

septa (Fig. 1). The cells formed unilayered or multilayered groups of cells. CK5/6 was heterogeneously positive, frequently in luminal cells. P63 was negative in the NEH tumorlets and foci (including in luminal cells). Lymphocytes were detected at proximity for some of the NEH lesions.

Of interest would be the heterogeneous expression of CK5/6 in the chromogranin-positive and TTF1-positive NEH foci. The expression of CK5/6 in luminal cells, as compared with the normal expression pattern in basal cells of normal bronchial-type epithelia (Supplementary Fig. 1, Supplemental Digital Content 1, <http://links.lww.com/AIMM/A246>), suggested that the chromogranin-positive hyperplastic or proliferative cells (negative for CK5/6) develop extraluminally, toward the alveolar septum tissue rather than toward the lumina, possibly “pushing” luminally the CK5/6-positive cells. Interestingly, p63 was negative in these foci, including in luminal cells, whereas it was positive in the adjacent bronchiolar or bronchiolar-metaplasia-epithelium.

The presence of chromogranin-positive NEH lesions in alveolar septa suggest a multistep process, of bronchiolar metaplasia of the alveoli, undergoing a second change, that of NEH.

In conclusion, NEH foci may show CK5/6 immunohistochemical heterogeneity, suggesting an origin from bronchiolar-metaplasia epithelia besides that from the bronchiolar epithelium.

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HER2-positive Metastatic Melanoma: A Cautionary Tale!

To the Editor:

Malignant melanoma (MM) is well known for its propensity to exhibit varying phenotypic mimicry to a wide range of different malignant neoplasms with diagnostic and therapeutic implications. Metastatic MM with strong HER2 (3+) expression is extremely rare. Antecedent literature on the frequency of HER2 expression is conflicting, ranging from 0% to 5.2% with slight preponderance in primary cutaneous MM over metastatic MM.^{1–4} Emerging genomic analysis of MM indicates the rate of *ERBB2* amplification was 3% in acral and mucosal MM, respectively.⁵ Indeed, a recent report by Gottesdiener et al⁵ documented a patient with advanced-stage (T4bN1a) acral MM with lung metastasis who was

successfully treated with trastuzumab (Her2/Neu receptor tyrosine kinase inhibitor) with durable complete response after failing treatment with combinatorial ipilimumab and nivolumab, suggesting a potential therapeutic role for a subset of MM. Importantly, given its rarity, MM with diffuse and strong HER2 (3+) reactivity may elicit an alternate diagnosis particularly in the context of the relevant clinical history of breast cancer and no prior history of MM. Herein, we report a cautionary tale of strong HER2 (3+)-positive metastatic MM of the unknown primary site.

A 73-year-old woman presented for increasing pain in the right hip. Two months ago, she had a right total hip arthroplasty secondary to arthritis. Imaging studies including plain radiographs and computed tomography scans demonstrated a lytic lesion in the supra-acetabular ilium just above her total hip arthroplasty cup (Fig. 1). On physical examination, there was no palpable mass over her right hip and the surgical incision was well-healed. Her past medical history is significant for clear cell carcinoma of right ovary



FIGURE 1. Computed tomography scan image (coronal view). A lytic lesion is noted in the supra-acetabular ilium just above the arthroplastic hip cup.

The authors declare no conflict of interest.

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status post resection and adjuvant chemotherapy in 2004 and left breast ductal carcinoma in situ status post bilateral mastectomy in 2012. Computed tomography-guided bone biopsy was performed. Microscopic examination shows infiltrative epithelioid cells exhibiting a nested and trabecular pattern composed of a small amount of amphiphilic cytoplasm with

