Diagnostic dilemma: HMB-45 and Melan-A negative tumor, can it be still a melanoma?: MITF (Microphthalmia-associated transcription factor) stain may confirm the diagnosis

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Abstract
We report a case of dermal malignant melanoma that stained negatively for commonly done immunostains, HMB-45, and Melan-A. It stained weakly positive for S-100 protein, a less specific marker for melanocytes. The diagnosis was established by strongly positive immunostaining by MITF (microphthalmia-associated transcription factor). A brief review of the MITF and its usefulness in the diagnosis of melanoma are presented.

SOURCE OF SUPPORT
None

CASE REPORT
An 82-year-old male presented with a 1-cm raised dermal nodule on the medial side of the right foot that has been present for unknown duration. There was no pigmented lesion of the skin. The patient denied any previous history of melanoma.

The biopsied skin measured 1.8 x 1.4 x 1.0 cm and showed a well-circumscribed white, firm dermal nodule. The epidermis was intact.

On microscopic examination, the tumor mass was composed of large dysplastic epithelioid and spindle cells forming nests and sheets. The cell nests were surrounded by thin bundles of collagen. The tumor cells contained large, hyperchromic nuclei with prominent red nucleoli. There were many mitotic figures. There was no ulceration or epidermal invasion by the tumor cells. The lesion extended from papillary to deep dermis (Figures 1, 2).

Figure 1
Figure 1: Malignant melanoma, H&E, 4x
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- **Figure 2**: Malignant melanoma, H&E, 20x
- **Figure 3**: Tumor is negative for HMB-45
- **Figure 4**: Tumor is negative for Melan-A
- **Figure 5**: Weakly positive nuclear and cytoplasmic stain of the melanoma cells by S-100 protein
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Figure 6
Figure 6: Strongly positive nuclear stain of the melanoma cells by MITF

The tumor was immunostained with HMB-45, Melan-A, and S-100 protein. The tumor cells were completely negative for HMB-45 and Melan-A and were weakly positive for S-100 protein (Figures 3, 4, 5).

Additional immunostains, such as, tyrosinase, CD 68, and SMA were performed to exclude melanocytic-, histiocytic- or smooth muscle origin of the tumor; they all stained negatively. Finally, the tumor was immunostained with MITF, because the light microscopic feature was very suggestive of melanoma. The MITF stain showed a strongly positive nuclear stain of the tumor cells (Figure 6) confirming the diagnosis of melanoma.

COMMENT
Malignant melanoma is the most serious form of skin cancer. Although it accounts for only 4 percent of all dermatologic cancers, it is responsible for 80 percent of deaths from skin malignancy. In the clinical practice, one may rarely find a dermal nodule in the absence of a primary melanocytic lesion. A biopsy of the lesion may show a neoplasm with histological features of melanoma. Usually, the diagnosis is confirmed by immunostaining with HMB-45, Melan-A, and S-100 protein, all of which are usually positive in melanocytes. The nodule may represent a primary melanoma in the dermis or a metastatic nodule from some other sites. If such a tumor does not stain for HMB-45 or Melan-A, a specific diagnosis of melanoma cannot be made with certainty.

Microphthalmia-associated transcription factor (MITF) is a melanocyte-specific transcription factor that plays a key role in melanocyte development, survival and differentiation. MITF appears to contribute to melanocyte survival by increasing the expression of the BCL-2 gene, a key antiapoptotic component. It also regulates the transcription of silver homologue (SILV) the melanocytic-specific genes melan-A(MLANA), whose immunohistochemical detection points to the diagnosis of melanoma. Malignant melanocytic cells appear to have an increased number of MIFT loci. This increase is accompanied by the amplification of the MITF protein, which subsequently enhances the expression of BCL-2 gene [1]. King et al [2] first reported that the malignant melanoma cells showed a 100% positive staining for MITF with a nuclear pattern of reactivity. MITF staining was positive for 76 specimens of melanoma that failed to stain for either HMB-45 or S-100. Additional reports [3, 4] have confirmed that MITF is a very sensitive and specific tumor marker for melanoma cells.

HMB-45 is a widely used immunohistochemical stain for detection of primary as well as metastatic melanoma. This method uses monoclonal antibodies to a glycoprotein (gp100) that is present in cytoplasmic premelanosomes. In immunohistochemical assays, this antibody reacts with melanoma cells, junctional nevus cells, and fetal melanocytes. Melan-A is a differentiation antigen expressed in all melanocytic cytoplasm, and is reported to be positive in most cases of melanoma. It also stains positively in adrenal cortex, granulosa and theca cells of ovary, and ledig cells. S-100 protein is calcium binding protein, which mostly distributed in the cytoplasm. This antibody recognizes all the S-100 isoforms and stains schwannomas, ependymomas, astrogliomas, and almost all benign and malignant melanomas and their metastases. S-100 protein is also expressed in the antigen presenting cells such as the Langerhan cells in skin and interdigitating reticulum cells in the paracortex of lymph nodes.

In our case, the morphology of tumor indicated a malignant melanoma. However, the tumor cells stained negatively for traditional melanocytic markers, HMB-45 and Melan-A, and weakly positive for S-100. It did, however, show strong positivity for MITF. Our observation confirms that a stain for MITF, a specific nuclear marker for melanocytes may be very useful in evaluating biopsies from a suspicious melanoma cases when all other traditional melanocyte markers are negative. Otherwise an HMB-45
and Melan-A negative tumor could be easily interpreted as a non-melanocytic tumor.

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References
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