

Aberrant Expression of CD56 in Metastatic Malignant Melanoma

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PRACTICE POINTS

- The diagnosis of melanoma often is challenging as tumors can show notable histologic diversity and have the potential to express aberrant immunophenotypes including CD56 expression.
- Because expression of CD56 in melanoma is rare, it is important to be aware of this potential aberrant staining pattern.
- Recognizing this heterogeneity and divergent differentiation as well as knowing potential aberrant immunohistochemical staining patterns are imperative for accurate and timely diagnosis.

To the Editor:

Many types of neoplasms can show aberrant immunoreactivity or unexpected expression of markers.¹ Malignant melanoma is a tumor that can show not only aberrant immunohistochemical staining patterns but also notable histologic diversity,^{1,2} which often makes the diagnosis of melanoma challenging and ultimately can lead to diagnostic uncertainty.²

The incidence of malignant melanoma continues to grow.³ Maintaining a high degree of suspicion for this disease, recognizing its heterogeneity and divergent differentiation, and knowing potential aberrant immunohistochemical staining patterns are imperative for accurate diagnosis.

A 36-year-old man presented to a primary care physician with right-sided chest pain, upper and lower back aches, bilateral hip pain, neck pain, headache, night sweats, chills, and nausea. After infectious causes were ruled out, he was placed on a steroid taper without improvement. He presented to the emergency department a few days later with muscle spasms and was found to also have diffuse abdominal tenderness and guarding. The patient's medical history was noncontributory; he was a lifelong nonsmoker. Laboratory studies revealed elevated levels of alanine aminotransferase and C-reactive protein. Computed tomography of the chest and abdomen revealed innumerable liver and lung lesions that were suspicious for metastatic malignancy. A liver biopsy revealed nests and sheets of metastatic tumor with pleomorphic nuclei, inconspicuous nucleoli, and areas of intranuclear clearing (Figures 1 and 2). Immunohistochemical staining was performed to further characterize the tumor. Neoplastic cells were positive for MART-1 (also known as Melan-A and melanoma-associated antigen recognized by T cells) (Figure 3), SOX10, S-100, HMB-45, and vimentin. Nonspecific staining with CD56 (Figure 4), a neuroendocrine marker, also was noted; however, the neoplasm was negative for synaptophysin, another neuroendocrine marker. Other markers for which staining was negative included pan-keratin, CD138 (syndecan-1), desmin, placental alkaline phosphatase (PLAP), inhibin, OCT-4, cytokeratin 7, and cytokeratin 20. This staining pattern was compatible with metastatic melanoma with aberrant CD56 expression.

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The authors report no conflict of interest.

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doi:10.12788/cutis.0901

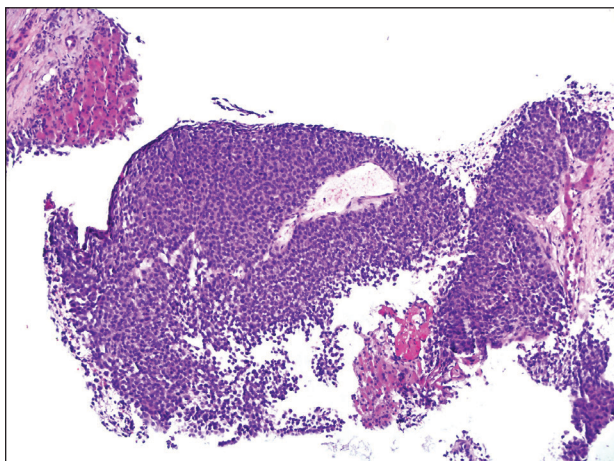


FIGURE 1. Histopathology of a liver biopsy revealed metastatic melanoma adjacent to uninvolved liver parenchyma as well as large nests and sheets of tumor with frequent mitotic figures (H&E, original magnification $\times 100$).

