

Pleural diffuse mesothelial lesions: A challenge for pathologists

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Abstract

Malignant mesothelioma (MM) is a highly aggressive tumor deriving from the mesothelial cells normally lining the body cavities. Histologically, MM is classified in three major histopathological patterns, such as epithelioid, sarcomatoid and mixed type. It is well known that the diagnosis of MM can be very challenging, especially in small bioptic fragments or cytological specimens.

The most common diagnostic pitfalls involve the distinction between primary epithelioid MM and metastatic adenocarcinoma as well as that between reactive epithelial/fibrous benign proliferations and MM. Recently, a pathologist's panel suggested new practical strategies and recommendations for the MM diagnosis, regarding the interpretation of histo-cytological features and the composition of appropriate immunohistochemical algorithm. Finally, according to the updated international guidelines, morphological data require a careful clinico-pathological correlation to achieve an accurate diagnosis of pleural lesions.

Keywords: Immunohistochemistry; Reactive Mesothelial Lesions; Malignant Mesothelioma; Differential Diagnosis.

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Introduction

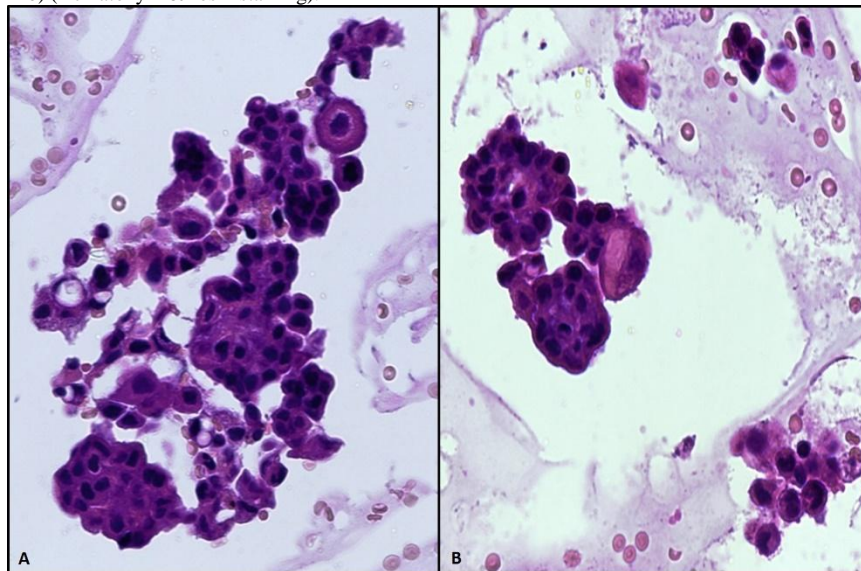
Malignant mesothelioma (MM) is the highly malignant neoplasm deriving from the mesothelial cells that normally line the body cavities, including the pleura, peritoneum, pericardium and tunica vaginalis testis (1-3).

Mesothelial neoplasms present a variable disease progression, formerly by locally extension in chest wall and lung; subsequently, a direct involvement of mediastinal structure may be common (2). Lymphatic spread may realize ipsilateral and contralateral lymph node metastases, while distant metastasis are common elsewhere (1-3). Grossly, early MM presents small nodules distributed on the parietal or rarely on the visceral pleura. Successively, nodules produce coalescence to form a diffuse growth, compressing the lung parenchyma and the pleura may become several centimeters thick (2). Finally, the tumor is black-grey in colour, not hard in consistency, with occasional cystic mucoid areas (2).

Histologically, according to the 2015 WHO classification, MM is classified in three major

morphological types: epithelioid, sarcomatoid, and mixed (or biphasic) (4,5). In particular, the epithelioid pattern is present in about 70% of mesotheliomas, while 25% is biphasic and 5% sarcomatoid (1-5). The tubulo-papillary pattern represents the most commonly diagnosed histotype, characterized by the presence of small tubular associated with papillae structures with delicate fibrovascular core, often with clefts and trabeculae (Fig1a-b). The microglandular-type (also called adenomatoid) pattern shows a proliferation of small gland-like structures lined by bland flat to cuboidal cells, which can make difficult in the differential diagnostic with pleural involvement of metastatic adenocarcinoma (6-9).

