

# Application of Immunohistochemistry to the Diagnosis of Malignant Mesothelioma

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• **Context.**—The diagnosis of malignant mesothelioma (MM) is rendered with the aid of immunohistochemistry to demonstrate the presence of “mesothelial,” “epithelial,” or “sarcomatous” differentiation. Antibody panels that have been proposed for the distinction between MM and other neoplasms usually include 2 or more epithelial markers used to exclude the diagnosis of a carcinoma, such as monoclonal and polyclonal carcinoembryonic antigen, Ber-EP4, B72.3, CD15, MOC-31, thyroid transcription factor 1, BG8, and others, and 2 or more mesothelial markers used to confirm the diagnosis of MM, such as cytokeratin 5/6, calretinin, HBME-1, thrombomodulin, WT-1, mesothelin, D2-40, and podoplanin. In general, most antibody panels provide excellent sensitivity and specificity for the differential diagnosis between MM epithelial variant and adenocarcinoma, particularly of lung origin. However, the accuracy of these markers is lower for the diagnosis of sarcomatous MM and for the differential diagnosis between

MM and squamous cell carcinoma and carcinomas of renal, ovarian, and other origin.

**Objective.**—To identify optimal antibody panels for the diagnosis of MM.

**Data Sources.**—Literature review to determine how many and which mesothelial and epithelial markers need to be included in differential diagnosis antibody panels.

**Conclusions.**—Various antibody panels have been recommended for the diagnosis of MM, with no overall consensus about how many and which markers should be used. A recent study with Bayesian statistics has demonstrated that the use of many markers does not provide higher diagnostic accuracy than the use of selected single antibodies or various combinations of only 2 markers. There is a need for the development of evidence-based or consensus-based guidelines for the diagnosis of MM in different differential diagnosis situations.

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**M**alignant mesothelioma (MM) is an uncommon neoplasm arising from the serosal surfaces of the pleura, peritoneum, pericardium, tunica vaginalis, and other body cavities.<sup>1,2</sup> The tumor cells can exhibit epithelial, sarcomatous, and/or biphasic differentiation. Epithelial MM is composed of epithelial cells arranged in tubules, papillary patterns, and many other histologic patterns that closely resemble adenocarcinomas and other epithelial tumors.<sup>3</sup> Sarcomatous MM is usually composed of solid sheets of pleomorphic spindle cells that closely resemble a spindle cell or pleomorphic sarcoma. The diagnosis of MM is currently established pathologically with the aid of immunohistochemistry to demonstrate the presence of “mesothelial,” “epithelial,” or “true sarcomatous” differentiation in the malignant cells.<sup>4</sup> Other ancillary methods such as histochemistry and electron microscopy can also be helpful for the diagnosis of MM but are currently considered less effective than immunohistochemistry.<sup>1,5</sup>

There is currently no individual immunohistochemical mesothelial marker that provides 100% specificity and high sensitivity for the diagnosis of MM or an epithelial

