

Metastatic melanoma with heterologous bone after neoadjuvant immunotherapy: diagnostic insights

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Summary

We report a BRAF V600E-mutated cutaneous melanoma (pT3b) with nodal metastases treated with neoadjuvant anti-PD-1 therapy. Axillary lymph node dissection demonstrated residual viable melanoma intimately associated with extensive heterologous lamellar bone formation within the post-treatment tumor bed. Histologic assessment supported a melanoma-related heterologous component rather than a purely reactive stromal phenomenon, underscoring a relevant diagnostic pitfall in treated specimens. The observation also has practical implications for pathological response evaluation after neoadjuvant immunotherapy: in this case, the osseous component was integrated into the viable tumor compartment to avoid underestimation of residual disease. Overall, this case exemplifies the evolving morphobiological spectrum of melanoma in the immunotherapy era, and emphasizes that careful correlation of morphology with the clinical context remains the mainstay to avoid misinterpretation, particularly when uncommon heterologous or metaplastic patterns emerge after immune checkpoint blockade.

Keywords: melanoma, neoadjuvant immunotherapy, anti-PD-1, heterologous ossification, pathological response assessment

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Dear Editor,

We present the case of pT3b, BRAF V600E-mutated melanoma of the shoulder with nodal metastases, treated with neoadjuvant anti-PD-1 therapy.

On subsequent axillary lymph node dissection, clearly recognizable viable melanoma tissue was scored as 30% residual tumor volume (RTV) with an additional 25% represented by lamellar bone at varying degrees of maturation, featuring osteocytes within lacunae and associated osteoclast-like giant cells. The bone tissue was located primarily in the inter-nodal spaces, intimately associated with neoplastic cells. Areas of fibrosis, necrosis, and numerous melanophages were distributed throughout the remaining 45% of the tissue. Histopathological findings are illustrated in Figure 1.

Although current pan-tumor recommendations for pathologic response assessment do not mandate ancillary immunohistochemistry, we performed a focused immunophenotypic work-up given the unusual heter-

