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Value of melanocytic-associated immunohistochemical markers in the diagnosis of malignant melanoma: a review and update☆

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Summary Since the identification of S100 protein as an immunohistochemical marker that could be useful in the diagnosis of melanoma in the early 1980s, a large number of other melanocytic-associated markers that could potentially be used to assist in the differential diagnosis of these tumors have also been investigated. A great variation exists, however, among these markers, not only in their expression in some subtypes of melanoma, particularly desmoplastic melanoma, but also in their specificity because some of them can also be expressed in nonmelanocytic neoplasms, including various types of soft tissue tumors and carcinomas. This article reviews the information that is currently available on the practical value of some of the markers that have more often been recommended for assisting in the diagnosis of melanomas, including those that have only recently become available.

1. Introduction

Melanomas characteristically can present a diverse array of cytomorphologic features and grow in a wide array of histologic patterns. Based on their morphology, a broad range of histopathologic variants including spindle cell, small cell, clear cell, signet ring–like cell, myxoid, desmoplastic, rhabdoid, ballooning, and plasmacytoid have been described [1-5]. In addition, melanomas can undergo Schwannian, fibroblastic/myofibroblastic, smooth muscle, rhabdomyoblastic, osteocartilaginous, and ganglionic/ganglioneuroblastic differentiation [4]. Owing to their wide range of morphologic features and because some melanomas lack melanin, these tumors can potentially be confused with a diverse array of other neoplasms including lymphomas, poorly differentiated carcinomas, neuroendocrine carcinomas, sarcomas, and germ-cell tumors. Immunohistochemical studies, however, can greatly facilitate the differential diagnosis. The purpose of this article is to review the current information on the various melanocytic-associated immunohistochemical markers that have been recommended to assist in the diagnosis of melanomas (Table 1). Particular emphasis will be placed on newly identified markers and those for which there is great interest among surgical pathologists.

2. S100 protein

The S100 protein family constitutes the largest group within the Ca^{2+}-binding EF-hand (helix-E–loop–helix-F) protein superfamily. In 1965, Moore [6] discovered a protein fraction extracted from bovine brain that he named S100

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Table 1 Melanocytic-associated markers that have been suggested as being useful in the diagnosis of melanoma

Marker	Current value/comments
S100 protein	Useful. It was the first marker that proved to be useful in the diagnosis of melanoma. The sensitivity is very high (~93%-100%), and it is commonly expressed in all subtypes of melanoma, including desmoplastic melanoma. Its specificity, however, is low because it can be expressed in a wide variety of other tumors. Because of this, S100 should be used in association with other markers. The staining pattern is nuclear and cytoplasmic, and typically strong and diffuse.
HMB-45	Very useful. It is very specific for melanocytic tumors, but its sensitivity for melanoma is lower (~70%-90%) than that in S100. Only ~10% of desmoplastic melanomas are HMB-45 positive. Clear cell sarcomas, PEComas, melanocytic schwannomas, meningeal melanocytomas, some ovarian steroid tumors, and renal cell carcinomas with the t(6;11)(p29;q12) translocation express this marker. The staining pattern is cytoplasmic and finely granular.
NKI/beteb	Useful on limited information. Similar to HMB-45, the NKI/beteb monoclonal antibody reacts with the PMEL17/pg100 antigen, but it recognizes a different epitope. In contrast to HMB-45, NKI/beteb stains adult melanocytes of the skin.
Melan A (MART-1)	Very useful. It has a sensitivity of ~85%-97% for primary and ~57%-92% for metastatic melanoma and a specificity of 95%-100%. It is also expressed in PEComas and clear cell sarcomas. Clone A103 also stains adrenal cortical and sex-cord tumors. In contrast to S100, melan A is not expressed in dendritic cells in lymph nodes. The staining pattern is cytoplasmic.
Tyrosinase	Very useful. Approximately 80%-90% of melanomas express this marker. It is also highly specific (~97%-100%). Only a small percentage (~6%) of desmoplastic melanomas are positive. Most clear cell sarcomas and pigmented neurofibromas, and a small percentage of angiomyolipomas (~20%) express this marker. The staining pattern is cytoplasmic.
PNL2	Very useful. It is positive in most (~75%-100%) primary and metastatic epithelioid melanomas. Desmoplastic melanomas are almost invariably negative. Clear cell sarcomas, PEComas, and melanocytic schwannomas can be positive. All nonmelanocytic tumors investigated, including various types of carcinomas, have been negative. The staining pattern is cytoplasmic.
MITF	Limited utility. It is expressed in most (~80%-100%) of all melanoma subtypes including desmoplastic (~50%). Its specificity, however, is low because it is present in a wide variety of neoplasms, especially spindle cell mesenchymal and lymphoid neoplasms, as well as in some carcinomas. The staining pattern is nuclear.
KBA.62	Limited utility. It is positive in a high percentage (~90%) of all primary and metastatic melanoma subtypes. Its specificity is low because it can be expressed in a wide range of epithelial and mesenchymal neoplasms. Because of its high sensitivity for desmoplastic melanomas, when used in conjunction with S100, it can assist in their diagnosis. It can also be helpful in the detection of micrometastases in sentinel lymph nodes. The staining pattern is membranous and cytoplasmic.
SOX10	Very useful on limited information. It is the most recently recognized marker that has been found to be useful in the diagnosis of melanomas. The few studies that have been published indicate that this marker is very sensitive (97%-100%) for both primary and metastatic melanomas. It is expressed in all melanoma subtypes including desmoplastic melanoma (~80%-100%). It is also positive in clear cell sarcomas and peripheral nerve sheath tumors, but appears to be absent in angiomyolipomas. All other mesenchymal tumors and carcinomas have been negative, but the number of studies on these tumors is limited. Because of its high sensitivity and specificity, it is useful in the detection of micrometastases in sentinel lymph nodes. The staining pattern is nuclear.
MC1R	Insufficient information. It appears to be a very sensitive marker for melanoma; however, information regarding its expression in nonmelanocytic tumors is very limited.
CD146 (Mel-CAM)	Limited utility. It is commonly expressed in advanced and metastatic melanomas. Because of its high sensitivity for desmoplastic melanomas, it has been suggested that, when used in conjunction with S100, this marker can assist in the diagnosis of these tumors.
NKI/C3	Not useful. It is very sensitive for melanocytic tumors, but its specificity is very low.
p75NGFR	Not useful. It has been suggested that this marker can assist in the diagnosis of desmoplastic melanomas when S100 is negative or focally positive. Better markers that can assist in this diagnosis, however, are currently available.

because of its solubility in a 100% saturated solution with ammonium sulfate at neutral pH. Several years later, it was shown that this was a protein fraction that consisted of 2 closely related proteins (S100B and S100A, also known as S100A1) and that it was not brain specific as was initially thought [7,8]. At present, the S100 protein family comprises at least 25 members, which are encoded by several genes, and many of which are located on chromosome 1q21 in the so-called epidermal differentiation cluster, an area that is frequently rearranged in several tumors including melanomas [9,10]. The nomenclature of S100 proteins is very complex because each protein is known by several names. This, however, has been simplified by the introduction of the current nomenclature [11]. S100 proteins are small, acidic proteins, 10 to 12 kd in size, that are exclusively found in vertebrates and that have the ability to form homodimers,