



Update on the pathologic diagnosis of malignant mesothelioma

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Abstract: Malignant mesothelioma is an uncommon tumor that may be difficult to diagnose. The International Mesothelioma Interest Group has been writing guidelines for pathological diagnosis that are periodically updated. The guidelines are being updated based on published literature in the last 3 years, and experience of more than 20 leading international pathologists in the field who will be co-authors. Updates were discussed by attendees of the Pulmonary Pathology Society Biennial Meeting (Dubrovnik, Croatia, June 2019). Areas with significant advancements/changes include utilization of immunohistochemistry (establishing mesothelial lineage and benign versus malignant), prognosis and nuclear grading, biphasic malignant mesothelioma, transitional pattern, malignant mesothelioma *in situ*, and therapeutic/molecular targets.

Keywords: Malignant mesothelioma; nuclear grading; BAP1; MTAP; mesothelioma *in situ*

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Introduction

Malignant mesothelioma is a rare neoplasm of the serosal membranes. The World Health Organization provides guidance on the classification of malignant mesothelioma (1), but its diagnosis remains a challenge for many practicing surgical pathologists. To aid accurate diagnosis, the International Mesothelioma Interest Group (iMig) periodically publishes pathologic guidelines on the diagnosis of malignant mesothelioma, the most recent being the 2017 update (2-4). Since that time, numerous publications on biomarker utilization in malignant mesothelioma and on understanding of mesothelioma biology and genetics have led to a plethora of new and emerging concepts with implications in the diagnosis of malignant mesothelioma. The diagnostic guidelines will be updated based on this published literature from the last 3 years, and on experiences of an international group of leading pathologists in the field. These updates have been discussed by attendees of the Working

Group for Multidisciplinary Classification of malignant mesothelioma (Lyon, France, July 2018) (5), International Mesothelioma Panel meeting (Washington, DC, March 2019) and Pulmonary Pathology Society Biennial Meeting (Dubrovnik, Croatia, June 2019).

Current strategies and updates in the utilization of immunohistochemical biomarkers

Establishment of mesothelial lineage

To establish mesothelial lineage by immunohistochemistry, current recommendations are to utilize a panel of at least two mesothelial markers [most commonly CK5/6, calretinin, WT-1, and/or D2-40 (podoplanin)] and two carcinoma markers (Ber-EP4, MOC-31, among others) (4). The exact panel of immunohistochemical markers used varies between the pleural and peritoneal cavities and depends upon the differential diagnosis. More recently, claudin-4, a component of epithelial tight junctions,

has emerged as an excellent discriminatory marker in the differential between epithelial and mesothelial proliferations. Claudin-4 is now viewed by many expert mesothelioma pathologists, and supported by the literature, as a superior marker of epithelial differentiation (6-8). Positive immunoreactivity for claudin-4 is defined as strong membranous expression, with only granular cytoplasmic or very focal staining reported in mesothelioma (7,9). While the historically described mesothelial markers remain in use, more recently, HEG1 (heart development protein with EGF-like domains), has been described as a sensitive and specific marker of mesothelial differentiation with excellent discriminatory expression between mesothelial and epithelial proliferations (10-12). Currently, HEG1 is limited in use as it is not widely available outside of Japan.

