Pathology of Malignant Pleural Mesothelioma

Yin P. Hung, MD, PhD[a], Lucian R. Chirieac, MD[b,*]

KEYWORDS

• Mesothelioma • Pathology • Epithelioid • Biphasic • Sarcomatoid • Immunohistochemistry • BAP1 • Differential diagnosis

KEY POINTS

- Diagnosis of malignant mesothelioma is based on assessment of histologic and immunophenotypic features.
- Classification of malignant mesothelioma (into epithelioid, biphasic, and sarcomatoid types) is based on assessment of cytologic features and has prognostic value.
- A panel of immunohistochemical markers is needed to distinguish sarcomatoid mesothelioma from sarcomatoid carcinoma, sarcomas, and mimics.
- Loss of BAP1 nuclear staining, MTAP cytoplasmic staining, and CDKN2A copy number assessment by fluorescence in situ hybridization may aid in distinguishing malignant mesothelioma from reactive mesothelial proliferations.
- Correlation with clinical, radiologic, and molecular features is helpful in diagnostic conundrums.

INTRODUCTION

Malignant mesothelioma originates from the cells in the serosal lining that surrounds the body cavities. Of all mesotheliomas, approximately 85% arise from the pleura, approximately 15% arise from the peritoneum, and the remainder (<1%) originates from the pericardium or the tunica vaginalis.[1] In the United States, diffuse malignant pleural mesothelioma affects approximately 3000 patients each year, with an annual incidence of approximately 1 in 100,000.[2,3] Diffuse malignant pleural mesothelioma shows a predilection for men and affects mostly the elderly,[4–6] although the age of distribution is wide, with young patients including adolescents reported.[7] The signs and symptoms can be nonspecific and, depending on the extent of tumor involvement, include pleuritic chest pain, dyspnea, night sweats, and weight loss.[8] Patients with diffuse malignant pleural mesothelioma are managed by trimodality therapy including surgery, chemotherapy, and radiotherapy.[9,10] The use of immunotherapy is under active clinical investigations.[11] The clinical outcome nonetheless remains generally dismal, with a median overall survival of 1 to 2 years.[6] Regarding the pathogenesis of diffuse malignant pleural mesothelioma, a history of asbestos exposure was noted in approximately 70% of patients.[4] Other etiologic factors include exposure to nonasbestos mineral fibers,[12] therapeutic radiation exposure for prior malignancy,[13,14] and in the setting of chronic inflammatory conditions.[15–17] Furthermore, germline alterations in *BAP1* and other tumor suppressors have been implicated in the development of diffuse malignant pleural mesothelioma in a subset of patients.[18,19]

The definitive diagnosis of diffuse malignant pleural mesothelioma is based on the pathologic assessment of tumor tissue, which is obtained from core biopsy sampling, pleurectomy, or other more extensive resections. To establish a pathologic diagnosis of malignant mesothelioma, diagnostic tools that are used clinically include

[a] Department of Pathology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114, USA; [b] Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
* Corresponding author.
E-mail address: lchirieac@bwh.harvard.edu

Thorac Surg Clin 30 (2020) 367–382
https://doi.org/10.1016/j.thorsurg.2020.08.007

histologic assessment, immunohistochemistry, electron microscopy, cytogenetics, and molecular techniques (eg, targeted next-generation sequencing, fluorescence in situ hybridization, and single-nucleotide polymorphism arrays). Despite the multiple diagnostic toolkits, the diagnosis of diffuse malignant pleural mesothelioma relies primarily on proper histologic assessment. Given its rarity and overlapping microscopic features with other benign and neoplastic conditions, the histologic diagnosis of diffuse malignant pleural mesothelioma is challenging, with misdiagnoses reported in greater than 60% of cases in some regions in the world as determined by retrospective review.[20] In this review, we discuss the pathologic features and the differential diagnosis of diffuse malignant pleural mesothelioma, including select diagnostic pitfalls.

GROSS FEATURES

Grossly, diffuse malignant pleural mesothelioma presents with circumferential pleural thickening or multifocal-to-diffuse pleural nodules that display a tan-white cut surface (**Fig. 1**A). Invasion into adjacent structures, such as diaphragm, chest wall, pericardium, and interlobular septae of lung, may be seen. In exceptionally rare cases, diffuse malignant pleural mesothelioma presents with diffuse lung parenchymal involvement, with radiographic and gross appearances mimicking an interstitial lung disease.[21]

MICROSCOPIC FEATURES

Diffuse malignant pleural mesothelioma is classified into three histologic types: (1) epithelioid, (2) biphasic (mixed), and (3) sarcomatoid.[1] The determination of histologic types is based on the cytologic features of the tumor. Epithelioid mesothelioma is characterized by epithelioid-to-round cells (**Fig. 1**B, C). Sarcomatoid mesothelioma is characterized by spindled cells with tapered nuclei (**Fig. 1**E, F). Biphasic mesothelioma harbors epithelioid and sarcomatoid components in various proportions, with each comprising at least 10% of the tumor (**Fig. 1**D).

Within each histologic type, diffuse malignant pleural mesothelioma is divided into several subtypes and patterns based on its cytologic, architectural, and background stromal features.[22] In epithelioid mesothelioma, tumor cells are usually epithelioid-to-round; other rare variants include clear cell, signet ring cell, rhabdoid, deciduoid, and small cell.[23–25] Tumor cells are arranged in diverse architectural patterns that include tubulopapillary, trabecular, solid, acinar, micropapillary, or adenomatoid, among others. In sarcomatoid mesothelioma, subtypes described include conventional/spindle cell, desmoplastic,[26,27] and lymphohistiocytoid.[28–30] A subset of sarcomatoid mesothelioma exhibits heterologous differentiation with osteosarcomatous, chondrosarcomatous, and/or rhabdomyosarcomatous elements.[27]

The assignment of histologic type is challenging, given the intertumoral and intratumoral morphologic heterogeneity. In some cases, it is difficult to distinguish between neoplastic spindled tumor cells (sarcomatoid component) and reactive stromal fibroblasts; the diagnosis of biphasic mesothelioma and epithelioid mesothelioma with prominent stroma is challenging.[31] Furthermore, there is considerable interobserver variability in the recognition of histologic types, even among mesothelioma expert pathologists, with the lowest interobserver agreements in biphasic mesotheliomas.[31–33] Proper type assignment in malignant mesothelioma is nonetheless important, given the prognostic differences among different histologic types. In addition, the accuracy of histologic types varies with the extent of tissue sampling.[34–36] In a study comparing the concordance between histologic types in initial biopsies with subsequent resections, the accuracy of typing increases with a higher number of biopsies.[36] Although sarcomatoid histology in biopsies is highly predictive of sarcomatoid histology in resections, epithelioid histology in biopsies is not entirely specific and is changed to biphasic or sarcomatoid types in resections in up to 20% of patients.[36]

HISTOLOGIC CRITERIA FOR DIFFUSE MALIGNANT PLEURAL MESOTHELIOMA

In diffuse malignant pleural mesothelioma, the goals of histologic assessment are to confirm the pathologic diagnosis and to determine the histologic type, which allows for prognostication and treatment planning. For the diagnosis of diffuse malignant pleural mesothelioma, one needs to establish each of the three conditions discussed next.

