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CASE REPORT

Malignant melanoma with osteosarcomatous differentiation in a lymph node metastasis

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Osteocartilaginous differentiation in malignant melanoma is rare and can pose a diagnostic challenge. In previously reported cases, melanomas were predominantly located on acral and mucosal sites, with osteocartilaginous differentiation present in either primary or recurrent lesions. We report a case of a 52-year-old female with malignant melanoma located on the right upper back exhibiting osteosarcomatous differentiation only in the axillary lymph node metastasis. This case serves to highlight that the divergent differentiation can occur in lymph node metastases while being absent in the primary lesion. The patient's medical history, careful histological examination, and immunohistochemistry may be necessary for establishing the correct diagnosis.

KEYWORDS

differentiation, heterologous elements, malignant melanoma, metastasis, osteosarcomatous

1 | INTRODUCTION

Malignant melanoma may exhibit divergent differentiation. Reported types of heterologous elements observed in melanoma include fibroblastic/myofibroblastic, Schwannian and perineurial, smooth muscle, rhabdomyosarcomatous, osteocartilaginous, ganglionic and ganglioneuroblastic, neuroendocrine, and epithelial.[1] Osteocartilaginous differentiation of malignant melanoma is very rare, with only 38 cases being previously reported.[2–29] The heterologous elements were mostly present in the primary or recurrent lesions, but seen only in the cutaneous metastases in 2 cases and in the lymph node metastases in 2 other cases.[6,9,17,25] These metastases displayed cartilaginous/chondrosarcomatous differentiation. Rhabdomyosarcomatous differentiation has also been reported in metastases, while not being observed in the primary melanoma.[30] We present an extraordinary case of malignant melanoma of the right upper back with osteosarcomatous differentiation restricted to the lymph node metastasis.

2 | CASE PRESENTATION

A 52-year-old female with no known history of malignancy presented with a skin lesion on her right upper back. On physical examination, a 2.5 cm raised, variegated, hyperpigmented skin lesion with irregular borders was identified (Figure 1). The lesion had been present for many years and remained asymptomatic until 1 year prior to the initial biopsy, when it started to itch. The patient reported that it became tender and blistered 7 months later.

An initial biopsy of the primary skin lesion was performed at an outside facility and reviewed for patient management in our Multidisciplinary Melanoma Clinic. A subsequent excisional biopsy for microstaging was performed at our institution for final melanoma prognostic parameters. Histological examination of the microstaging specimen revealed cytologically atypical epithelioid and spindled cells with finely vesicular chromatin and conspicuous nucleoli within the epidermis and dermis, consistent with superficial spreading melanoma invasive to Clark level IV and 1.65 mm Breslow thickness (Figure 2). The mitotic rate was 5/mm^2. There was no lymphovascular invasion, ulceration, or osteosarcomatous differentiation present within either specimen. Immunohistochemical staining of the primary tumor demonstrated that constitutive cells were positive for S-100, HMB-45, MiTF, SOX-10, and p16. Melan-A, BRAF V600E, and p63 were negative.

A wide local excision and sentinel lymph node biopsy were performed. The sentinel lymph node biopsy revealed a metastatic neoplasm with cytomorphology identical to the patient's primary

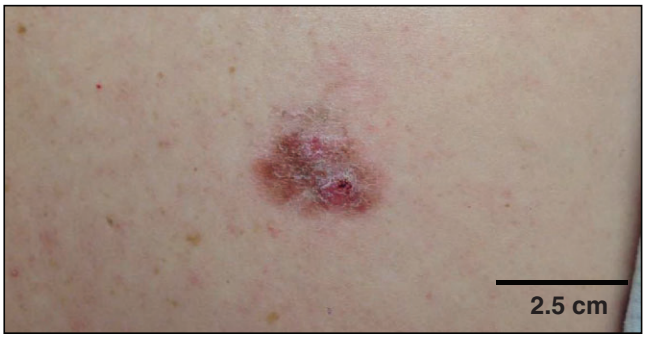

FIGURE 1 Clinical appearance of residual primary melanoma on the right upper back following initial biopsy

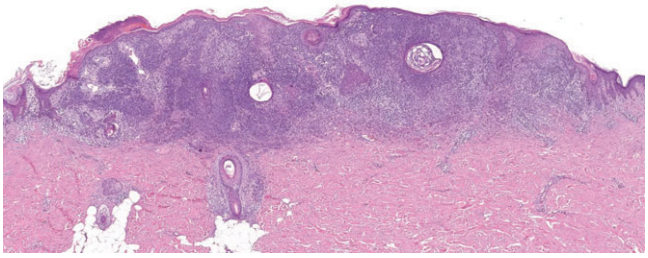

FIGURE 2 Microstaging excision of melanoma reveals a superficial spreading melanoma invasive to Clark's level IV and 1.65 mm Breslow thickness (H&E, original magnification ×23)

melanoma (Figure 3). The tumor was intimately associated with malignant osteoid in keeping with focal osteosarcomatous differentiation. No cartilaginous differentiation was identified. Malignant cells in the metastatic lymph node deposit were immunohistochemically positive for S-100, MiTF, and SOX-10, but failed to express HMB-45, and Melan-A (Figure 4).