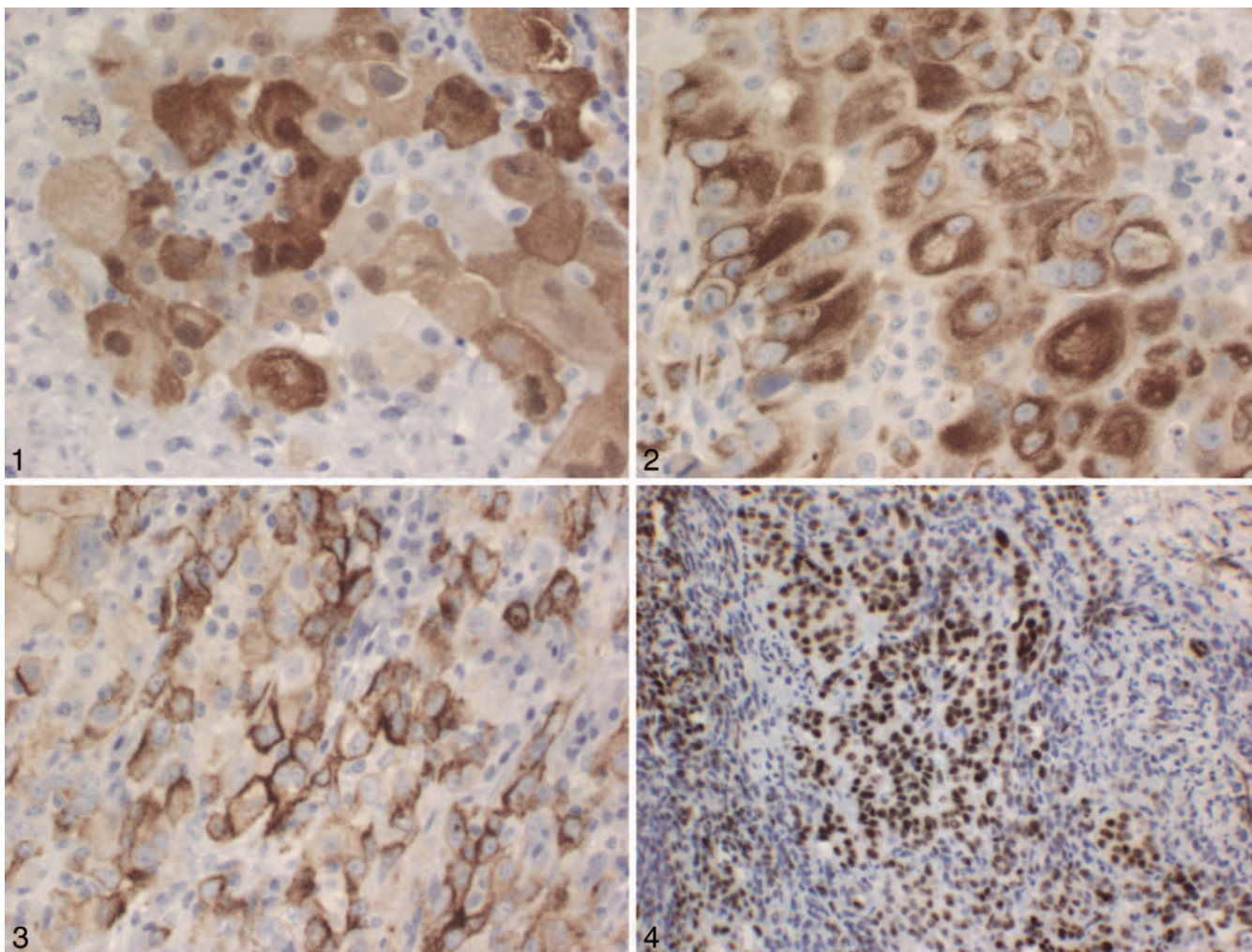
marker that provides high sensitivity and 100% negative predictive value for the diagnosis of MM.<sup>5–9</sup> This difficult problem has stimulated the development of multiple mesothelial and epithelial markers of variable sensitivity and specificity (Figures 1 through 4). These markers generally have very good sensitivity and specificity for the differential diagnosis of MM and adenocarcinomas of lung and other origin but yield lower accuracy for the differential diagnosis of MM and other epithelial neoplasms, such as squamous cell carcinoma and carcinomas of the kidney, bladder, ovary, and other sites.<sup>10</sup> Mesothelial markers other than calretinin also show very low sensitivity and specificity for the diagnosis of sarcomatous MM.<sup>11</sup> These technical limitations have promoted the use of antibody panels rather than the use of 1 or 2 markers for the diagnosis of MM.<sup>12</sup> These antibody panels generally combine the use of 2 or more mesothelial markers with 2 or more epithelial markers. However, there are no widely accepted evidence-based guidelines for the use of immunohistochemistry in the diagnosis of various subtypes of MM. As recently shown by King and colleagues<sup>13</sup> in their systematic review of the best evidence available in the literature regarding the diagnosis of epithelial MM, different experts have variable preferences about which antibodies are most helpful for the distinction between these neoplasms and adenocarcinomas. This systematic review did not include data regarding “new” mesothelial markers such as mesothelin, D2-40, and podoplanin and demonstrated that there is no consensus in the literature regarding how many of these antibodies should be included in a diagnostic panel.<sup>6,9,14–20</sup>

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**Figure 1.** Cytologic preparation from a patient with pleural mesothelioma, epithelioid variant, stained with antibody to calretinin. The cells exhibit nuclear and cytoplasmic immunoreactivity (original magnification  $\times 400$ ).