The Lesion Is Diffuse and Not Solitary

First, correlation with clinical and radiologic findings is needed to confirm that the distribution of the tumor is diffuse rather than solitary. Although nearly all (>99%) malignant pleural mesotheliomas are diffuse, rare cases of localized pleural mesothelioma have been described, which are solitary, have a different pathogenesis, and harbor a less aggressive clinical course.[37–40]

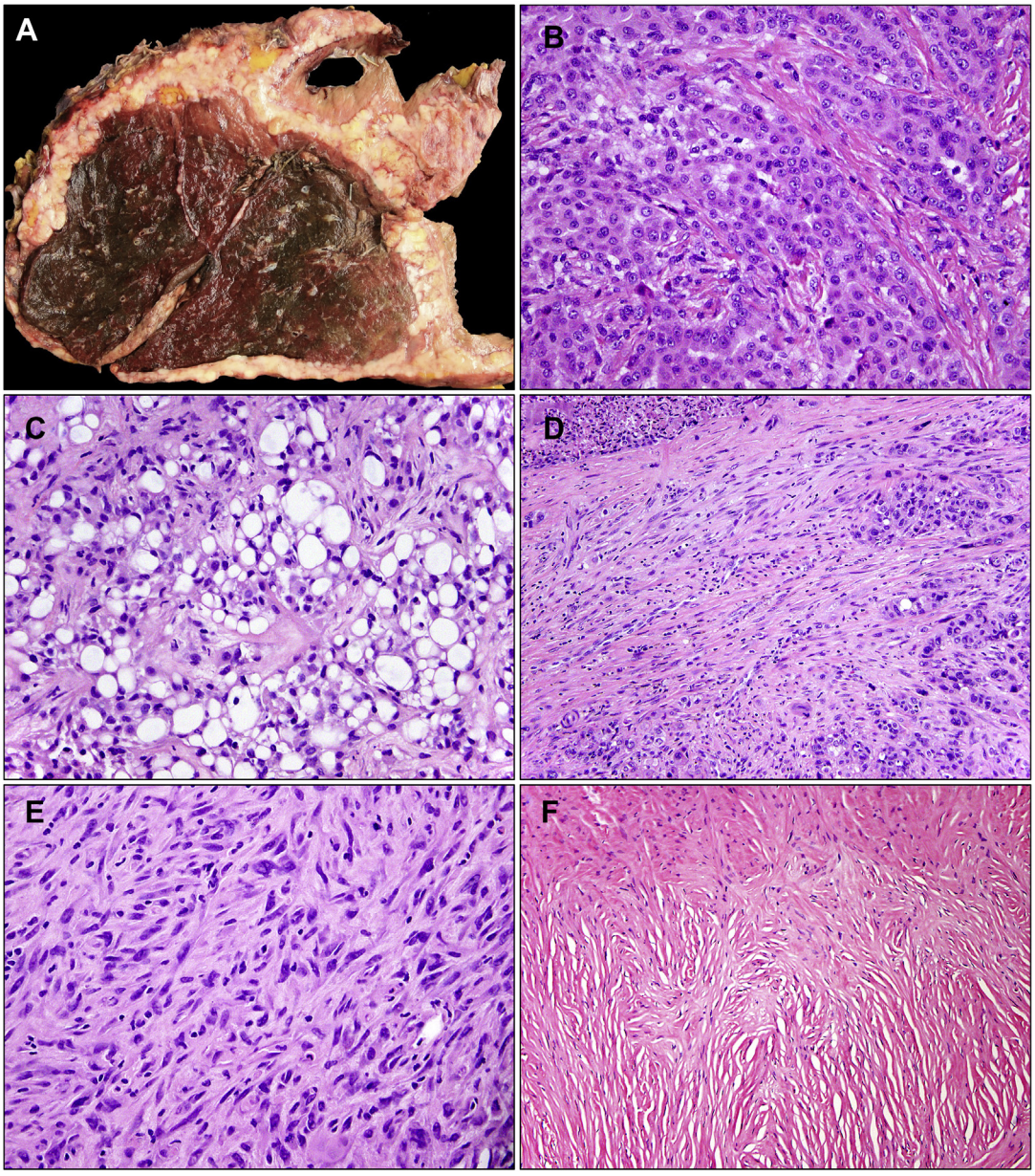

Fig. 1. Gross and histologic features of diffuse malignant pleural mesothelioma. (*A*) Gross photograph of diffuse malignant pleural mesothelioma surrounding lung parenchyma. (*B*) Epithelioid mesothelioma with tubulopapillary pattern. (*C*) Epithelioid mesothelioma with prominent vacuolation, mimicking signet ring cell carcinoma. (*D*) Biphasic mesothelioma, with sarcomatoid and epithelioid components. (*E*) Sarcomatoid mesothelioma. (*F*) Desmoplastic mesothelioma, with tumor cells scattered among storiform fibrosis.

The Lesional Cells Are Mesothelial

Given the morphologic overlap between malignant mesothelioma and diverse mimics, such as carcinomas, immunohistochemistry and, less commonly, electron microscopy is used to confirm the presence of mesothelial differentiation in the tumor cells. Other tools, such as cytogenetics and molecular analysis, may also be helpful in some instances (discussed later).

The Lesional Cells Are Malignant

Histologic assessment is integral to establish that the mesothelial cells are malignant. Morphologic

features that distinguish malignant mesothelioma from reactive conditions (Fig. 2) include:

- Invasion into adjacent tissue, such as adipose tissue, skeletal muscle, and lung
- Full-thickness pleural involvement
- Formation of expansile nodules (considered as a type of stromal invasion)

The presence of invasion is considered to be the most reliable criterion in distinguishing malignant mesothelioma from reactive mesothelial proliferations.[41,42] However, such features as necrosis, cytologic atypia, and mitoses should be interpreted with caution, because each are seen in reactive pleuritis and do not necessarily indicate malignancy. Although the diagnosis of malignant mesothelioma can be straightforward when the morphologic features are overtly malignant, some cases are challenging: sarcomatoid/desmoplastic mesothelioma may mimic chronic fibrosing pleuritis. Interpretation is difficult when there is limited diagnostic tissue, tangential sectioning, artifacts from histologic processing, and/or entrapment of adjacent structures mimicking invasion.[41,43] For a mesothelial proliferation that is suspicious for but not definitive for malignancy, one may report the findings as "atypical mesothelial proliferation" and recommend rebiopsy and/or close follow-up. In the distinction between malignant mesothelioma and reactive mesothelial proliferations, the role of ancillary studies had been limited until recently, when BAP1 or MTAP immunohistochemistry and *CDKN2A* copy number assessment by fluorescence in situ hybridization may aid the distinction in some instances (discussed later).

IMMUNOHISTOCHEMICAL FEATURES

Diagnostic Markers to Confirm Mesothelial Differentiation

Immunohistochemistry is integral to the pathologic diagnosis of malignant pleural mesothelioma in clinical practice. Useful immunohistochemical markers include positive markers to confirm mesothelial differentiation, such as WT1, calretinin, and D2-40 (Fig. 3A–C); and negative markers to exclude mimics, such as polyclonal CEA, TTF-1, and claudin-4.[44–46] Broad-spectrum keratins

