Q & A Column, 7/14

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Submit a Question

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Q. Our laboratory is thinking of validating additional immunostains to aid in identifying metastatic melanoma. What are the best markers to identify metastatic melanoma?

A. Antibodies to S100 protein were the first immunostains used to identify melanomas. Although many studies have shown that S100 demonstrates a very high rate of sensitivity as a melanoma marker (approaching 100 percent), it lacks specificity due to its expression in a subset of carcinomas and mesenchymal neoplasms. Therefore, use of antibodies to S100 protein to identify metastatic melanoma has required the addition of confirmatory melanocyte-restricted markers, such as HMB45 and melan A (MART-1), which have conventionally been the primary go-to melanoma markers for many years.[1]

Both HMB45 and melan A exhibit a sensitivity of at least about 85 percent in the setting of metastatic melanoma (specifically, in those tumors showing epithelioid morphology), but are typically negative in spindle cell melanomas.[1,2] Furthermore, other neoplasms can exhibit HMB45 or melan A expression, or both, including PEComa, melanotic schwannoma, adrenal cortical neoplasms (melan A only), clear cell sarcoma, and a subtype of translocation-associated renal cell carcinoma. Additional markers that have demonstrated varying levels of success at identifying metastatic melanomas include antibodies to tyrosinase (enzyme involved in the synthesis of melanin), microphthalmia-associated transcription factor (MITF, transcription factor involved in differentiation of melanocytes among other cells), and NKI/C3 (melanoma-associated antigen). Although tyrosinase exhibits a similar level of sensitivity and specificity as HMB45 and melan A, the use of NKI/C3 and MITF is limited due to their lack of specificity.[1]

More recently, a novel monoclonal antibody, PNL2 (antigen not yet identified), has been introduced as a potential marker of melanomas and has exhibited a very high level of sensitivity (surpassing melan A and HMB45 in the limited number of published studies). PNL2 is also expressed in some spindle cell melanomas but not desmoplastic melanomas and is similarly reported in clear cell sarcoma, PEComa, and melanotic schwannomas.[1,3]

Of very recent interest is the neural crest transcription factor SOX10, which at this juncture has been evaluated in a limited number of studies but has shown great promise at identifying melanomas, particularly desmoplastic melanomas. A very high rate of SOX10 expression has been identified in desmoplastic melanomas (97–100 percent, most often in a diffuse pattern of staining), superior to the traditionally used S100 protein.[4,5] Also in comparison with S100, SOX10 exhibits a higher level of specificity, in general, in distinguishing between the non-neural, non-melanocytic sarcomas such as synovial sarcoma, Ewing sarcoma, chondrosarcoma, and rhabdomyosarcoma.6 Additionally, in the setting of potential histologic mimics of desmoplastic melanomas, all other tumors except for malignant peripheral nerve sheath tumors were reported as negative for SOX10 (including

cutaneous spindle cell carcinomas, atypical fibroxanthomas, and dermal/subcutaneous sarcomas).[4] Furthermore, because of the lack of expression in dendritic cells, in contrast to S100, SOX10 may be more useful in screening for micrometastatic melanoma in sentinel lymph nodes. Lastly, studies have shown thus far that similar to HMB45 and melan A, SOX10 is expressed in clear cell sarcomas, but in contrast does not appear to be expressed in angiomyolipoma.[1,7]

In summary, although a combination of S100 and primarily HMB45 and/or melan A have been the typical panel used in the past to identify melanomas, there seems to be sufficient evidence, even in the relatively limited number of studies, to justify the addition of SOX10, in an attempt to improve identification of desmoplastic melanoma, and potentially PNL2, in an attempt to increase sensitivity beyond HMB45 and melan A at identifying melanomas with epithelioid morphology.

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Q. In light of the development of high-sensitivity cardiac troponin assays, is there a clinically significant reason to continue performing CK-MB assays and, if so, are there standardized criteria for when to report an index rather than the mass units?

A. More than a decade ago, prominent cardiac disease and laboratory medicine experts called for a change from CK-MB assays to earlier generation cardiac troponin tests as the new standard of cardiac disease biomarker tests.[1] Since then, a central role for troponin testing in management of chest pain patients with suspected acute myocardial infarction and in prognostic identification of patients at increased risk of adverse cardiac disease outcomes has been the focus of recommendations in major clinical cardiology and laboratory management practice guidelines.[2,3] But development of high-sensitivity cardiac troponin assays is more recent, and the FDA had not yet approved any high-sensitivity cardiac troponin assays at the time of this writing. Generally, contemporary cardiac troponin tests are considered to be fourth-generation assays while high-sensitivity cardiac troponin tests are fifth-generation assays.

In the aforementioned clinical practice guidelines and others that cover a spectrum of cardiac diseases, CK-MB mass testing, including relative index calculation, is described as having limited clinical utility. It is recommended only when troponin testing is unavailable or, potentially, in one infrequent clinical scenario: a recent AMI patient suffers a second AMI in the window in which a cardiac troponin level would still be elevated. In this instance, CK-MB mass and relative index measurement would be of use if there was no way to make this diagnosis other than with these results, the levels of which would have returned to normal after the initial AMI and before the second AMI. These two general situations are rarely encountered in practice. Therefore, some institutions have removed CK-MB mass assays from their test menu altogether, and a large majority of institutions have at least removed CK-MB mass determinations and relative index calculations from their chest-pain triage pathways.

Historically, the criterion for when to report an index value for CK-MB mass as an additional result component to (but not instead of) the mass result is if the total CK activity is abnormally elevated. This is the convention that should be used in labs that continue to report CK-MB mass results. Reporting a relative index value result along with CK-MB mass and total CK activity may be useful in the workup of selected clinical problems, such as skeletal muscle disorders and crush injury due to trauma. But these scenarios are rarely encountered in routine clinical practice, thereby further limiting the utility of CK-MB measurements. A relative index value is calculated by dividing the CK-MB mass level (in ng/mL) by the total CK activity (in IU/L) and multiplying the result by 100. While this is identical to a percentage calculation, the result is referred to as a CK-MB relative index value since units of the numerator (mass) and denominator (activity) are not the same.

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