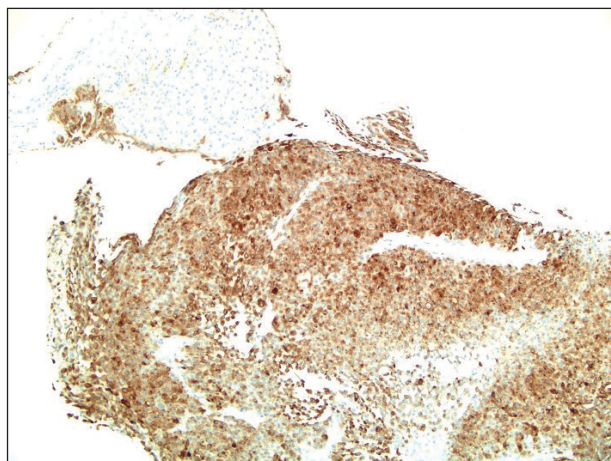


FIGURE 3. Neoplastic cells of metastatic melanoma demonstrated strong and diffuse staining with MART-1 (also known as Melan-A and melanoma-associated antigen recognized by T cells) immunostain (original magnification $\times 100$).

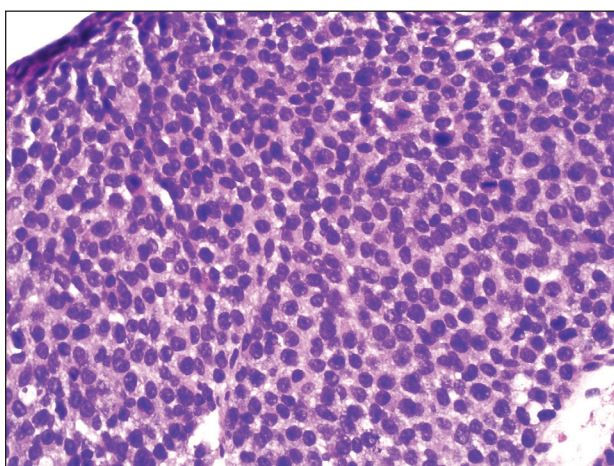


FIGURE 2. Histopathology revealed large neoplastic cells of malignant melanoma with pleomorphic nuclei, inconspicuous nucleoli, and areas of intranuclear clearing (H&E, original magnification $\times 200$).

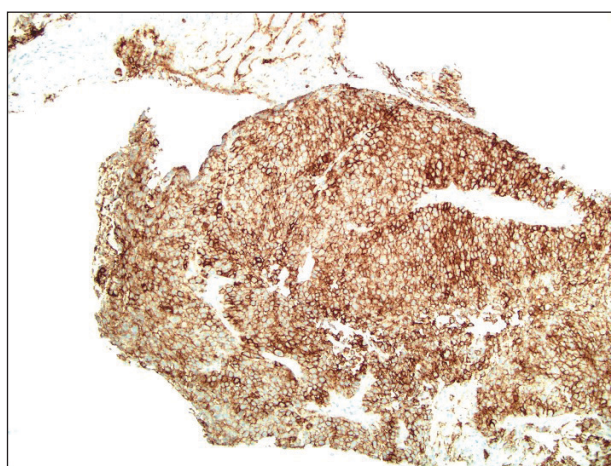


FIGURE 4. Neoplastic cells of malignant melanoma demonstrated strong and diffuse staining with CD56 immunohistochemical stain (original magnification $\times 100$).

BRAFV600E immunohistochemical staining also was performed and showed strong and diffuse positivity within neoplastic cells. A subsequent positron emission tomography scan revealed widespread metastatic disease involving the lungs, liver, spleen, and bones. The patient did not have a history of an excised skin lesion; no primary cutaneous or mucosal lesions were identified.

The patient was started on targeted therapy with trametinib, a mitogen-activated extracellular signal-related kinase kinase (MEK) inhibitor, and dabrafenib, a BRAF inhibitor. The disease continued to progress; he developed extensive leptomeningeal metastatic disease for which palliative radiation therapy was administered. The patient died 4 months after the initial diagnosis.