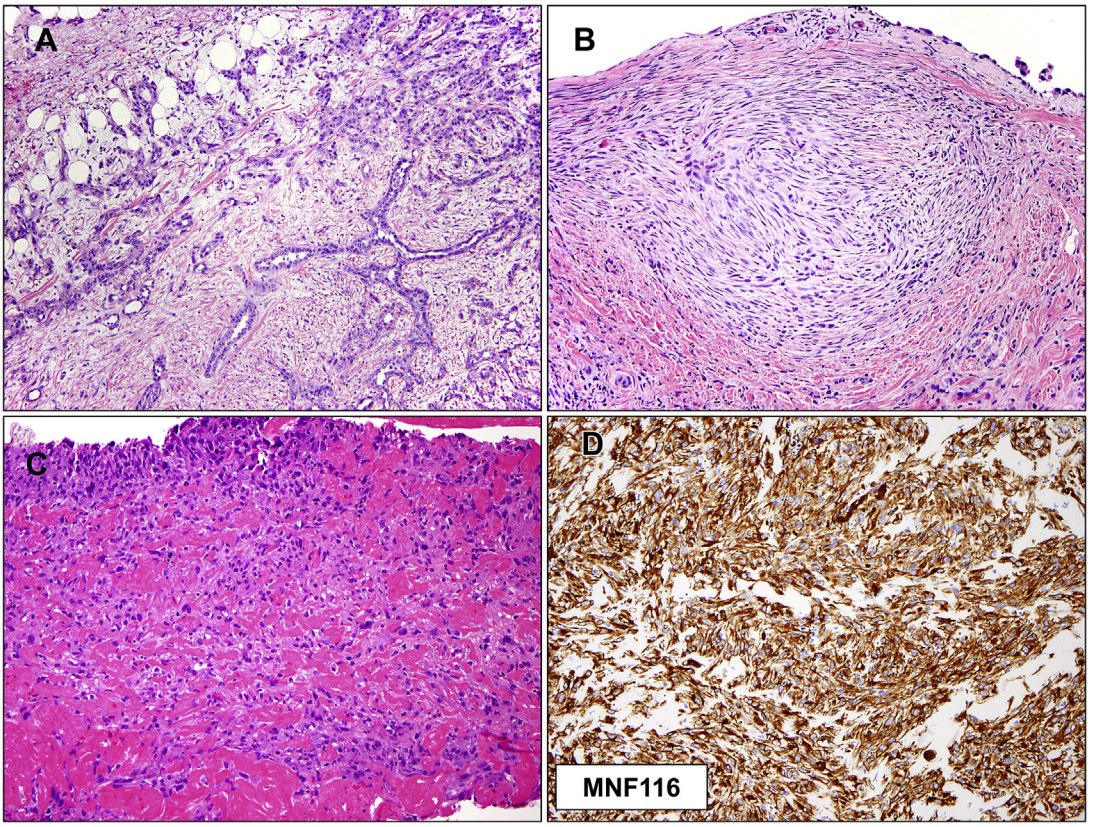

Fig. 2. Diagnostic features of diffuse malignant pleural mesothelioma. (*A*) Invasion into fibroadipose tissue. (*B*) Formation of expansile nodules. (*C*) Lack of zonation with full-thickness involvement. (*D*) Immunohistochemistry for keratin MNF116 in *C* highlights the increased number of tumor cells.

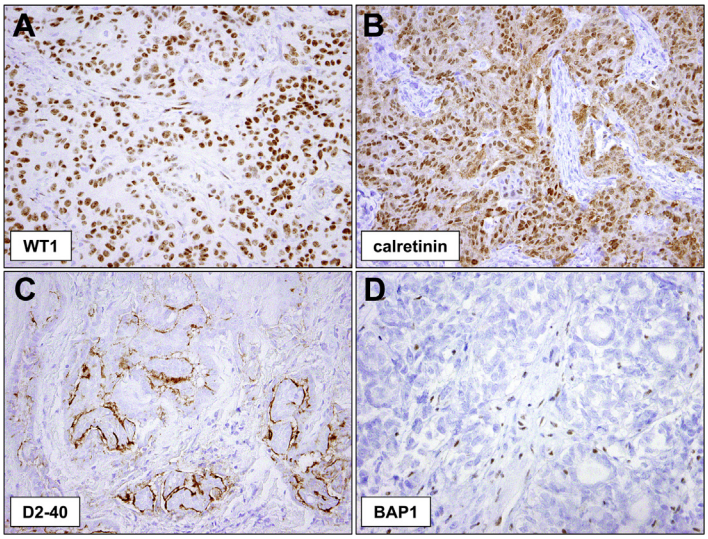

Fig. 3. Immunophenotypic features of diffuse malignant pleural mesothelioma. (*A*) Nuclear WT1 expression. (*B*) Cytoplasmic and nuclear calretinin staining. (*C*) Membranous D2-40 staining. (*D*) Loss of BAP1 nuclear staining.

are not specific and are expressed in mesotheliomas and carcinomas. Other novel markers recently described include glypican-1 as a positive marker for epithelioid mesothelioma,[47] HEG1 as a positive marker for mesotheliomas,[48,49] and MUC4 as a negative marker,[50,51] although data on their performance in clinical practice remain limited. As one of the caveats, no individual immunohistochemical marker is entirely sensitive and specific. Each of the established mesothelial markers (WT1, calretinin, and D2-40) is expressed in a subset of carcinomas. Conversely, epithelial markers (BerEP4 and MOC31) are expressed in a subset of mesotheliomas, although TTF1 (for adenocarcinoma), p40 (for squamous cell carcinoma), and claudin 4 (for carcinoma)[45] are generally specific although not entirely sensitive. In the guidelines from the International Mesothelioma Panel (MesoPath) and International Mesothelioma Interest Group (iMig), a panel comprising at least two mesothelial markers (calretinin, WT1, D2-40) and two epithelial markers (Claudin-4, TTF1, polyclonal CEA) should be used to establish the diagnosis.[52] In the evaluation of positive markers, the expression of mesothelial markers is focal and limited (especially in sarcomatoid mesothelioma[53]; in fact, there is no consensus on the minimum percentage of cells needed to show marker expression).[54] A 10% staining cutoff has been proposed to be most sensitive and specific in using TTF1 and calretinin immunohistochemistry to distinguish between epithelioid mesothelioma and lung adenocarcinoma,[55] although whether these cutoffs are applicable for other antibodies, histologic types of mesothelioma, and differential diagnoses remains unclear.

BAP1 (BRCA1-associated protein-1) is a tumor suppressor implicated in the pathogenesis of malignant mesothelioma, uveal melanoma, cholangiocarcinoma, and clear cell renal cell carcinoma.[56] Recurrent somatic and/or germline mutations in *BAP1* are present in malignant mesothelioma. As a surrogate for *BAP1* genomic status, BAP1 immunohistochemistry is used as a diagnostic marker for malignant mesothelioma. Aberrant BAP1 protein expression, defined as complete loss of nuclear BAP1 staining (**Fig. 3**D; including absence of staining or the presence of cytoplasmic BAP1 staining only), is seen in approximately 50% to 70% of diffuse malignant pleural mesothelioma, epithelioid type[57–63] but less than 20% in sarcomatoid type.[64] Aberrant BAP1 expression is seen in 20% of cholangiocarcinoma[65]; 10% of clear cell renal cell carcinoma[66]; and rarely most other carcinomas, including in less than 1% of non–small cell lung carcinomas.[67,68] In diagnostically problematic cases, aberrant BAP1 expression favors malignant mesothelioma and excludes lung carcinoma.[67,68]

Sarcomatoid mesothelioma and sarcomatoid (pleomorphic/spindle cell) carcinoma overlap in their histologic and immunohistochemical features, therefore requiring the use of multiple markers for definitive distinction. Sarcomatoid mesothelioma often shows focal to absent expression for most mesothelial markers, with the most sensitive marker being D2-40/podoplanin.[53,69] Immunohistochemical markers that may aid the distinction between sarcomatoid mesothelioma

and sarcomatoid carcinoma include p40 and p63 (for squamous cell carcinoma), TTF1 (for adenocarcinoma), and calretinin (for mesothelioma).[54] Recently, GATA3 has been explored as a potential diagnostic marker for sarcomatoid mesothelioma,[70] with GATA3 expression in only approximately 10% to 20% of non–small cell lung carcinomas[71] including sarcomatoid carcinoma.[70] One can render an accurate diagnosis of sarcomatoid mesothelioma when encountering a spindle/pleomorphic tumor that expresses multiple mesothelial but not epithelial markers; conversely, a diagnosis of carcinoma is made for a sarcomatoid tumor that expresses multiple epithelial but not mesothelial markers. For sarcomatoid tumors that do not show clear-cut mesothelial or epithelial differentiation despite extensive immunohistochemistry work-up, one may not render a definitive diagnosis.[54] In these instances, correlation with clinical, radiologic, and molecular findings may be helpful.[27]

Diagnostic Markers to Confirm a Malignant Mesothelial Proliferation

Although the distinction between malignant mesothelioma and reactive mesothelial proliferations primarily relies on histologic assessment, this is challenging in some cases. Immunohistochemical markers, such as glucose transporter-1 (GLUT1), insulin-like growth factor II mRNA binding protein 3 (IMP3), epithelial membrane antigen (EMA), desmin, and p53, have been explored over the years as potential diagnostic adjuncts. Because they are not entirely sensitive or specific, their utility to distinguish malignant mesothelioma from reactive proliferations on a case-by-case basis is limited.[72,73]