The patient had a completion lymph node dissection of the right axilla. The patient's American Joint Committee on Cancer stage was IIIA (T2a, N1, M0). She was subsequently lost to follow-up 1 month after the lymph node dissection.

3 | DISCUSSION

Metastatic malignant melanoma with osteocartilaginous differentiation has been reported in a very small number of case reports. Divergent heterologous elements have been observed in various primary locations, including subungual sites of the fingers and toes, mucosal areas in the nose, mouth, and vagina, and other sites of the body including, the face, back, and shoulder.[1] However, previously reported cases were predominantly of melanomas from subungual, acral, and mucosal sites, with osteocartilaginous differentiation present in the primary or recurrent lesion.[1] Our case is extraordinary in that only the lymph node metastasis revealed osteosarcomatous heterologous elements, with no evidence of divergent differentiation observed in the primary lesion in the routine sections examined.

The mechanism of osteosarcomatous differentiation in metastatic melanoma has not been well characterized. Some cases reported ossification in melanomas that developed at sites of previous surgical trauma, suggesting that the divergent differentiation may represent a

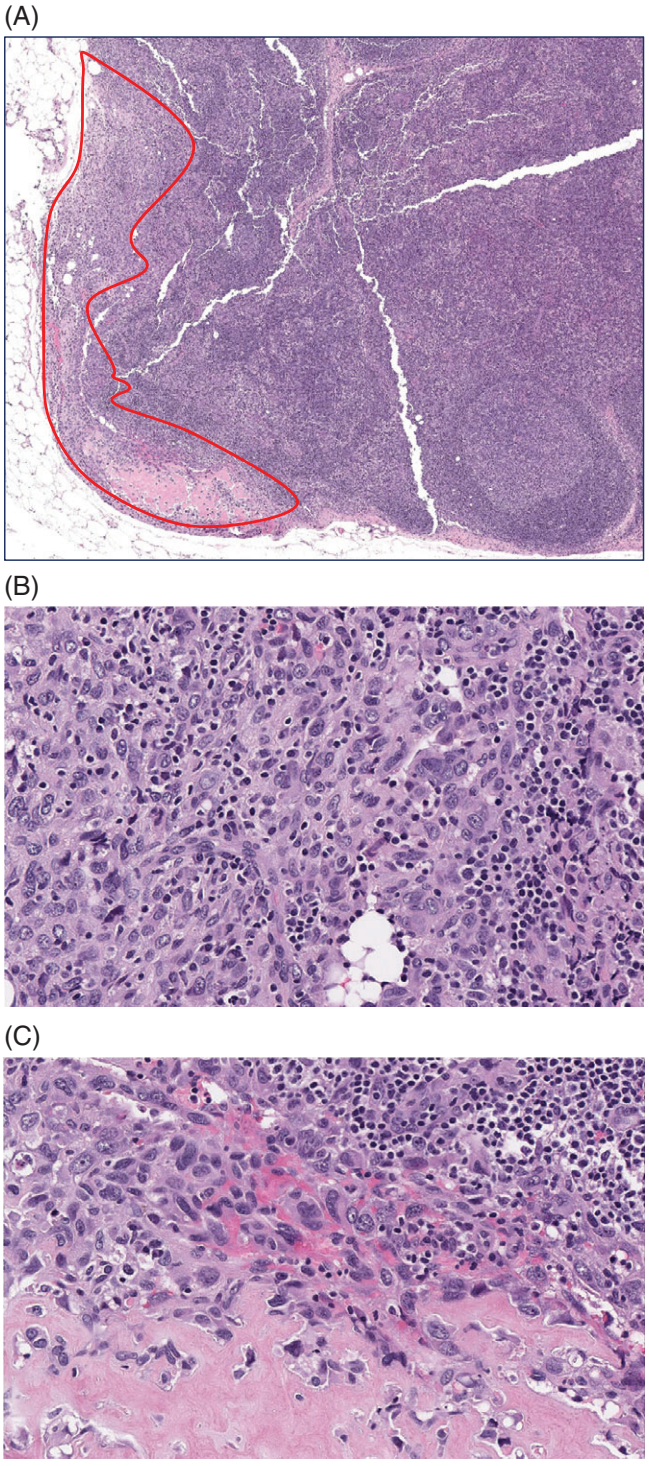

FIGURE 3 Metastatic melanoma (outlined in red) is identified in the right axillary sentinel lymph node with focal osteosarcomatous differentiation (A) (H&E, original magnification ×28). High-power magnifications of melanoma at a distance from the osteoid (B) and adjacent to the osteoid (C) are shown (H&E, original magnification ×400)

reparative response to injury.[25] It has also been hypothesized that melanoma cells undergo mesenchymal metaplasia to form osteosarcomatous elements.[25] In addition, invading melanoma cells in a lymph node may induce molecular cascades that promote further proliferation of tumor cells and activate subsequent divergent differentiation.[25]