Benign versus malignant mesothelial proliferations

The diagnosis of a mesothelial proliferation as malignant is most easily accomplished by identification of invasion of the mesothelial cells into underlying tissue (lung, skeletal muscle, fibroadipose tissue, etc.), and invasion can be highlighted with immunohistochemistry directed against cytokeratin and/or calretinin (4). Identification of invasion can be difficult, especially on small biopsies, which may preclude evaluation of invasion into underlying tissue. Numerous markers have been proposed to differentiate benign from malignant mesothelial proliferations but have not achieved adequate sensitivity and specificity regarding this differential. More recently, nuclear loss of BRCA associated protein 1 (BAP1; *Figure 1*) has emerged as a specific marker of malignancy in mesothelial proliferations (13-16), although loss of BAP1 is not entirely specific for malignant mesothelioma and can be observed in melanoma, renal cell carcinoma, and other malignancies (17). Immunohistochemical loss of BAP1 does correlate with *BAP1* mutation (13,18), however loss of BAP1 lacks sensitivity, only occurring in 50–65% of epithelioid malignant mesotheliomas, and around 15% of sarcomatoid malignant mesotheliomas (13,14,18-23). Cytoplasmic loss of MTAP (methylthioadenosine phosphorylase; *Figure 2*), which correlates to homozygous deletion of *CDKN2A*, has also recently emerged as a specific marker of malignancy in mesothelial proliferations, but like BAP1, lacks sensitivity (24-27). Lastly, nuclear loss of 5-hydroxymethylcytosine (5-hmC), a byproduct of gene demethylation, has been shown to be a specific marker of malignancy in

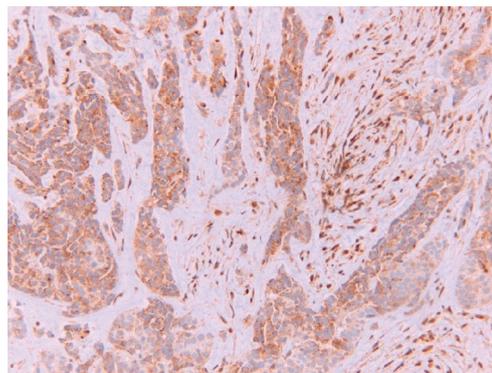


Figure 1 Epithelioid mesothelial proliferation showing nuclear loss of BAP1. There is some granular staining in the cytoplasm, but the nuclear loss indicates that this is a malignant mesothelioma (×200).

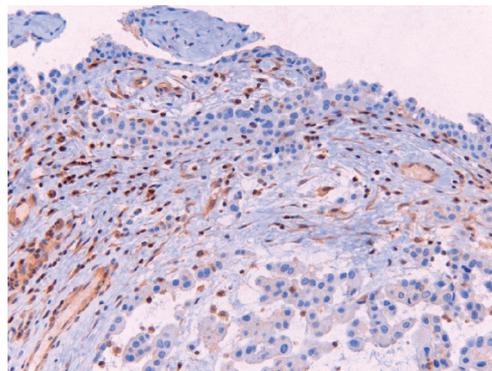


Figure 2 Epithelioid mesothelial proliferation showing cytoplasmic loss of MTAP, indicative of a malignant mesothelioma (×200).

mesothelial proliferations (28). By combining these various immunohistochemical markers, the vast majority of cases should be properly classified as either benign or malignant.

Sarcomatoid malignant mesothelioma differential diagnosis

Although large confirmatory studies are needed, there is evidence that GATA3 may be a relatively specific mesothelial marker in the differential between sarcomatoid mesothelioma and sarcomatoid carcinoma of the lung (29). Conversely, MUC4 may be a relatively specific marker of carcinoma in the differential of lung carcinoma versus mesothelioma, and may also be utilized in the differentiation between the sarcomatoid forms of lung carcinoma and mesothelioma (30,31). Beyond the diagnostic challenge

differentiating sarcomatoid malignant mesothelioma from sarcomatoid carcinoma, is differentiating sarcomatoid malignant mesothelioma from other sarcomas. Keratin positivity should be observed, at least focally, in a sarcomatoid malignant mesothelioma, which should rule out most, but not all sarcomas. Genetic testing for sarcoma and other mesenchymal neoplasm specific translocations may also be utilized, especially if immunohistochemistry is inconclusive (32-37).