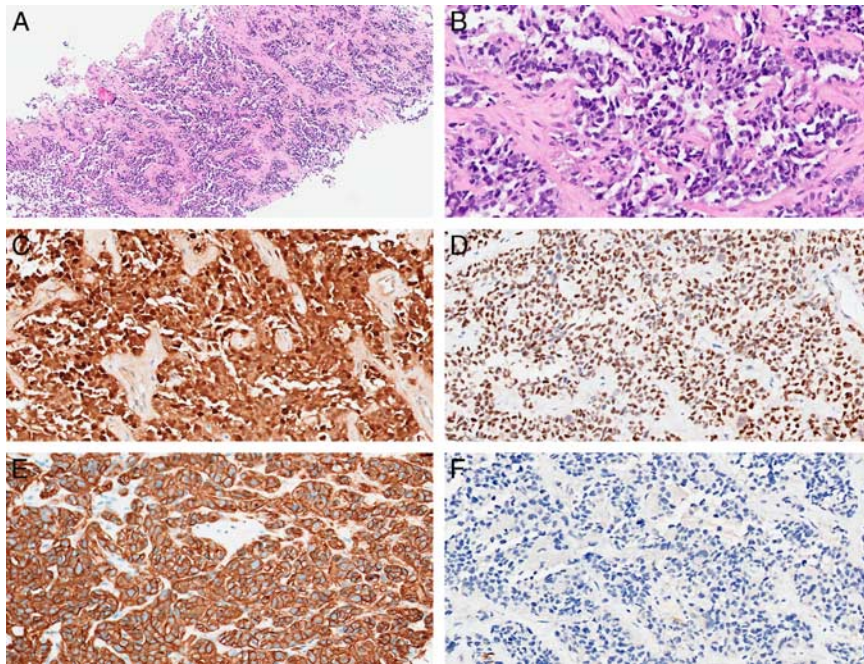


FIGURE 2. A and B, Hematoxylin and eosin stains of core biopsy of the lesion. The tumor cells show infiltrating nested or trabecular pattern with amphiphilic cytoplasm and round or ovoid nuclei (original magnification: A, $\times 10$; B, $\times 40$). The cells are diffusely positive for S-100 (C) and SOX-10 (D), negative for pan-cytokeratin AE1/3 (F); HER2 is strongly positive, score 3+ (E) (HER2 antibody: clone 4B5; Ventana Medical Systems Inc., Tuscon, AZ).

round or ovoid nuclei (Figs. 2A, B). In view of the history of ovarian clear cell carcinoma and breast cancer, immunostains for these 2 entities were

first attempted. By immunohistochemistry, the cells were strongly and diffusely positive for HER2 (3+) and negative for AE1/3, CK7, GATA3,

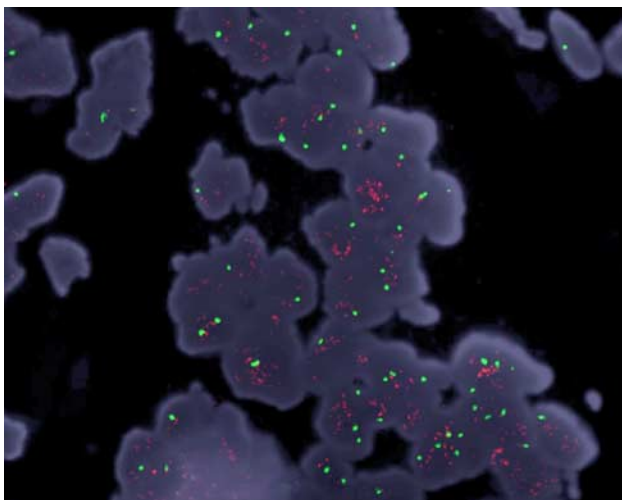


FIGURE 3. HER2 fluorescence in situ hybridization result. The fluorescence in situ hybridization analysis with CEP17 probe was performed using the dual-color Vysis Food and Drug Administration (FDA)-approved PathVysion HER2 DNA Probe Kit (Abbott Molecular, Des Plaines, IL). The signals for the HER2 gene and CEP17 were visualized under a fluorescence microscope using appropriate filters. Red dots represent HER2 signals, green dots represent CEP17 signals.

PAX8, HNF-1 β , Napsin A, estrogen receptor, and progesterone receptor. HER2 fluorescence in situ hybridization test is positive for HER2 gene amplification (HER2 to CEP17 ratio is 5.9, average HER2 copy per cell is 14) (Fig. 3). This immunoprofile does not support metastatic breast or ovarian cancer. Additional immunohistochemical stains showed the tumor cells were strongly and diffusely positive for SOX-10, S-100, and MiTF, and negative other markers including MNF116, CAM5.2, CK20, TTF-1, CDX2, CD31, ERG, HMB45, and MART-1 (Figs. 2C–F). These results raise the differential diagnosis of metastatic melanoma or primary clear cell sarcoma of bone. Primary clear cell sarcoma of bone is extremely rare, and the overwhelming majority of such cases have EWSR1 translocation.⁶ Fluorescence in situ hybridization analysis for EWSR1 gene rearrangement on this biopsy specimen was negative. Next-generation sequencing analysis was wild-type for BRAF, NRAS, KRAS, KIT, and CDKN2A/p16 except for TP53 mutation.⁷ In the end, the overall features were considered to be consistent with metastatic MM. Careful clinical examination did not uncover any primary cutaneous MM and the patient does not have a known history of MM. Nonetheless, this clinical scenario is not uncommon as there are several reported cases of metastatic MM in which no primary site was discovered. It is conceivable that a patient's primary cutaneous MM lesion may have undergone regression. Unfortunately, the patient deteriorated very quickly and succumbed to the disease shortly after the presentation.

In summary, we present a unique and exquisitely rare case of strong and diffuse HER2 expression in metastatic MM with no prior history of cutaneous MM. Previous studies have shown that only limited numbers of melanomas are HER2-positive.⁴ This observation expands the spectrum of the broad range of immunophenotypic profile of MM that warrants caution in the interpretation of HER2-positive metastatic tumor. More so, it also suggests a potential therapeutic benefit from anti-HER2 targeted therapy.

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