Fig.1 The peculiar morphological features of well-differentiated epithelioid papillary MM in cell-block specimen: neoplastic aggregates of round epithelioid cells with hyperchromatic nuclei and distinct nucleoli arranged in pseudo-glandular and papillary structures (a,b original magnification X40) (Hematoxylin&Eosin staining).



Deciduoid mesothelioma is a rare variant characterized by a solid pattern with large round to polygonal elements, abundant glassy eosinophilic cytoplasm and prominent nucleoli, similar to decidualized tissue (9). Recently, it has been identified a pleomorphic variant of MM, showing marked anaplastic cells or pleomorphic giant cells in more than 10% of the tumors (9).

The sarcomatoid MM is the least frequent, but it represents the most aggressive variant of mesothelioma; morphologically, it is composed of a proliferation of spindle-shaped elements arranged in a fascicular pattern of growth (10-13). By routine evaluation, the differentiation between this rare MM subtype and true soft tissue tumours is very difficult (14-16). Rarely, sarcomatoid MM may present heterologous elements including immature cartilage and bone tissue (17,18).

In desmoplastic MM, the proliferation consists of extensive fibro-collagenous tissue with occasional storiform pattern (17,18). Neoplastic elements are scanty and associated with

no significant cellular atypia, noted only in highly-cellular areas (17,18). In small biopsy specimen, the diagnosis of desmoplastic mesothelioma is very challenging; in fact, in those cases the peculiar CT imaging with diffuse pleural thickening associated with reduction of pleural cavity, can support this diagnosis (19).

Biphasic mesothelioma accounts for 20-35% of all MM subtypes and, as a rule, it exhibits mixed features of epithelioid and sarcomatoid MM in varying proportions (9). However, each pattern should constitute at least 10% of the neoplasm; when there is less of either, the MM can be diagnosed predominantly sarcomatoid or epithelioid ones. In this variant, the prognosis may vary depending on the mixture of cells, being more favourable in cases that contain more epithelial cells than sarcomatoid cells (9).

Differential diagnosis of benign and malignant mesothelial proliferations

In practical terms of differential diagnosis, the principal MM mimickers are benign reactive mesothelial proliferations (6). This represent a critical point for the patient management and for potential medical-legal consequences regarding the occupational relationship between MM and asbestos exposure (1, 20-22). Typically, reactive mesothelial conditions tend to show a monomorphic growth with regular sheets and sweeping fascicles of cells in contrast to the disorganized growth and haphazardly intersecting features of MM (4). However, sometimes, either in bioptic either in cytologic specimens, it may resemble a neoplastic proliferation with specific characteristics such as high cellularity, mitotic figures and cytologic atypia, foci of necrosis and papillary formation (21). Although reactive mesothelial proliferations are non-invasive, the entrapment of benign mesothelial cells within fibrous tissue can mimic neoplastic invasion (1). In these cases, the demonstration of stromal or fat invasion is the crucial feature in the diagnosis of MM (1). Therefore, this differential diagnosis is often morphologically difficult, making it necessary to resort to many ancillary procedures (23-25).

Another difficult condition for pathologist appears the separation of benign fibrous entities from desmoplastic MM that could be made by identifying one or more of the following characteristics in a spindle cell pleural component: invasive growth, bland necrosis, frankly sarcomatoid areas and metastatic localization (1, 12-14). The invasion into adjacent tissue by neoplastic cells is often more difficult to recognize than in epithelioid ones (1, 12-14). However, the pathologist should be careful to not confuse the true invasion of desmoplastic MM with the fatlike spaces that may be present in some organizing pleuritic; modification caused by a traction artefact due to the organization of

fibrous connective tissue (1,12-14). Finally, a useful additional morphological feature of pleuritis is the presence of small capillaries oriented perpendicular to the surface opposite to the inconspicuous capillaries in the tumor (12-14).