BAP1 immunohistochemistry is a specific (although not sensitive) marker to distinguish malignant mesothelioma from reactive mesothelial proliferations. Aberrant BAP1 expression (complete loss of staining or cytoplasmic staining only) is seen in approximately 50% to 70% of diffuse malignant pleural mesothelioma[57–63]; whereas, reactive proliferations show intact BAP1 nuclear staining.[57,58,61,63] In particular, the utility of BAP1 to distinguish sarcomatoid mesothelioma from reactive pleuritis is limited, because BAP1 expression loss occurs in less than 20% of sarcomatoid mesothelioma.[64] Of note, in the absence of corroborative histologic features of malignancy (ie, invasion), aberrant BAP1 expression in mesothelial cells alone is not sufficient for the diagnosis of malignant mesothelioma. Mesothelioma in situ, as characterized by a single layer of surface mesothelial cells showing BAP1 expression loss with no evidence of invasion and absence of any pleural nodules or masses, has recently been described and may represent a precursor lesion to developing malignant mesothelioma, albeit with a protracted course in some cases.[74]

MTAP (methylthioadenosine phosphorylase) immunohistochemistry has been used as a diagnostic marker for malignant mesothelioma. *MTAP* is located near *CDKN2A* on the chromosomal region 9p21; loss of cytoplasmic MTAP staining is considered a surrogate for chromosomal 9p loss as determined by concurrent *CDKN2A* fluorescence in situ hybridization testing[75] and has been reported in approximately 40% to 60% of malignant mesothelioma but rarely in reactive proliferations.[61–63] In distinguishing malignant mesothelioma from reactive mesothelial proliferations, although MTAP alone is not sensitive, combined use of BAP1 and MTAP immunohistochemistry may improve the sensitivity and specificity.[61–63] Of note, because approximately 10% to 20% of lung adenocarcinoma shows MTAP loss,[62] MTAP immunohistochemistry is not specific in the distinction between malignant mesothelioma and lung carcinoma.

Additional markers, such as cyclin D1 and 5-hmC (5-hydroxymethylcytosine), have been explored as potential tools to distinguish malignant mesothelioma from reactive mesothelial proliferations, although their utility in clinical practice remains unclear. One study used tissue microarrays and found diffuse nuclear cyclin D1 staining, indicative of Hippo pathway activation, in most malignant mesotheliomas and minimal to focal cyclin D1 staining in reactive mesothelial proliferations.[76] Reduction of 5-hmC has been noted in diverse tumor types including malignant mesothelioma[77]; multifocal (>50%) loss of 5-hmC staining was seen in most malignant mesotheliomas but not reactive mesothelial proliferations in one study.[78]

ULTRASTRUCTURAL FEATURES

Electron microscopy is performed in fresh tumor tissue that is saved at the time of gross examination. In malignant mesothelioma, tumor cells characteristically display elongated microvilli, with a length-to-width ratio of greater than 10:1, on the luminal and abluminal surfaces.[79,80] Prominent desmosomes and abundant intermediate filaments are present. These ultrastructural features are prominent in epithelioid mesothelioma but is subtle to absent in sarcomatoid mesothelioma.[80]

CYTOGENETIC FEATURES

Most diffuse malignant pleural mesotheliomas are characterized by complex numerical and structural karyotypic alterations.[81] Although no specific chromosomal abnormalities are pathognomonic for malignant mesothelioma, loss of chromosomal region 9p including *CDKN2A* or 22q including *NF2* is noted in a subset of tumors. With fluorescence in situ hybridization testing, homozygous loss of *CDKN2A* is found in approximately 60% of diffuse malignant pleural mesothelioma[82–84]; hemizygous loss of *NF2* is present in approximately 50% of diffuse malignant pleural mesothelioma.[85] Although the presence of *CDKN2A* loss can aid the distinction of malignant mesothelioma from reactive mesothelial proliferations, *CDKN2A* loss alone is not useful in separating malignant mesothelioma from other tumor types, because *CDKN2A* loss is found in a substantial fraction of sarcomatoid mesothelioma, sarcomatoid carcinomas, and sarcomas.[86]

A rare subset of malignant pleural mesothelioma harbors a peculiar near-haploid karyotype, with extensive loss-of-heterozygosity involving nearly all chromosomes except chromosomes 5 and 7.[87]

MOLECULAR FEATURES

Most diffuse malignant pleural mesotheliomas are characterized by recurrent mutations in tumor suppressors and epigenetic regulators, including *BAP1*, *NF2*, *TP53*, *SETD2*, and others.[87–91] Alterations are identified in multiple pathways in the regulation of cell cycle, RNA processing, histone regulation, and cell growth.[89] *BAP1* is one of the most frequently altered genes; mechanisms of *BAP1* inactivation include point mutations, copy number loss, inactivating structural rearrangements, and minute chromosomal deletions.[87–89,92–94]

Furthermore, a small subset of diffuse malignant pleural mesothelioma harbors unusual genetic alterations: genomic near-haploidization has been described in rare malignant pleural mesotheliomas that harbor mutations in *TP53* and/or *SETDB1*.[87] Oncogenic *EWSR1-ATF1* fusion has been described in a malignant pleural mesothelioma from a young female.[95] Although *ALK* rearrangements have been identified in rare patients with diffuse malignant peritoneal mesothelioma,[96–98] this has not been identified in patients with diffuse malignant pleural mesothelioma.

Germline mutations are overall present in approximately 10% of patients with diffuse malignant pleural mesothelioma and primarily involve genes in the DNA repair and cell cycle regulation, such as *BAP1*, *BRCA2*, *CDKN2A*, *TMEM127*, *VHL*, *WT1*, *MRE11A*, and *MSH6*.[99,100] Germline mutations seem to be enriched in patients who are young, with family history of mesothelioma, or with peritoneal mesothelioma.[99,101,102]

Consistent with its histomorphologic heterogeneity, diffuse malignant pleural mesothelioma shows an impressive molecular diversity. Several research groups have proposed various molecular classification schemes to establish molecular groups of malignant mesothelioma, using data from genomics, transcriptomics, proteomics, epigenomics, immune features, or a combination of these approaches.[87,89,103–105] In addition, one study analyzed the data using a decomposition approach and proposed a histomolecular continuum in diffuse malignant pleural mesothelioma, with each tumor comprising epithelioid-like and sarcomatoid-like molecular features.[90]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of malignant pleural mesothelioma depends on the histologic type (epithelioid, biphasic, or sarcomatoid) under consideration (**Box 1**, **Figs. 4** and **5**). Diffuse malignant pleural mesothelioma can resemble reactive pleuritis or diverse tumor types, including carcinomas, melanoma, and sarcomas.

In addition to diffuse malignant pleural mesothelioma, the World Health Organization recognizes additional types of mesothelial lesions: localized malignant mesothelioma, well-differentiated papillary mesothelioma, and adenomatoid tumor.[1] Localized pleural mesothelioma is microscopically identical to diffuse malignant mesothelioma, although it is radiographically and grossly solitary and circumscribed[37–39]; genetically, localized pleural mesothelioma comprises three groups (*BAP1*-mutant, *TRAF7*-mutant, and near-haploid), with similarities but also differences from diffuse malignant pleural mesothelioma.[40] Well-differentiated papillary mesothelioma (see **Fig. 4**E), often an incidental finding in the peritoneum of women, can occur in the pleura[106] and is genetically characterized by recurrent mutations in *TRAF7* or *CDC42*.[107] Rarely, well-differentiated papillary mesothelioma shows back-to-back papillae with foci of invasion,[108] morphologically mimicking diffuse malignant mesothelioma. Furthermore, distinction between a malignant mesothelioma with prominent papillary surface