Updates in epithelioid malignant mesothelioma: subtyping according to prognostic factors and nuclear grade

It is well documented in the literature that epithelioid malignant mesothelioma carries a better prognosis than biphasic and sarcomatoid cases. Numerous reports have published on specific histologic parameters that have been shown to stratify patients into prognostic groups within epithelioid malignant mesothelioma. Accepted architectural patterns in epithelioid malignant mesothelioma are shown

Table 1 Architectural patterns observed in malignant mesothelioma

Tubulopapillary
Adenomatoid
Microcystic
Solid
Micropapillary
Transitional
Pleomorphic

Table 2 Proposed grading schemes in epithelioid malignant mesothelioma

Three tier nuclear grade
Nuclear grade = sum nuclear atypia score + mitotic count score
Nuclear atypia score: 1 = mild; 2 = moderate; 3 = severe
Mitotic count score: 1 = <1/10 HPF; 2 = 2-4/10 HPF; 3 = >5/10 HPF
Sum 2 or 3 = nuclear grade 1; Sum 4 or 5 = nuclear grade 2; Sum 6 = nuclear grade 3
Two tier grade
Utilizes nuclear grade from three tier system +/- presence of necrosis
Low grade = nuclear grade 1 +/- necrosis or nuclear grade 2 without necrosis
High grade = nuclear grade 2 with necrosis or nuclear grade 3 +/- necrosis

in *Table 1*. Architectural patterns, as well as cytologic and stromal features, are now recommended to be reported on diagnostic specimens as these features may help with prognostication or improve diagnostic accuracy (5).

Nuclear grading schemes have been proposed which are able to stratify epithelioid malignant mesothelioma into distinct prognostic groups (*Table 2*) (38,39). While the most recent iMig diagnostic guidelines did not formally endorse grading of epithelioid malignant mesothelioma, it is now favored by international consensus (5). While the previously published grading systems utilized a three tier approach based on nuclear atypia (*Figures 3,4,5*) and mitotic count, a two tier system of high (nuclear grade 2 with necrosis and nuclear grade 3) and low grade (nuclear grade 1 or nuclear grade 2 without necrosis) is favored and proposed (5).

Updates in biphasic malignant mesothelioma: issues with reproducibility, classification, and lingering issues

Biphasic malignant mesothelioma is arbitrarily defined by the most recent WHO as a malignant mesothelial tumor with at least 10% each of sarcomatoid and epithelioid components (1). Although robust data is lacking, two studies showed that prognostic cutoffs can be set at different percent sarcomatoid component (40,41). With this in mind, some experts believe in dropping the 10% requirement altogether. It is imperative, even on small biopsies, to recognize and record the percent of epithelioid and sarcomatoid components to properly diagnosis a tumor as biphasic (5). The challenges surrounding the diagnosis of biphasic malignant mesothelioma may stem from low interobserver reproducibility from lack of a

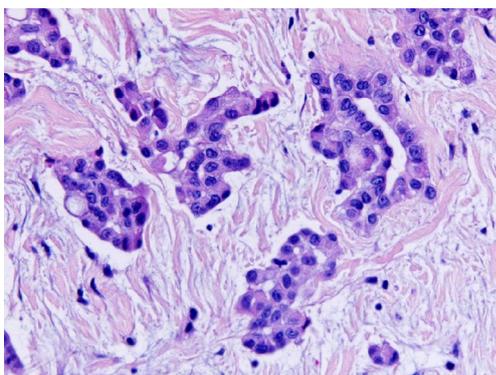


Figure 3 Epithelioid malignant mesothelioma showing nuclear atypia, score 1. The nuclei are small and round with occasional small nucleoli and only mild nuclear atypia (H&E, ×400).

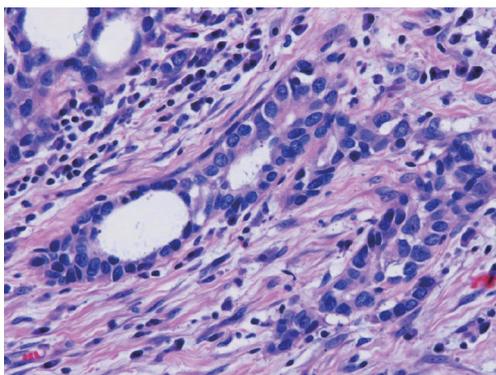


Figure 4 Epithelioid malignant mesothelioma showing nuclear atypia, score 2. The nuclei are enlarged with occasional large nucleoli and show increased nuclear pleomorphism in comparison to nuclear grade 1 (H&E, ×400).