**Figure 2.** Biopsy from a patient with malignant mesothelioma, epithelioid variant. The tumor cells exhibit strong cytoplasmic immunoreactivity for cytokeratin 5/6 (original magnification  $\times 400$ ).

**Figure 3.** Biopsy from a patient with malignant mesothelioma, epithelioid variant. The tumor cells exhibit membrane immunoreactivity for mesothelin (original magnification  $\times 400$ ).

**Figure 4.** Biopsy from a patient with a malignant mesothelioma, biphasic type. The epithelioid cells show strong nuclear immunoreactivity for WT-1. The sarcomatoid tumor cells are negative (original magnification  $\times 100$ ).

Table 1 shows the most useful mesothelial and epithelial markers that have been proposed for the diagnosis of MM and its differential diagnosis from selected carcinomas and sarcomas. In addition, antibodies to keratin AE1/AE3, epithelial membrane antigen (EMA), E-cadherin, N-cadherin, surfactant apoproteins, CD10, renal cell carcinoma marker, and others have been applied for the diagnosis of MM and its distinction from reactive mesothelial proliferations and other neoplasms.<sup>21-28</sup> It is beyond the scope of this review article to discuss the characteristics of all these antibodies in detail; however, I will briefly discuss their applications in 3 different diagnostic scenarios.

#### THE APPLICATION OF IMMUNOHISTOCHEMISTRY FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN MM AND REACTIVE MESOTHELIAL PROLIFERATIONS

Malignant mesothelioma epithelial type can be very difficult to distinguish from reactive mesothelial hyperplasia

with cytologic atypia.<sup>21,29</sup> Organizing pleuritis (organizing pleurisy, fibrous pleurisy) can be mistaken for MM sarcomatous type, particularly desmoplastic mesothelioma.<sup>21,29</sup> Several histopathologic features, such as the lack of true stromal invasion, presence of "zonation effect" resulting in a process that becomes more fibrotic toward the chest wall, presence of cytologic atypia confined to areas of organizing fibrinous effusion, presence of capillaries that are perpendicular to the mesothelial surface, absence of necrosis and of nodular expansion of the stroma, and lack of a prominent storiform pattern, are helpful to distinguish benign mesothelial reactions from malignant mesothelial neoplasms.<sup>2</sup>

The use of immunohistochemistry for the detection of keratin, p53, EMA, and desmin has been proposed for the distinction between MM and benign mesothelial reactions.<sup>21,29,30</sup> As summarized in Table 2, MMs frequently exhibit immunoreactivity for keratin, EMA, and p53, whereas the cells of reactive mesothelial proliferations usually

**Table 1. Immunostains in Malignant Mesothelioma (MM) and Other Malignant Neoplasms\***

Antibody	Epithelial MM, % Positive†	Sarcomatous MM, % Positive‡	Adenocarcinoma, % Positive†	Squamous Cell Carcinoma, % Positive§	Renal Cell Carcinoma, % Positive‡
Epithelial marker					
pCEA	5	0	83	7	0
mCEA	3	...	81	...	...
Ber-Ep4	10	0	80	40	0-58
B72.3	7	0	80	87	...
CD15 (Leu-M1)	7	0	72	30	25-100
MOC-31	7	0	93	97	0-75
TTF-1	Negative	0	Lung: 72 Other: Negative	Negative	...
Lewis-BG8	7	0	93	80	0-33
Mesothelial marker					
Cytokeratin 5/6	83	13	14.9	100	5
Calretinin	82	88	15	40	10
HBME-1	85	...	57	...	...
Thrombomodulin	61	13	20	...	0-32
WT-1	77	13	4	Negative	0-4
Mesothelin§	100	0	...	27	...
D2-40	86-100	0	36 (weak)	...	...
Podoplanin§	86-93§	0	...	15	...

\* pCEA indicates polyclonal carcinoembryonic antigen; mCEA, monoclonal carcinoembryonic antigen; and TTF-1, thyroid transcription factor 1.