Box 1
Differential diagnosis

Differential diagnosis of epithelioid malignant mesothelioma

- Metastatic carcinoma
  - Expresses epithelial markers (eg, claudin-4, MOC31, and MUC4)
  - Rarely or does not express mesothelial markers (eg, WT1, calretinin, and D2-40)
  - Most lung adenocarcinomas express TTF-1 and Napsin A
  - Most squamous cell carcinomas express p40 and p63
  - CK5/6 is expressed in squamous cell carcinoma and epithelioid mesothelioma and is not useful for distinction
  - Identification of genetic alterations characteristic of lung carcinomas (eg, *EGFR* activating or *MET* exon 14 skipping mutations) supports carcinomas and excludes sarcomatoid mesothelioma
- Metastatic melanoma
  - Variable architectural patterns and prominent nucleoli
  - Expresses melanocytic markers (eg, S-100 protein, SOX10, and HMB45)
- Epithelioid hemangioendothelioma
  - Rare distinctive malignant vascular tumor
  - Cord-like pattern, myxohyaline matrix, intracytoplasmic vacuoles
  - Expresses vascular markers (eg, ERG, CD31, and CD34) and CAMTA1 in most cases[134]
  - D2-40 is expressed in malignant mesothelioma and epithelioid hemangioendothelioma and is not useful for distinction
  - Recurrent *WWTR1-CAMTA1* or rarely *YAP1-TFE3* fusion[135,136]
- Well-differentiated papillary mesothelioma
  - Papillae with myxoid cores and single mesothelial cell layers
  - Recurrent *TRAF7* or *CDC42* mutations[107]
- Adenomatoid tumor
  - Microcystic architecture, with tubules and cords of epithelioid vacuolated cells
  - Recurrent *TRAF7* mutations[109]

Differential diagnosis of sarcomatoid malignant mesothelioma

- Sarcomatoid carcinoma
  - Expresses epithelial markers (eg, claudin-4, MOC31, and MUC4)
  - Rarely or does not express mesothelial markers (eg, WT1, calretinin, and D2-40)
  - Aberrant BAP1 expression favors sarcomatoid mesothelioma over sarcomatoid carcinoma
  - Identification of genetic alterations characteristic of lung carcinomas (eg, *EGFR* activating or *MET* exon 14 skipping mutations) supports carcinomas and excludes sarcomatoid mesothelioma
- Chronic fibrosing pleuritis
  - Does not show dense cellularity, expansile nodules, or absence of zonation effect
  - Invasion is the most reliable criterion to exclude a reactive process and to confirm malignancy
- Synovial sarcoma
  - Monophasic, biphasic, or poorly differentiated histology
  - Recurrent *SYT-SSX1* or *SYT-SSX2* fusion in most cases[137]
  - TLE1 is expressed in synovial sarcoma and malignant mesothelioma[138] and is thus not specific for distinction
- Solitary fibrous tumor
  - Collagenous background, hemangiopericytoma-like staghorn vessels, and monomorphic spindle cells
  - Recurrent *NAB2-STAT6* fusion[139,140]
  - Expresses STAT6 by immunohistochemistry[141]

Differential diagnosis of biphasic malignant mesothelioma

- Biphasic synovial sarcoma
  - Recurrent *SYT-SSX1* fusion in most cases
  - TLE1 is expressed in synovial sarcoma and malignant mesothelioma[138] and is thus not specific for distinction
- Epithelioid hemangioendothelioma
  - Rare distinctive malignant vascular tumor
  - Cord-like pattern, myxohyaline matrix, intracytoplasmic vacuoles
  - Expresses vascular markers (eg, ERG, CD31, and CD34) and CAMTA1 in most cases[134]
  - D2-40 is expressed in malignant mesothelioma and epithelioid hemangioendothelioma and is not useful for distinction
  - Recurrent *WWTR1-CAMTA1* or rarely *YAP1-TFE3* fusion[135,136]

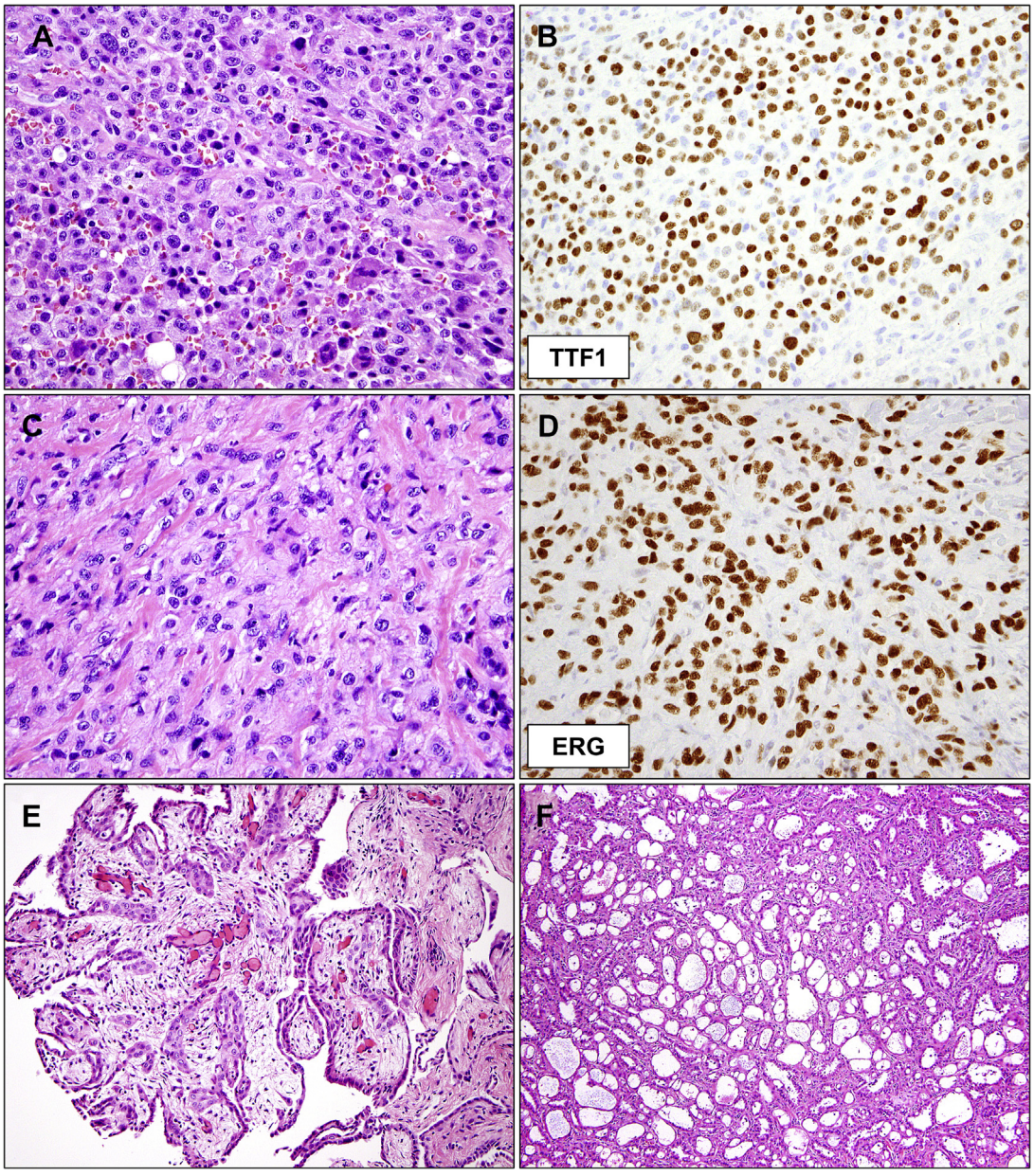

Fig. 4. Histologic mimics of diffuse malignant pleural mesothelioma. (*A*) Lung adenocarcinoma, mimicking an epithelioid mesothelioma. (*B*) Tumor cells in *A* show diffuse strong TTF1 expression and lacks mesothelial marker expression (not shown), confirming the diagnosis. (*C*) Epithelioid hemangioendothelioma, with cord-like growth pattern and rare vacuoles. (*D*) Tumor cells in *C* show diffuse strong ERG expression, along with expression of vascular markers CD31 and CAMTA1 (not shown), confirming the diagnosis. (*E*) Well-differentiated papillary mesothelioma, characterized by papillary architecture with each core lined by a single cell layer. (*F*) Adenomatoid tumor, characterized by a microcystic appearance with epithelioid-to-vacuolated tumor cells.