Differential diagnosis of MM and metastatic carcinomas involving the pleura

The differential diagnosis between MM and metastatic tumours differs in relation to the morphological and clinical information (23-25). In fact Indeed, the epithelioid MM needs to be distinguished from metastatic carcinomas, while the sarcomatoid should be distinguished from mesenchymal neoplasms and the biphasic variant from other mixed tumors, such as synovial sarcomas and metastatic pleomorphic lung carcinomas (23-25). Finally, lymphomas and poorly differentiated carcinomas may be confused with solid-poorly differentiated MM, while clear cell MM have to be differentiated from clear cell renal cell carcinomas, clear cell lung carcinomas, metastatic clear cell melanoma (23-25). Unusually, the occurrence of signet-ring cell MM needs a differential diagnosis from all neoplasms showing signet-ring features, either coming from lung or gastrointestinal tract (12-14). Small cell MM present diagnostic troubles regarding lung small cell carcinomas, desmoplastic small round cell tumors as well as lymphomas (12-14).

Taking into consideration the above mentioned heterogeneous morphologic appearance of MM, the diagnosis of this tumor may be not infrequently very difficult to establish and it should be based not only on both morphology, requiring appropriate immunohistochemical procedures (8).

Immunohistochemical (IHC) algorithm of MM

IHC is essential to the diagnosis of MM, representing the most useful and standard ancillary procedure to distinguish this malignancy from other types of cancer (25). In particular, the main immunohistochemical combination is dependent on the morphological MM pattern (sarcomatoid or epithelioid) (25). However, is essential to highlight that none of the antibodies actually used for the diagnosis of MM have 100% in terms of sensibility and specificity, suggesting that the final diagnosis based on the interpretation of a wide panel of antibodies (9).

The recent guidelines recommends an initial panel with comprising pancytokeratin (multiple keratins, such as AE1/AE3, CAM5.2) plus two mesothelial markers and two markers for potential metastatic tumors, considering the morphology (11-14). If the results are concordant, the diagnosis considered conclusive. If the results of this immunohistochemical panel are discordant, the pathologist should expand the panel of antibodies, always based on the differential diagnosis to resolve (11-14). The