† King et al.<sup>13</sup> Muller.<sup>19</sup>

‡ Osborn et al.<sup>28</sup> Ordonez.<sup>27</sup>

§ Ordonez.<sup>5,6,8,9,15,18,24</sup>

|| Ordonez.<sup>8</sup>

**Table 2. Immunohistochemistry for the Distinction Between Benign Mesothelial Reactions and Malignant Mesothelioma\***

Antibody	Benign Atypical Mesothelial Proliferations	Malignant Mesothelioma
Keratin AE1/AE3	+/-	+++
EMA	+/-	+++
p53	+/-	+++
Desmin	+++	+/-

\* +/- indicates present in some tumor cells; +++, present in most tumor cells; and EMA, epithelial membrane antigen.

exhibit desmin immunoreactivity and focal staining with antibodies to keratin, p53, and EMA. There is such an overlap in the immunophenotypes of benign reactive mesothelial proliferations and MM that this information needs to be carefully correlated with the histomorphologic features visible on hematoxylin-eosin-stained slides. In our experience, MM rarely shows significant immunoreactivity for desmin and generally exhibits nuclear p53 immunoreactivity; we are therefore particularly cautious to diagnose an MM in the absence of p53 immunoreactivity or the presence of strong desmin reactivity in the cells of origin. In contrast, there is such an overlap in lesions that express p53 and EMA that this information is less helpful for the differential diagnosis between MM and reactive atypia.

**THE APPLICATION OF IMMUNOHISTOCHEMISTRY FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN EPITHELIAL MM AND ADENOCARCINOMAS OR OTHER CARCINOMAS**

Table 1 summarizes the most useful mesothelial and epithelial markers that have been proposed for the distinction between MM epithelial and sarcomatous types

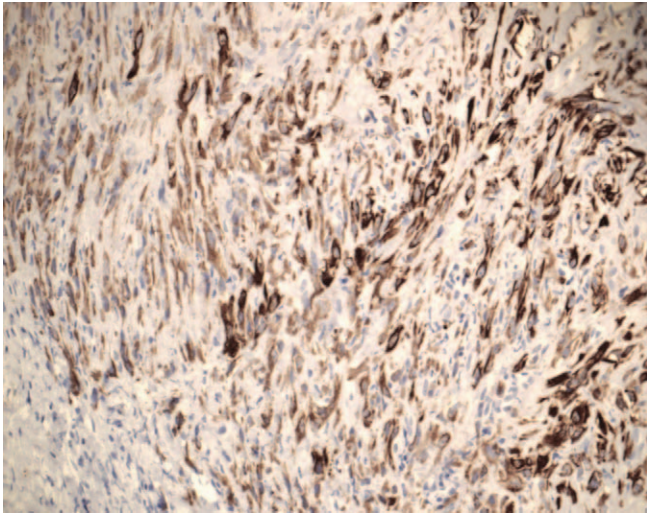
and adenocarcinoma of lung and other primary sites, squamous cell carcinoma, and renal cell carcinoma.<sup>5,7,8,31</sup> Table 1 clearly shows that several of these epitopes yield high sensitivity and specificity for the differential diagnosis of epithelial MM and pulmonary adenocarcinoma. However, most mesothelial markers exhibit considerably lower sensitivity and specificity for the diagnosis of sarcomatous MM. In addition, several of the best mesothelial markers such as cytokeratin 5/6, calretinin, mesothelin, and podoplanin stain 17% to 100% of squamous cell carcinomas (Figures 1 through 4). Table 1 does not include other antibodies that can stain MM such as h-caldesmon, N-cadherin, claudins 1 to 4, and others.<sup>22,32,33</sup>

The distinction between MM and renal cell carcinoma can be particularly difficult.<sup>26-28</sup> The renal neoplasms can express immunoreactivity with mesothelial markers, and MM can express immunoreactivity with antibodies that are usually reactive in renal cell carcinomas. For example, staining for CD10 can be positive in 54% of MMs, whereas renal cell carcinoma marker can stain 26% of MMs.<sup>26</sup>

The differential diagnosis between MM and ovarian carcinoma also deserves particular caution, as the carcinomas can stain with mesothelial markers such as D2-40 and WT-1.<sup>5,7,34,35</sup>

**THE APPLICATION OF IMMUNOHISTOCHEMISTRY FOR THE DIFFERENTIAL DIAGNOSIS BETWEEN SARCOMATOUS MM AND SARCOMA**

The diagnosis of sarcomatous mesothelioma is particularly difficult, as the sensitivity and specificity of mesothelial markers is considerably lower in these lesions than in epithelial MM.<sup>9,11,36-38</sup> For example, immunostains for calretinin, thrombomodulin, and WT-1 are positive in fewer than 20% of sarcomatous MMs. Immunostain for keratin AE1/AE3 is probably the most helpful immunostain to confirm the diagnosis of sarcomatous MM in a patient