projections and well-differentiated papillary mesothelioma is challenging, particularly in small superficial biopsies. Adenomatoid tumor (see **Fig. 4**F) primarily affects the genital tracts but rarely can involve the pleura; recurrent mutations in *TRAF7* have been described in adenomatoid tumors of genital-type.[109]

EMERGING PROGNOSTIC AND PREDICTIVE FACTORS

In diffuse malignant pleural mesothelioma, histologic type is an integral prognostic indicator: patients with epithelioid, biphasic, and sarcomatoid mesotheliomas have an overall median survival

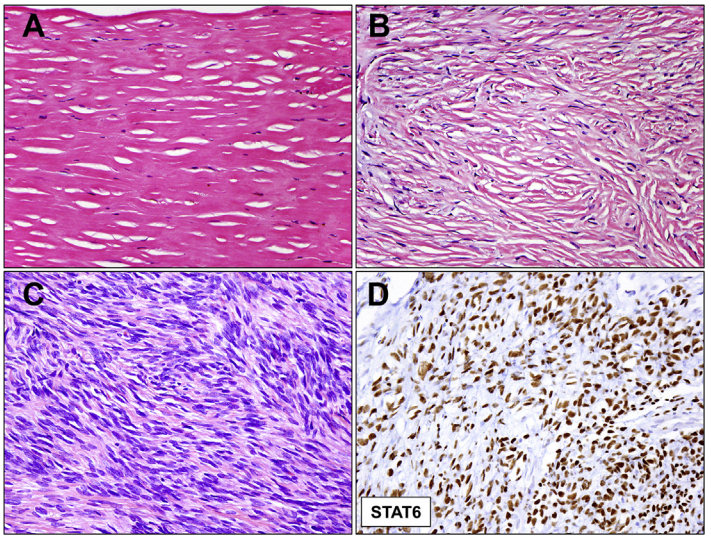

Fig. 5. Histologic mimics of diffuse malignant pleural mesothelioma. (*A*) Pleural plaque, showing orderly arrangement of mesothelial cells. (*B*) Desmoplastic mesothelioma, characterized by storiform arrangement of tumor cells, mimicking a pleural plaque or fibrosis. (*C*) Solitary fibrous tumor, mimicking sarcomatoid mesothelioma. (*D*) Tumor cells in *C* show diffuse strong STAT6 expression, along with absence of mesothelial marker expression (not shown), confirming the diagnosis.

of approximately 14, 10, and 5 months, respectively.[6,110,111] Over the years, additional histologic, immunohistochemical, molecular, and immune features have been described to be prognostic or predictive of select therapy.

In epithelioid mesothelioma, poor prognostic features described include the presence of micropapillary or solid patterns.[112] Pleomorphic mesothelioma is characterized by anaplasia and/or multinucleated tumor giant cells comprising at least 10% of the tumor.[113] Historically considered as a subtype of epithelioid mesothelioma including in the World Health Organization 2015 classification,[1] pleomorphic mesothelioma has an aggressive clinical behavior comparable with sarcomatoid mesothelioma.[114] Another emerging pattern to recognize is the transitional subtype, characterized by sheet-like growth of elongated plump tumor cells with well-defined cell borders and cohesion.[33] Although the histologic interobserver concordance is fair-to-moderate, transitional mesothelioma shows a poor prognosis comparable with sarcomatoid mesothelioma.[33,115] In addition to the assessment of architectural patterns, various three- or two-tiered grading schemes have been described over the years and include the assessment of mitotic activity, necrosis,[112,116–121] and, in one system, Ki67 proliferation index.[120] The recent European Reference Network for Rare Adult Solid Cancers/International Association for the Study of Lung Cancer proposal for histologic classification for epithelioid pleural mesothelioma has proposed that diagnostic reports should include the assessment of nuclear atypia, mitotic count, and necrosis and assign tumors into low and high grades.[122]

Recent studies explored immunohistochemical targets as potential prognostic and predictive markers. In a study of diffuse malignant pleural mesothelioma patients with epithelioid histology, prolonged survival has been noted in tumors with loss of BAP1 and retained p16 expression in univariate and multivariate analyses.[123] Certain molecular features seem to be prognostic in diffuse malignant pleural mesothelioma. In particular, patients with mesothelioma with germline *BAP1* mutations show a prolonged survival.[102,124] Patients with mesothelioma with germline mutations in one of the DNA repair genes also respond better to platinum chemotherapy as compared with patients without germline mutations,[100] thus highlighting the prognostic and predictive value of these mutations in patients with diffuse malignant pleural mesothelioma. Of note, although the presence of *ALK* gene rearrangements in rare patients with diffuse malignant peritoneal mesothelioma[96–98] raises the possibility of targeted treatment with ALK inhibitors,[125] this has not been demonstrated in patients with diffuse malignant pleural mesothelioma to date.

Programmed death-ligand 1 (PD-L1; CD274), a negative regulator of immune checkpoint, represents a target in immunotherapy, with PD-L1 immunohistochemistry evaluated as a predictive biomarker in diverse tumor types.[126] PD-L1 expression generally seems higher in sarcomatoid mesothelioma than in epithelioid mesothelioma.[127–130] Increased PD-L1 expression has been noted in sarcomatoid mesothelioma but not

in reactive mesothelial proliferations,[131] suggesting PD-L1 immunohistochemistry as a potential tool to separate sarcomatoid mesothelioma from reactive mesothelial proliferations.[131] In terms of its predictive value, the utility of PD-L1 immunohistochemistry and optimal assessment criteria in diffuse malignant pleural mesothelioma remain unclear.

Epithelioid mesothelioma rarely expresses PD-L1 but seems to rely on VISTA (V-domain Ig Suppressor of T-cell Activation; VSIR [V-set immunoregulatory receptor]) for immune blockade.[87,90] Immunohistochemistry for VISTA shows high expression in epithelioid mesothelioma but not in sarcomatoid mesothelioma.[132,133] Because VISTA is expressed in benign mesothelial cells, VISTA immunohistochemistry cannot distinguish between malignant epithelioid mesothelioma and reactive mesothelial proliferations.[132] However, non–small cell lung carcinomas do not seem to express VISTA,[132] suggesting a potential diagnostic role of using VISTA immunohistochemistry to distinguish epithelioid mesothelioma from lung carcinomas. In patients with diffuse malignant pleural mesothelioma, whereas PD-L1 expression correlates with worse survival,[133] VISTA expression correlates with better survival[132,133] and may suggest potential immunotherapy targets in these patients.

CLINICS CARE POINTS

- Histologic diagnosis of malignant mesothelioma is based on assessment of histologic and immunophenotypic features.
- Histologic typing of malignant mesothelioma (into epithelioid, biphasic, and sarcomatoid types) is based on assessment of cytologic features and has prognostic value.
- A panel of immunohistochemical markers is needed to distinguish sarcomatoid mesothelioma from sarcomatoid carcinoma and mimics.
- Loss of nuclear BAP1 staining by immunohistochemistry is specific but not sensitive in distinguishing malignant mesothelioma from reactive mesothelial proliferations.
- Correlation with clinical, radiologic, and molecular features is helpful in certain challenging diagnostic situations.

DISCLOSURE

L.R. Chirieac undertakes medicolegal work related to mesothelioma. Y.P. Hung has nothing to disclose.