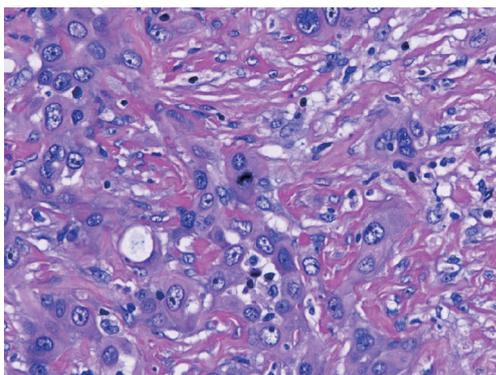


Figure 5 Epithelioid malignant mesothelioma showing nuclear atypia, score 3. There is frank nuclear pleomorphism and enlarged mitotic figures. Bizarre mitotic figures are also present (H&E, ×400).

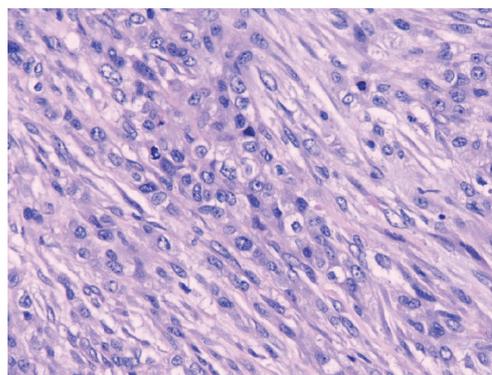


Figure 6 Transitional malignant mesothelioma showing a sheet of tumor cells with cohesion but elongation and a somewhat fascicular growth pattern (H&E, ×200).

standard definition (41). Other studies have shown better interobserver reproducibility in the identification of sarcomatoid components (42), and improved identification of mesothelial subtype following training (43). Lastly, appropriate classification of spindled mesothelial cells as benign or malignant hinders histologic subtyping of malignant mesothelioma. Recent studies have demonstrated discordant staining between epithelioid and sarcomatoid components for malignancy specific marker BAP1 (18,41). The exact role, if any, immunohistochemistry may play in the workup of biphasic mesothelioma is yet to be determined.

Pleomorphic and transitional mesothelioma

Malignant mesothelioma can show marked cytologic atypia with anaplasia and giant cells. The 2015 WHO defines such changes when present in epithelioid malignant mesothelioma, as pleomorphic mesothelioma (1). Noting that anaplasia and marked nuclear pleomorphism is not restricted to epithelioid subtype, recent guidelines suggest including pleomorphism as a cytologic feature of both epithelioid and sarcomatoid malignant mesothelioma (5). The transitional pattern of malignant mesothelioma (*Figure 6*) has been defined in the 2015 WHO as a feature of epithelioid malignant mesothelioma showing “sheet-like growth pattern in which the cells are cohesive but have elongated morphology” (1). However, recent data shows that tumors with transitional features have survival curves more closely resembling those of sarcomatoid malignant mesothelioma than epithelioid, and are genetically more

similar to sarcomatoid mesothelioma than epithelioid; these studies favor transitional features as a subset of sarcomatoid subtype (41,44).

Mesothelioma *in situ*

With advancements in understanding mesothelial biology and with increased utilization of immunohistochemical biomarkers, mesothelial malignancy specific markers, namely BAP1 and MTAP, have been demonstrated to be lost in mesothelium which does not show invasion or other features of malignancy. These few reported cases, termed malignant mesothelioma *in situ*, support the notion that a malignant mesothelioma *in situ* lesion likely exists prior to invasive disease (45-47).

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