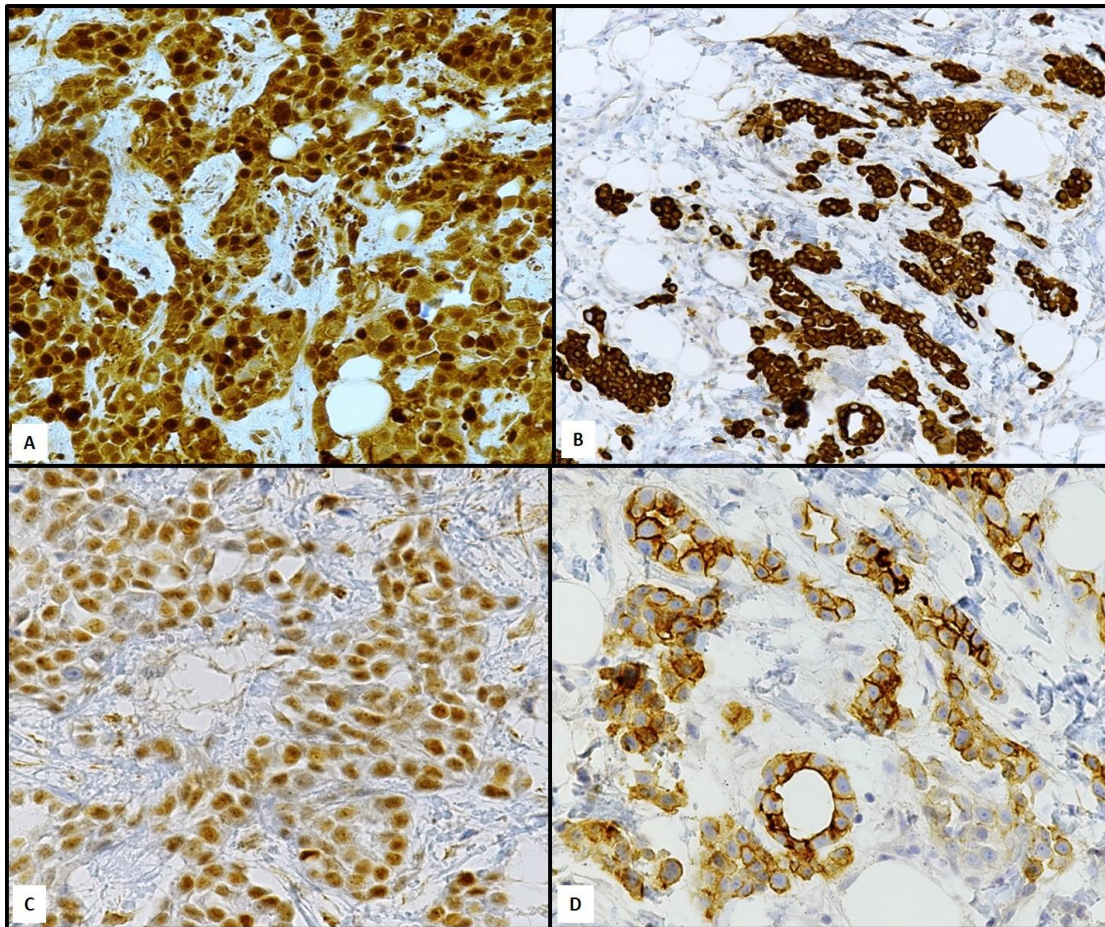
immunohistochemical markers should have sensitivity or specificity greater than 80%; moreover, the interpretation of immunostains should consider the localization of the stain (membrane, nuclear, cytoplasmic) as well as the percentage of positive cells (5).

Cytokeratins (panCK, AE1/AE3) are particularly useful in the diagnosis of MM, since all mesotheliomas potentially show positive results. By contrast, in a diffuse pleural thickening with panCK immunonegativity, other potential differential diagnoses have to consider such as malignant melanoma, epithelioid hemangioendothelioma, angiosarcoma and malignant lymphoma (2,3,6,25). In these conditions, it is mandatory introduce alternative immunomarkers such as CD45, CD20, CD3 and CD30 for large cell lymphomas; S100 and HMB-45 for melanoma; CD31, CD34, and ERG (or FLI-1) for angiosarcoma and epithelioid hemangioendothelioma. However, few (approximately 5–10%) sarcomatoid mesotheliomas are keratin-negative; in these cases, other mesothelial markers, such as calretinin and podoplanin (D2-40), could lead to the correct diagnosis (12,13).

Actually on the basis of their sensitivity and specificity, the most useful mesothelial markers to support a MM diagnosis are calretinin, Wilms' tumor gene (WT1), cytokeratin 5/6 (CK5/6), and D2-40 (podoplanin) (26,27). In detail, all epithelioid MM showed a strong, diffuse calretinin staining, localized in both nuclear and cytoplasmic site (Fig.2a). Nevertheless, caution is required since 5%–10% of lung adenocarcinomas are positive, even if with a focal staining. In addition, CK 5/6 is very useful, expressed in 75–100% MM (Fig.2b); a focal positivity has been found in 2–20% of lung adenocarcinomas. On the other hand, lung cancer is always negative for WT-1, which shows nuclear positivity in approximately 70–95% of MM (Fig.2c). D2-40 is observed in about 90–100% of MM, exhibiting a cell membrane immunoreactivity; only 15% of lung adenocarcinomas are focally positive (Fig.2d). Finally, a potential bias represented by a negativity for the aforementioned markers that not exclude the diagnosis of MM, since 30% of MM presents a “null” phenotype.