REFERENCES

1. Travis WD, Brambilla E, Burke A, et al. Pathology and genetics of tumors of the lung, pleura, thymus, and heart. 4th edition. Lyon (France): IARC Press; 2015.
2. Moolgavkar SH, Meza R, Turim J. Pleural and peritoneal mesotheliomas in SEER: age effects and temporal trends, 1973-2005. Cancer Causes Control 2009;20(6):935–44.
3. Beebe-Dimmer JL, Fryzek JP, Yee CL, et al. Mesothelioma in the United States: a Surveillance, Epidemiology, and End Results (SEER)-Medicare investigation of treatment patterns and overall survival. Clin Epidemiol 2016;8:743–50.
4. Delgermaa V, Takahashi K, Park EK, et al. Global mesothelioma deaths reported to the World Health Organization between 1994 and 2008. Bull World Health Organ 2011;89(10):716–24.
5. Mazurek JM, Syamlal G, Wood JM, et al. Malignant mesothelioma mortality—United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2017;66(8):214–8.
6. Nelson DB, Rice DC, Niu J, et al. Long-term survival outcomes of cancer-directed surgery for malignant pleural mesothelioma: propensity score matching analysis. J Clin Oncol 2017;35(29):3354–62.
7. Vivero M, Bueno R, Chirieac LR. Clinicopathologic and genetic characteristics of young patients with pleural diffuse malignant mesothelioma. Mod Pathol 2018;31(1):122–31.
8. Robinson BW, Lake RA. Advances in malignant mesothelioma. N Engl J Med 2005;353(15):1591–603.
9. Friedberg JS, Culligan MJ, Tsao AS, et al. A proposed system toward standardizing surgical-based treatments for malignant pleural mesothelioma, from the Joint National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma Applied Research Foundation Taskforce. J Thorac Oncol 2019;14(8):1343–53.
10. Gomez DR, Rimner A, Simone CB 2nd, et al. The use of radiation therapy for the treatment of malignant pleural mesothelioma: expert opinion from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol 2019;14(7):1172–83.
11. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol 2019;20(2):239–53.

12. Roushdy-Hammady I, Siegel J, Emri S, et al. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. Lancet 2001;357(9254):444–5.
13. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. Cancer 1996;77(7):1379–85.
14. Chirieac LR, Barletta JA, Yeap BY, et al. Clinicopathologic characteristics of malignant mesotheliomas arising in patients with a history of radiation for Hodgkin and non-Hodgkin lymphoma. J Clin Oncol 2013;31(36):4544–9.
15. Hillerdal G, Berg J. Malignant mesothelioma secondary to chronic inflammation and old scars. Two new cases and review of the literature. Cancer 1985;55(9):1968–72.
16. Kodama Y, Hoshi S, Minami M, et al. Malignant mesothelioma associated with chronic empyema with elevation of serum CYFRA19: A case report. Biosci Trends 2008;2(6):250–4.
17. Attanoos RL, Churg A, Galateau-Salle F, et al. Malignant mesothelioma and its non-asbestos causes. Arch Pathol Lab Med 2018;142(6):753–60.
18. Testa JR, Cheung M, Pei J, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43(10):1022–5.
19. Xu J, Kadariya Y, Cheung M, et al. Germline mutation of Bap1 accelerates development of asbestos-induced malignant mesothelioma. Cancer Res 2014;74(16):4388–97.
20. Guo Z, Carbone M, Zhang X, et al. Improving the accuracy of mesothelioma diagnosis in China. J Thorac Oncol 2017;12(4):714–23.
21. Larsen BT, Klein JR, Hornychova H, et al. Diffuse intrapulmonary malignant mesothelioma masquerading as interstitial lung disease: a distinctive variant of mesothelioma. Am J Surg Pathol 2013;37(10):1555–64.
22. Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2013;137(5):647–67.
23. Ordonez NG. Mesothelioma with rhabdoid features: an ultrastructural and immunohistochemical study of 10 cases. Mod Pathol 2006;19(3):373–83.
24. Ordonez NG. Deciduoid mesothelioma: report of 21 cases with review of the literature. Mod Pathol 2012;25(11):1481–95.
25. Ordonez NG. Mesotheliomas with small cell features: report of eight cases. Mod Pathol 2012;25(5):689–98.
26. Wilson GE, Hasleton PS, Chatterjee AK. Desmoplastic malignant mesothelioma: a review of 17 cases. J Clin Pathol 1992;45(4):295–8.
27. Klebe S, Brownlee NA, Mahar A, et al. Sarcomatoid mesothelioma: a clinical-pathologic correlation of 326 cases. Mod Pathol 2010;23(3):470–9.
28. Henderson DW, Attwood HD, Constance TJ, et al. Lymphohistiocytoid mesothelioma: a rare lymphomatoid variant of predominantly sarcomatoid mesothelioma. Ultrastruct Pathol 1988;12(4):367–84.
29. Yao DX, Shia J, Erlandson RA, et al. Lymphohistiocytoid mesothelioma: a clinical, immunohistochemical and ultrastructural study of four cases and literature review. Ultrastruct Pathol 2004;28(4):213–28.
30. Galateau-Salle F, Attanoos R, Gibbs AR, et al. Lymphohistiocytoid variant of malignant mesothelioma of the pleura: a series of 22 cases. Am J Surg Pathol 2007;31(5):711–6.
31. Galateau Salle F, Le Stang N, Nicholson AG, et al. New insights on diagnostic reproducibility of biphasic mesotheliomas: a multi-institutional evaluation by the International Mesothelioma Panel From the MESOPATH Reference Center. J Thorac Oncol 2018;13(8):1189–203.
32. Brcic L, Vlacic G, Quehenberger F, et al. Reproducibility of malignant pleural mesothelioma histopathologic subtyping. Arch Pathol Lab Med 2018;142(6):747–52.
33. Dacic S, Le Stang N, Husain A, et al. Interobserver variation in the assessment of the sarcomatoid and transitional components in biphasic mesotheliomas. Mod Pathol 2020;33(2):255–62.
34. Arrossi AV, Lin E, Rice D, et al. Histologic assessment and prognostic factors of malignant pleural mesothelioma treated with extrapleural pneumonectomy. Am J Clin Pathol 2008;130(5):754–64.
35. Kao SC, Yan TD, Lee K, et al. Accuracy of diagnostic biopsy for the histological subtype of malignant pleural mesothelioma. J Thorac Oncol 2011;6(3):602–5.
36. Chirieac LR, Hung YP, Foo WC, et al. Diagnostic value of biopsy sampling in predicting histology in patients with diffuse malignant pleural mesothelioma. Cancer 2019;125(23):4164–71.
37. Okike N, Bernatz PE, Woolner LB. Localized mesothelioma of the pleura: benign and malignant variants. J Thorac Cardiovasc Surg 1978;75(3):363–72.
38. Allen TC, Cagle PT, Churg AM, et al. Localized malignant mesothelioma. Am J Surg Pathol 2005;29(7):866–73.
39. Marchevsky AM, Khoor A, Walts AE, et al. Localized malignant mesothelioma, an unusual and poorly characterized neoplasm of serosal origin: best current evidence from the literature and the International Mesothelioma Panel. Mod Pathol 2020;33(2):281–96.

