors (19). In our case, we had a breast tumor with clear positive staining for S100, vimentin and melan-A and strong expression of polyclonal S100 (Figure 3). PMMB is a rare disease accounting for 3-5% of all melanomas and for <0.5% of malignant breast tumors (1, 3). One hundred and eighty-seven cases of PMMB have been reported in the literature (3-13). Radical surgical resection with free margins combined with axillary node resection or axillary sentinel node resection is the primary treatment of choice. Mastectomy is not necessary nor is regional dissection of the internal mammary chain (3, 6).

Discussion

PMMB is a rare disease with a poor prognosis despite radical local resection with survival rates of <50% (7/15). In addition to these monocentric case series, a number of authors reported cases of women with PMMB (8-12) including one case of amelanotic melanoma (13).

Herein, we describe the case of a 54-year-old woman with the largest PMMB ever reported, 10 cm in diameter, treated with surgical excision. We review the literature on PMMB and outline current treatment strategies and prognosis of women with PMMB. This case report and the data in the literature indicate that PMMB is a rare disease with a poor prognosis. Surgery is the mainstay of treatment with radical local excision and axillary sentinel lymph node dissection. Adjuvant and primary advanced treatment strategies for women with PMMB follow the guidelines applying to melanoma.
S100 and melan-A. Mib-1 was expressed by 90% of the cells and all other markers were negative, thus establishing the diagnosis of a PMMB.

Therapeutic options for malignant melanoma have significantly evolved during the last few years with new compounds targeting the CTLA-4 (ipilimumab) and BRAF pathways (vemurafenib, dabrafenib, trametinib) having either reached FDA and EMA approval or entered phase II/III clinical trials as mono- or combination therapy, like the class of PD-1 inhibitors (nivolumab, pembrolizumab) (20, 21).

Further clinical trials, especially with the aforementioned compounds, are eagerly awaited to evaluate their potential for preventing progressive disease.

Adjuvant treatment strategies for PMMB follow melanoma guidelines and include interferon alpha as the...
standard of care in high-risk cases, such as those with regional lymph node metastasis, deep infiltration and ulceration (20, 21). Randomized evidence suggests that adjuvant radiotherapy improves lymph-node field control in patients at high risk of relapse but has no effect on overall survival (23). Thus, radiotherapy after lymphadenectomy for patients at high risk of further lymph-node field and distant recurrence is an additional adjuvant therapy option, which, however, remains controversial. Treatment strategies for primary advanced and recurrent PMMB also follow melanoma guidelines including immunotherapies with ipilimumab, vemurafenib and systemic chemotherapy with dacarbazine, temozolomide, cisplatin and paclitaxel (20, 21, 23). Due to the rarity of PMMB, it is unclear whether these treatment strategies, known to be effective in malignant melanoma, are also effective in PMMB. Although it is reasonable to assume therapeutical equipotency in the cases of cutaneous PMMB, this is less clear in cases of PMMB arising from the glandular parenchyma of the breast.

Melanozytic lesions can alter their appearance in pregnancy and some melanomas express steroid receptors (23). Thus, exists a theoretical role of endocrine therapy in melanomatous lesions, such as PMMB. In contrast to breast cancer, there is no established role for adjuvant endocrine therapy in PMMB. The prognosis of PMMB is poor with estimated long-term survival rates <50% based on case series published in the literature (7, 8).

The clinical presentation and management of our PMMB case is in accordance with the literature on PMMB. Of note, the tumor was particularly large and ranks among the largest PMMBs reported so far. This is interesting because it demonstrates that even large and poorly differentiated PMMBs may stay localized without regional and distant metastasis. Due to the fact that the tumor was completely resected and lymph node-negative, no adjuvant therapy was necessary based on guidelines’ recommendations (20, 21). Based on the unusually large size of the tumor, however, we assumed a high risk of relapse. Both adjuvant interferon alpha and local radiotherapy were discussed in the tumor board. Finally, adjuvant immunotherapy with interferon alpha was suggested to the patient but she declined any form of adjuvant therapy and opted for follow-up care.

**Conclusion**

We presented the case of a 54-year-old woman with the largest PMMB ever reported treated with surgical excision. This case report and the data in the literature indicate that PMMB is a rare disease with a poor prognosis. Radical surgical excision is the primary treatment. Adjuvant and primary advanced treatment strategies for women with PMMB follow the guidelines applying to melanoma.

**Clinical Practice Points**

- PMMB is a rare disease accounting for 3-5% of all melanomas and for <0.5% of malignant breast tumors.
- Based on a PUBMED literature research, controlled clinical trials of women with PMMB are lacking; 187 cases have only been published.
- Immunohistochemical markers, such as S100 and melan-A, are used to characterize PMMB.
- Breast and axillary surgery is the mainstay of treatment of PMMB.
- Adjuvant treatment strategies follow the recommendations applicable to melanoma.
- The available data in the literature suggest that PMMB has a poor prognosis with survival rates of <50%.

**Conflicts of Interest**

The Authors declare that they have no conflict of interests.

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**References**


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