More than 90% of melanoma cases are of cutaneous origin; however, 4% to 8% of cases present as a metastatic

lesion in the absence of an identified primary lesion,⁴ similar to our patient. The diagnosis of melanoma often is challenging; the tumor can show notable histologic diversity and has the potential to express aberrant immunophenotypes.^{1,2} The histologic diversity of melanoma includes a variety of architectural patterns (eg, nests, trabeculae, fascicular, pseudoglandular, pseudopapillary, or pseudorosette patterns), cytomorphic features, and stromal changes. Cytomorphic features of melanoma can be large pleomorphic cells; small cells; spindle cells; clear cells; signet-ring cells; and rhabdoid, plasmacytoid, and balloon cells.⁵

Melanoma can mimic carcinoma, sarcoma, lymphoma, benign stromal tumors, plasmacytoma, and germ-cell tumors.⁵ Nuclei can binucleated, multinucleated, or lobated and may contain inclusions or grooves. Stroma may become

myxoid or desmoplastic in appearance or rarely show granulomatous inflammation or osteoclastic giant cells.⁵ These variations render the diagnosis of melanoma challenging and ultimately can lead to diagnostic uncertainty.

Melanomas typically express MART-1, HMB-45, S-100, tyrosinase, NK1C3, vimentin, and neuron-specific enolase. However, melanoma is among the many neoplasms that sometimes exhibit aberrant immunoreactivity and differentiation toward nonmelanocytic elements.⁶ The most commonly expressed immunophenotypic aberration is cytokeratin, especially the low-molecular-weight keratin marker CAM5.2.⁵ CAM5.2 positivity also is seen more often in metastatic melanoma. Melanomas rarely express other intermediate filaments, including desmin, neurofilament protein, and glial fibrillary acidic protein; expression of smooth-muscle actin is rare.⁵

Only a few cases of melanoma showing expression of neuroendocrine markers have been reported. However, one study reported synaptophysin positivity in 29% (10/34) of cases of primary and metastatic melanoma, making the stain a relatively common finding.¹

In contrast, expression of CD56 (also known as neural-cell adhesion molecule 1) in melanoma has been reported only rarely. CD56 is a nonspecific neuroendocrine marker that normally is expressed on neurons, glial tissue, skeletal muscle, and natural killer cells. Riddle and Bui⁷ reported a case of metastatic malignant melanoma with focal CD56 positivity and no expression of other neuroendocrine markers, similar to our patient. Suzuki and colleagues⁴ also reported a case of melanoma metastatic to bone marrow that showed CD56 expression in true nonhematologic tumor cells and negative immunoreactivity with synaptophysin and chromogranin A.

It is important to document cases of melanoma that express neuroendocrine markers to prevent an incorrect diagnosis of a neuroendocrine tumor.¹ In some cases, distinguishing amelanotic melanoma from poorly differentiated squamous cell carcinoma, neuroendocrine tumor, and lymphoma can be difficult.⁵

The term *neuroendocrine differentiation* is reserved for cases of melanoma that show areas of ultrastructural

change consistent with a neuroendocrine tumor.² Neuroendocrine differentiation in melanoma is not common; its prognostic significance is unknown.⁸ We do not consider our case to be true neuroendocrine differentiation, as the tumor lacked the morphologic changes of a neuroendocrine tumor. Furthermore, CD56 is a nonspecific neuroendocrine marker, and the tumor was negative for synaptophysin.

Melanoma has the potential to show notable histologic diversity as well as aberrant immunohistochemical staining patterns.^{1,2} Our patient had metastatic melanoma with aberrant neuroendocrine expression of CD56, which could have been a potential diagnostic pitfall. Because expression of CD56 in melanoma is rare, it is imperative to recognize this potential aberrant staining pattern to ensure the accurate diagnosis of melanoma and appropriate provision of care.

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