**Figure 5.** Biopsy from a patient with malignant mesothelioma, sarcomatoid type. The malignant spindle cells exhibit strong cytoplasmic immunoreactivity for keratin AE1/AE3 (original magnification  $\times 100$ ). Immunostains for mesothelial markers calretinin, WT-1, and cytokeratin 5/6 were negative.

with a diffuse sarcomatous infiltrating process involving the pleural cavity<sup>2</sup> (Figure 5). However, this epitope can also yield positive immunoreactivity in sarcomatoid carcinomas and synovial sarcoma, malignancies that can occasionally involve the pleural cavity.<sup>9,11,36–41</sup> The latter neoplasms usually present as discrete tumor masses, rather than as a diffuse infiltrating pleural process, and exhibit slightly different histopathologic features than seen in sarcomatous MM. Sarcomatous carcinomas usually exhibit more prominent cytologic atypia than is seen in MM, whereas synovial sarcomas of the pleura present as a single discrete mass with considerable nuclear atypia and high mitotic activity. Pathologists need to be cautious in the interpretation of biphasic tumors, as mesothelial markers such as D2-40 and podoplanin can stain the epithelioid cells of biphasic synovial sarcomas.<sup>9,37</sup>

Recent studies have suggested that more recently described mesothelial markers such as mesothelin, D2-40, and podoplanin are not particularly helpful for the diagnosis of sarcomatous MM.<sup>6,9</sup>

#### ANTIBODY PANELS FOR THE DIAGNOSIS OF MM: THE NEED FOR CONSENSUS- OR EVIDENCE-BASED GUIDELINES THAT ADDRESS SPECIFIC DIFFERENTIAL DIAGNOSES

To my knowledge, there are no consensus- or evidence-based guidelines for the selection of immunostains for the differential diagnosis between MM and various neoplasms. A recent review article by Ordonez<sup>39</sup> provides a comprehensive summary of the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma. The Association of Directors of Anatomic and Surgical Pathology has published recent recommendations for the reporting of pleural mesothelioma that does not prescribe a particular panel of immunostains and recommends the use of at least 2 mesothelial markers and 2 or more epithelial markers.<sup>40</sup> Yaziji et al<sup>12</sup> recently proposed a panel composed of 3 antibodies, calretinin, BG8, and MOC-31, selected by logistic regression analysis. This panel provided more than 96% sensitivity and specificity for

distinguishing epithelioid mesothelioma from adenocarcinoma. King and colleagues,<sup>13</sup> based on a systematic review of the literature, selected 7 epithelial and mesothelial markers, carcinoembryonic antigen, MOC-31, thyroid transcription factor 1 (TTF-1), BG8, cytokeratin 5/6, WT-1, and HBME-1, for their best sensitivity and specificity but offered no guidelines regarding how many of these antibodies need to be included in a diagnostic panel. Our analysis of the review data published by King and colleagues with Bayesian statistics shows that the use of panels composed of only 2 antibodies, 1 mesothelial and 1 epithelial, such as WT-1 and TTF-1, or 2 epithelial epitopes, such as MOC-31 and TTF-1, provides the best odds ratios for the differential diagnosis between epithelial MM and pulmonary adenocarcinoma.<sup>10</sup> Future studies analyzing the data with odds ratios, logistic regression, or other Bayesian statistical methods are needed to develop evidence-based, cost-effective guidelines for the use of immunohistochemistry in the differential diagnosis between MM and other neoplasms.

Until such guidelines become available, we currently use in our laboratory a diagnostic panel that usually includes calretinin, WT-1, cytokeratin 5/6, TTF-1, carcinoembryonic antigen, and B72.3.

#### CONCLUSIONS

Immunohistochemistry has become an essential tool for the diagnosis of MM. Current markers have excellent sensitivity and specificity for the distinction between epithelial MM and metastatic adenocarcinoma but lower accuracy for the distinction between epithelial MM and other epithelial malignancies and for the diagnosis of sarcomatous MM. The current availability of multiple antibodies to detect with immunohistochemistry the presence or absence of mesothelial or epithelial epitopes in neoplastic cells raises the need for the development of consensus- or evidence-based guidelines for the use of these tests in different differential diagnosis situations.

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