Currently, the new markers to improve the diagnostic accuracy suggested p53, insulin-like growth factor II mRNA binding protein 3 (IMP3), glucose transporter protein 1 (GLUT-1) these antibodies have shown statistically significant differences in large series, but they offer an inadequate improvement in singular cases (28-31).

Fig. 2 The most useful immunohistochemical markers in MM diagnosis: uniform nuclear and cytoplasmic calretinin staining (a, original magnification X40); diffuse membranous CK5 /6 positivity in neoplastic elements (b, original magnification X20); intense nuclear WT-1 stain (c, original magnification X40); strong membranous D2-40 reactivity in epithelioid MM (c, original magnification X40) (Mayer's Haemalum nuclear counterstain).



However, BRCA1 associated protein 1 (BAP1) detected by immunohistochemistry and *p16* by fluorescent in situ hybridization (FISH), represent the most effective procedures to discriminate between benign and malignant pleural lesions (28-31). BAP1 somatic mutations resulting in protein loss appear to be common in hereditary and sporadic mesotheliomas. Currently, there is substantial variability in the reported frequency of BAP1 protein loss; epithelioid/mixed mesotheliomas lose BAP1 more frequently than the sarcomatoid pattern, approximately 60–70% and 15%, respectively. Interestingly, recent studies have shown BAP1 protein expression in all benign mesothelial proliferations and, although more data needed, the specificity of BAP1 loss is 100%, making BAP1 an excellent biomarker in the distinction between benign and malignant mesothelial proliferations (28-31) (Table 1).

Several recent studies have shown that the homozygous deletion of *p16* by FISH found only in mesotheliomas, whereas none of benign mesothelial proliferations showed a loss of *p16* with a specificity of 100% (29). However, not all mesotheliomas harbor this deletion, and the sensitivity for epithelioid/biphasic MPM ranges from approximately 45% to 85%.

Table 1: The recommended immunohistochemical panel in mesothelial pathology.

Positive Markers	Negative Markers
Pan-CK	<i>CK20</i>
CK 5/6	<i>MOC-31</i>
CK7	<i>BER-EP4</i>
Calretinin	<i>TTF-1</i>
WT1	<i>Napsin-A</i>
D2-40	<i>Claudin-4</i>
HBME-1	<i>P40</i>
EMA	<i>P63</i>
GLUT-1	<i>PAX-8</i>
P-53	<i>CDX2</i>
IMP-3	<i>Desmin</i>
BAP1	<i>Estrogen receptor</i>

The sensitivity of the *p16* FISH test is much higher in sarcomatoid mesothelioma; in some reports, the deletion reported in up to 100% of cases; however, other studies report a lower proportion of *p16*-deleted sarcomatous tumors (29).

In this article, we have briefly described a practical strategy, supported by the updated international guidelines, for making the diagnosis of MM, considering its poor prognosis and relevant medicolegal implications. First, the histologic and immunohistochemical characteristics should be used for a differential diagnosis between benign and malignant mesothelial lesions. Second, ancillary techniques (immunohistochemical stains, electron microscopy and molecular markers) showed some limitations, mainly in small biopsies and cell block specimens. Finally, in MM diagnosis, 2 mesothelioma markers as well as 2 carcinoma markers may be used, applying additional markers when there are discordant results.

Author contributions

Conception and design: Antonio Ieni, Francesco Arena, Giovanni Tuccari;

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Collection data: Francesco Arena, and Giuseppe Angelico;

Data analysis and interpretation: Antonio Ieni, Francesco Arena, Giovanni Tuccari;

Manuscript writing: All authors;

Final approval of manuscript: All authors

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