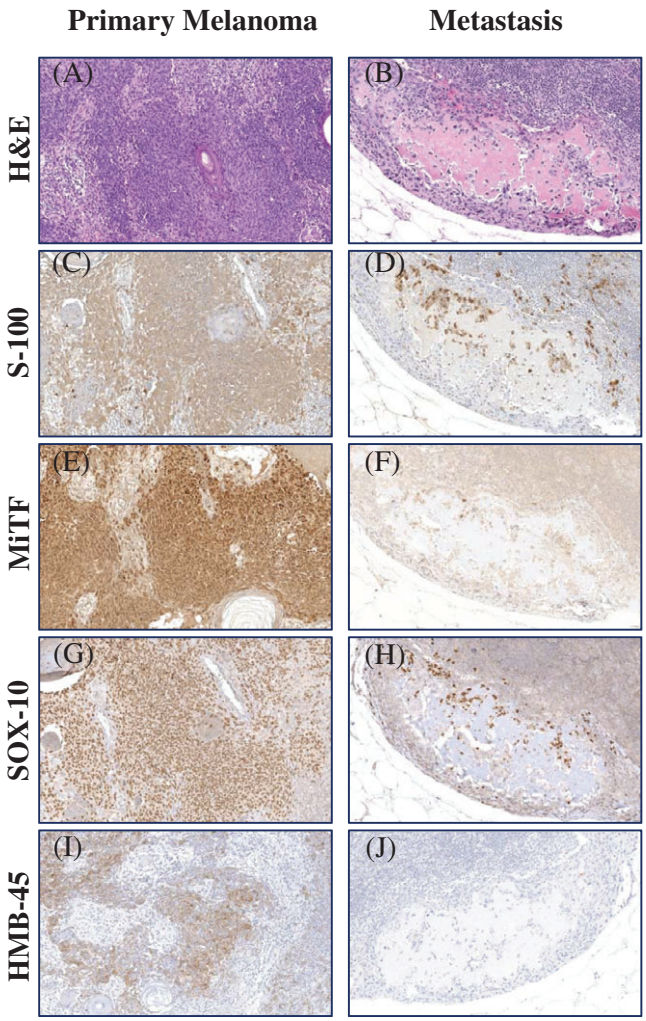

FIGURE 4 Osteosarcomatous differentiation is not observed in the primary lesion (A, H&E) but rather in lymph node metastasis (B, H&E). There is expression of S-100 (C, D), MiTF (E, F), and SOX-10 (G, H) in both the primary melanoma and metastasis. Loss of HMB-45 (I, J) is noted in the metastasis compared to the primary (original magnification ×152)

Melanomas with osteogenic and/or cartilaginous differentiation can pose a diagnostic challenge. They can mimic various other tumors, including metaplastic carcinomas, sarcomas, neuroendocrine tumors, lymphomas, or germ cell tumors.[25] Of the previously reported 38 cases with osteocartilaginous differentiation, 9 were initially misdiagnosed as either osteosarcoma,[10–12,17,27] chondrosarcoma,[19,21,25] or an extraosseous osteogenic sarcoma.[3] In our case, the absence of primary bony involvement, adjacent non-osteosarcomatous melanoma in the metastasis, expression of melanocytic markers by immunohistochemistry (eg, S-100, MiTF, and SOX-10), histological examination revealing identical morphology in a subset of metastatic malignant to those seen in the primary lesion and foci of osteosarcomatous differentiation supported our final diagnosis.

Distinguishing melanoma with osteosarcomatous differentiation from osteosarcoma is clinically very significant, as these diseases require different treatments.[19] Furthermore, osteosarcoma rarely metastasizes to regional lymph nodes and often responds to chemotherapy, whereas metastatic melanoma is not typically responsive to conventional chemotherapy.[19] Our findings suggest that melanoma should be considered in the differential diagnosis for a metastatic bone-forming malignancy of unknown primary in a patient with a history of melanoma, regardless of whether osteosarcomatous differentiation was present in the primary tumor. As in our case, demonstration of melanocytic marker expression may be useful for supporting the diagnosis of melanoma in such cases. The prognosis of malignant melanoma with osteosarcomatous differentiation remains unknown due to the small number of reported cases with significant follow-up.[25]

4 | CONCLUSION

Melanoma with osteosarcomatous differentiation has been documented in a very small number of cases and may pose a diagnostic challenge. Melanomas with divergent heterologous elements can mimic various other tumors that may require different treatments regiments. Attention to the patient's past medical history and careful histopathologic and immunohistochemical examination of representative patient specimens will assist in making the correct diagnosis and ensure appropriate subsequent clinical management.

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