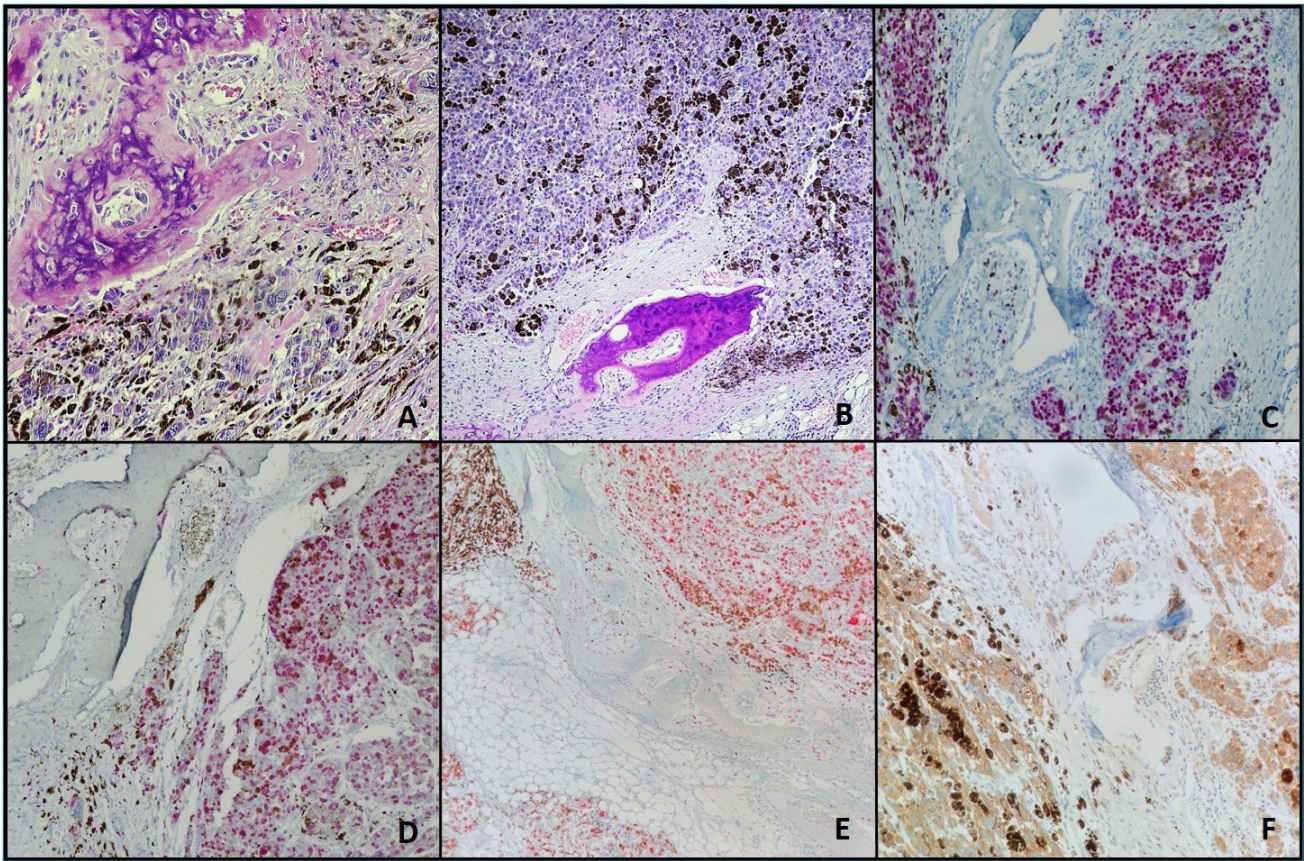


Figure 1. (A) Detail of mature lamellar bone within the metastatic lesion, with osteocytes embedded in lacunae (hematoxylin and eosin, $\times 40$). (B) Close admixture of mature osseous tissue and pigmented epithelioid melanocytic tumor cells (hematoxylin and eosin, $\times 20$). (C) SOX10 immunohistochemistry highlighting melanocytic tumor cells closely apposed to, but not intermingled with, the osseous component ($\times 40$). (D) Ki-67 (MIB1) immunostaining showing a high proliferative index in the melanocytic tumor cells, with absence of labeling in the bone tissue ($\times 40$). (E) Lamellar bone surrounded by a rim of PRAME-positive neoplastic cells ($\times 10$). (F) Lamellar bone surrounded by a rim of BRAF V600E-positive neoplastic cells ($\times 40$).

ologous ossification and the potential diagnostic pitfalls in post-treatment specimens.

Immunohistochemically, the conventional melanoma component expressed melanocytic markers (SOX10, S100, HMB45, and Melan-A) and showed BRAF V600E (VE1) expression. Notably, the atypical cells bordering the osteoid/lamellar bone were negative for SOX10 and Melan-A, but positive for BRAF V600E (VE1) and PRAME, an immunophenotype consistent with de-differentiated melanoma¹. Osteoblasts and some osteocytes were SATB2-positive and negative for melanocytic markers. The Ki-67 (MIB1) proliferative index was 90% in the cellular component, whereas it was unremarkable in the bone component.

Metaplastic melanoma is a rare variant that may present with osseous or chondroid metaplasia, often associated with dedifferentiation and loss of melano-

cytic markers¹. Bone/osteoid formation has been described in both primary and metastatic melanoma in prior reports²⁻⁴. Melanoma metastases with osseous metaplasia are reported in fewer than 50 cases in the literature, with only a minority of such cases involving the nodes^{5,6}; so far, only one case of melanoma transdifferentiation has been reported following neoadjuvant anti-PD-1 therapy⁷.

Recent evidence indicates that immune checkpoint blockade can modulate tumor phenotype, selectively enriching resistant subclones or promoting epigenetic reprogramming toward mesenchymal and osteogenic states⁸. Although PD-1 blockade modulates the RANK-RANKL axis, particularly via increased RANKL expression in activated tumor-infiltrating T cells⁹, there is currently no evidence that immune checkpoint inhibitors directly induce osteogenic differentiation or

heterologous bone formation. Instead, the available data suggest that PD-1 inhibition profoundly reshapes the immune–stromal microenvironment, creating conditions where melanoma can undergo unconventional differentiation. In this context, the temporal association between immunotherapy and the onset of osteogenic morphology supports the hypothesis that treatment contributed to lineage plasticity, rather than simply causing stromal ossification. Only one prior case in the literature documents melanoma transdifferentiation following neoadjuvant anti-PD-1 therapy ⁷. This adaptive reprogramming remodels the tumor microenvironment, contributes to metastatic progression and plays a key role in resistance to systemic therapies ⁸. We therefore think that in our case bone tissue should not be regarded as a stromal response but, instead, as a neoplastic metaplasia, thereby computed as viable tumor (and not as a regression bed), in the pan tumor scoring system ¹⁰.

This case exemplifies the evolving morphobiological spectrum of melanoma in the immunotherapy era. Careful correlation of morphology with the clinical data context remains the mainstay to avoid any misinterpretation.

CONFLICTS OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: GF. Data curation: LP, ML. Investigation (histology/IHC interpretation): LP, GF, ML. Writing – original draft: VF, LP, GF, MV, AF, MS. Writing–review & editing: GF, FB. Supervision: GF, ML. All authors approved the final manuscript.

ETHICAL CONSIDERATION

Written informed consent, as part of the routine diag-

nosis and treatment procedures, was obtained from patients or their guardians according to the Declaration of Helsinki and the study adhered to Good Clinical Practice guidelines.

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