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Editorial

Immunohistochemical Diagnostic Approach in Neoplastic Pathology of Mesothelium

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Editorial

Malignant mesothelioma (MM) is a highly aggressive tumor originating from the mesothelial cells lining the serosal cavities; therefore, the most common locations of this tumor include the pleura, followed by peritoneum, pericardium and tunica vaginalis testis [1].

According to the 2015 WHO classification, MM is classified in three major histopathologic patterns including epithelioid, sarcomatoid, and mixed (biphasic) [2]. In detail, about 70% of mesotheliomas are predominantly epithelioid, 25% biphasic and 5% sarcomatoid [2,3]. Within the category of epithelioid mesothelioma, a variety of growth patterns has been described including tubulo-papillary, papillary, micropapillary, trabecular/glandular/acinar, solid, deciduoid and pleomorphic [4]; less commonly, MM cells may be clear, signet ring, small cells or rhabdoid. The sarcomatoid MM is the least frequent, but the most aggressive variant of mesothelioma [5]; histologically, it is composed of a proliferation of spindle-shaped cells arranged in a fascicular pattern of growth that may closely mimic other soft tissue tumours like fibrosarcoma or malignant fibrous histiocytoma. In addition, heterologous elements such as immature cartilage and bone tissue may be encountered in sarcomatoid MM [6]. Finally, a subset of MM, referred as "desmoplastic MM", displays extensive stromal collagenization and 'bland' histological appearance, difficult to distinguish from benign fibrous pleuritis [7]. Biphasic mesothelioma is histologically characterized by a combination of epithelioid cells and sarcomatoid cells in varying proportions. In this MM variant, the prognosis depends on the mixture of cells, being more favourable in cases containing more epithelial cells than sarcomatoid cells [2,4].

The diagnosis of pleural MM can be very challenging because it usually depends upon pathological assessment of small pleural bioptic fragments or cytological specimens; moreover, MM displays a wide variety of morphological features with a tendency to mimic other malignant neoplasms or benign/reactive conditions [2-5]. Indeed, the common challenge in mesothelial pathology is represented by the distinction between reactive mesothelial proliferations and MM, since morphological features between these two entities may overlap [8]. In fact, mesothelial cells can exhibit reactive changes as a consequence of several benign conditions that determine an injury such as chronic inflammation and infection, heart failure, cirrhosis, nephrotic syndrome, lung infarction and collagenopathies [8,9]. In all these conditions, in pleural effusions as well in serosal tissue fragments, a cellular increase associated with papillary/morular clusters or solid sheets can be observed. In comparison to normal mesothelium, the reactive cells exhibit an increased size with nuclear enlargement, prominent nucleoli and numerous mitotic figures [8,9]. In difficult cases, the morphological crucial characteristic helping to distinguish reactive mesothelial hyperplasia from MM is represented by the stromal tissue invasion [9,10]; however, when morphological features alone are insufficient for the distinction between malignant and benign mesothelial lesions, further analyses are mandatory. Another intriguing point is represented by the differential diagnosis between MM and other entities, such as metastatic carcinomas (lung, breast and gastrointestinal tract), sarcomas and lymphomas [10,11].

Taking into consideration the above mentioned heterogeneous morphologic appearance of MM, the diagnosis of this tumor may be not uncommonly very difficult to establish and it should be based not only on morphology, requiring appropriate immunohistochemical procedures [2,4,11].

Recently, practical strategies and recommendations for the MM diagnosis have been suggested and updated by expert pathologists in national consensus conferences [2,12,13]. However, there are still several controversies regarding the reliable immunohistochemical algorithm to apply in the differential diagnosis between MM and reactive mesothelial proliferations, MM and adenocarcinomas, MM and sarcomas with spindle cell components. The diagnostic immunohistochemical algorithm usually depends on the histologic MM subtype as well as on the MM location (pleural versus peritoneal). Accordingly, the recent guidelines on the diagnosis of MM, recommend that at least 2 mesothelial and 2 carcinoma markers should be always used in MM cases, utilizing either immunopositivity either negativity to achieve the final diagnosis [10-13]. Nevertheless, if the results are discordant, a next expanded algorithm has to be applied (Table 1) [11,13]. Once the neoplastic nature of the lesion has been confirmed, a further necessary step is represented by the correct identification of the MM subtype and its differentiation from other malignancies.

Cytokeratins (panCK, AE1/AE3) are typically the first-line antibodies utilized in the diagnosis of MM because nearly all epithelioid MM and most sarcomatoid MM will exhibit positive immunostaining [5,10,11,14]. Consequently, if a panCK immunonegativity is found

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Table 1: Most useful positive and negative immunostains in mesothelial pathology.

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

in a diffuse pleural thickening, other potential differential diagnoses should be considered such as malignant melanoma, epithelioid hemangioendothelioma, angiosarcoma and malignant lymphoma [10,11,14]. In these circumstances, 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 [10,11,14].

The most useful mesothelial markers are represented by calretinin, WT-1, cytokeratin 5/6 (CK5/6) and D2-40. In detail, calretinin has been demonstrated in fairly all epithelioid mesotheliomas, with a strong, diffuse staining localized in both nuclear and cytoplasmic site. Nevertheless, caution is required since 5%–10% of lung adenocarcinomas are positive, even if with a focal staining [11,15]. In addition, CK 5/6 is very useful for diagnostic purpose, being expressed in 75–100% MM; a focal positivity has been found in 2–20% of lung adenocarcinomas [11,15]. On the other hand, lung cancer is always negative for WT-1, which in turn shows nuclear positivity in approximately 70–95% of MM. Finally, D2-40 is observed in about 90–100% of MM, exhibiting a cell membrane immunoreactivity; only 15% of lung adenocarcinomas are focally positive [15,16].

According to recent suggestions, the new proposed markers to improve the diagnostic accuracy are p53, insulin-like growth factor II mRNA binding protein 3 (IMP3), glucose transporter protein 1 (GLUT-1) and BRCA1 associated protein 1 (BAP1) [9,17-19]; these antibodies have shown statistically significant differences in large series, but they offer a limited improvement in individual cases [17-19]. In detail, the tumor suppressor gene p53 has also been found overexpressed more frequently in MM than reactive mesothelial proliferations, with a sensitivity ranging between 41% and 61% and a specificity of 91% [9]. Recently, two novel antibodies, GLUT-1 and IMP3 have been shown to stain exclusively MM cells but not reactive lesions, although further studies on large series are needed to validate their diagnostic utility [18,19]; moreover, BAP1 protein loss, detected by immunohistochemistry, together with the homozygous deletion of p16 by fluorescent in situ hybridization (FISH), have been considered the useful biomarker for the diagnosis of MM either in cytologic or tissue biopsy samples [9,17,20].

We would furtherly stress that lack of immunostainings in MM can be caused by an over fixation in formalin, mainly in small bioptic fragments; on the other hand, a negative immunostain may also be present in alcohol-fixed tissues if antigen retrieval is used, underlining the relevance of precise knowledge concerning the utilized fixative [11,21].

Finally, we contend that immunohistochemistry represents a useful diagnostic tool needed to integrate the morphological, clinical and radiographic data in order to achieve a precise final MM diagnosis.

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