40. Hung YP, Dong F, Dubuc AM, et al. Molecular characterization of localized pleural mesothelioma. Mod Pathol 2020;33(2):271–80.
41. Churg A, Colby TV, Cagle P, et al. The separation of benign and malignant mesothelial proliferations. Am J Surg Pathol 2000;24(9):1183–200.
42. Churg A, Galateau-Salle F. The separation of benign and malignant mesothelial proliferations. Arch Pathol Lab Med 2012;136(10):1217–26.
43. Churg A, Cagle P, Colby TV, et al. The fake fat phenomenon in organizing pleuritis: a source of confusion with desmoplastic malignant mesotheliomas. Am J Surg Pathol 2011;35(12):1823–9.
44. Ordonez NG. Immunohistochemical diagnosis of epithelioid mesothelioma: an update. Arch Pathol Lab Med 2005;129(11):1407–14.
45. Facchetti F, Gentili F, Lonardi S, et al. Claudin-4 in mesothelioma diagnosis. Histopathology 2007; 51(2):261–3.
46. Anttila S. Epithelioid lesions of the serosa. Arch Pathol Lab Med 2012;136(3):241–52.
47. Amatya VJ, Kushitani K, Kai Y, et al. Glypican-1 immunohistochemistry is a novel marker to differentiate epithelioid mesothelioma from lung adenocarcinoma. Mod Pathol 2018;31(5):809–15.
48. Tsuji S, Washimi K, Kageyama T, et al. HEG1 is a novel mucin-like membrane protein that serves as a diagnostic and therapeutic target for malignant mesothelioma. Sci Rep 2017;7:45768.
49. Naso JR, Tsuji S, Churg A. HEG1 is a highly specific and sensitive marker of epithelioid malignant mesothelioma. Am J Surg Pathol 2020. https://doi.org/10.1097/PAS.0000000000001469.
50. Amatya VJ, Kushitani K, Mawas AS, et al. MUC4, a novel immunohistochemical marker identified by gene expression profiling, differentiates pleural sarcomatoid mesothelioma from lung sarcomatoid carcinoma. Mod Pathol 2017;30(5):672–81.
51. Mawas AS, Amatya VJ, Kushitani K, et al. MUC4 immunohistochemistry is useful in distinguishing epithelioid mesothelioma from adenocarcinoma and squamous cell carcinoma of the lung. Sci Rep 2018;8(1):134.
52. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma 2017 Update of the Consensus Statement From the International Mesothelioma Interest Group. Arch Pathol Lab Med 2018;142(1): 89–108.
53. Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. Am J Cancer Res 2011;1(1):14–24.
54. Marchevsky AM, LeStang N, Hiroshima K, et al. The differential diagnosis between pleural sarcomatoid mesothelioma and spindle cell/pleomorphic (sarcomatoid) carcinomas of the lung: evidence-based guidelines from the International Mesothelioma Panel and the MESOPATH National Reference Center. Hum Pathol 2017;67:160–8.
55. Le Stang N, Burke L, Blaizot G, et al. Differential diagnosis of epithelioid malignant mesothelioma with lung and breast pleural metastasis: a systematic review compared with a standardized panel of antibodies—a new proposal that may influence pathologic practice. Arch Pathol Lab Med 2020; 144(4):446–56.
56. Carbone M, Yang H, Pass HI, et al. BAP1 and cancer. Nat Rev Cancer 2013;13(3):153–9.
57. Sheffield BS, Hwang HC, Lee AF, et al. BAP1 immunohistochemistry and p16 FISH to separate benign from malignant mesothelial proliferations. Am J Surg Pathol 2015;39(7):977–82.
58. Cigognetti M, Lonardi S, Fisogni S, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. Mod Pathol 2015; 28(8):1043–57.
59. Andrici J, Jung J, Sheen A, et al. Loss of BAP1 expression is very rare in peritoneal and gynecologic serous adenocarcinomas and can be useful in the differential diagnosis with abdominal mesothelioma. Hum Pathol 2016;51:9–15.
60. Carbone M, Shimizu D, Napolitano A, et al. Positive nuclear BAP1 immunostaining helps differentiate non-small cell lung carcinomas from malignant mesothelioma. Oncotarget 2016;7(37): 59314–21.
61. Hida T, Hamasaki M, Matsumoto S, et al. Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: comparison with 9p21 FISH and BAP1 immunohistochemistry. Lung Cancer 2017;104:98–105.
62. Berg KB, Dacic S, Miller C, et al. Utility of methylthioadenosine phosphorylase compared with BAP1 immunohistochemistry, and CDKN2A and NF2 fluorescence in situ hybridization in separating reactive mesothelial proliferations from epithelioid malignant mesotheliomas. Arch Pathol Lab Med 2018;142(12):1549–53.
63. Kinoshita Y, Hamasaki M, Yoshimura M, et al. A combination of MTAP and BAP1 immunohistochemistry is effective for distinguishing sarcomatoid mesothelioma from fibrous pleuritis. Lung Cancer 2018;125:198–204.
64. Hwang HC, Sheffield BS, Rodriguez S, et al. Utility of BAP1 immunohistochemistry and p16 (CDKN2A) FISH in the diagnosis of malignant mesothelioma in effusion cytology specimens. Am J Surg Pathol 2016;40(1):120–6.
65. Misumi K, Hayashi A, Shibahara J, et al. Intrahepatic cholangiocarcinoma frequently shows loss of BAP1 and PBRM1 expression, and demonstrates specific clinicopathological and genetic

characteristics with BAP1 loss. Histopathology 2017;70(5):766–74.
66. Joseph RW, Kapur P, Serie DJ, et al. Loss of BAP1 protein expression is an independent marker of poor prognosis in patients with low-risk clear cell renal cell carcinoma. Cancer 2014;120(7): 1059–67.
67. Andrici J, Parkhill TR, Jung J, et al. Loss of expression of BAP1 is very rare in non-small cell lung carcinoma. Pathology 2016;48(4):336–40.
68. Owen D, Sheffield BS, Ionescu D, et al. Loss of BRCA1-associated protein 1 (BAP1) expression is rare in non-small cell lung cancer. Hum Pathol 2017;60:82–5.
69. Padgett DM, Cathro HP, Wick MR, et al. Podoplanin is a better immunohistochemical marker for sarcomatoid mesothelioma than calretinin. Am J Surg Pathol 2008;32(1):123–7.
70. Berg KB, Churg A. GATA3 immunohistochemistry for distinguishing sarcomatoid and desmoplastic mesothelioma from sarcomatoid carcinoma of the lung. Am J Surg Pathol 2017; 41(9):1221–5.
71. Miettinen M, McCue PA, Sarlomo-Rikala M, et al. GATA3: a multispecific but potentially useful marker in surgical pathology: a systematic analysis of 2500 epithelial and nonepithelial tumors. Am J Surg Pathol 2014;38(1):13–22.
72. Churg A, Sheffield BS, Galateau-Salle F. New markers for separating benign from malignant mesothelial proliferations: are we there yet? Arch Pathol Lab Med 2016;140(4):318–21.
73. Lee AF, Gown AM, Churg A. IMP3 and GLUT-1 immunohistochemistry for distinguishing benign from malignant mesothelial proliferations. Am J Surg Pathol 2013;37(3):421–6.
74. Churg A, Galateau-Salle F, Roden AC, et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. Mod Pathol 2020;33(2): 297–302.
75. Chapel DB, Schulte JJ, Berg K, et al. MTAP immunohistochemistry is an accurate and reproducible surrogate for CDKN2A fluorescence in situ hybridization in diagnosis of malignant pleural mesothelioma. Mod Pathol 2020;33(2):245–54.
76. Pors J, Naso J, Berg K, et al. Cyclin D1 immunohistochemical staining to separate benign from malignant mesothelial proliferations. Mod Pathol 2020; 33(2):312–8.
77. Roulois D, Deshayes S, Guilly MN, et al. Characterization of preneoplastic and neoplastic rat mesothelial cell lines: the involvement of TETs, DNMTs, and 5-hydroxymethylcytosine. Oncotarget 2016; 7(23):34664–87.
78. Chapel DB, Husain AN, Krausz T. Immunohistochemical evaluation of nuclear 5-hydroxymethylcytosine (5-hmC) accurately distinguishes malignant pleural mesothelioma from benign mesothelial proliferations. Mod Pathol 2019;32(3):376–86.
79. Warhol MJ, Hickey WF, Corson JM. Malignant mesothelioma: ultrastructural distinction from adenocarcinoma. Am J Surg Pathol 1982;6(4): 307–14.
80. Oury TD, Hammar SP, Roggli VL. Ultrastructural features of diffuse malignant mesotheliomas. Hum Pathol 1998;29(12):1382–92.
81. Sandberg AA, Bridge JA. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors. Mesothelioma. Cancer Genet Cytogenet 2001;127(2):93–110.
82. Illei PB, Rusch VW, Zakowski MF, et al. Homozygous deletion of CDKN2A and codeletion of the methylthioadenosine phosphorylase gene in the majority of pleural mesotheliomas. Clin Cancer Res 2003;9(6):2108–13.
83. Dacic S, Kothmaier H, Land S, et al. Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas. Virchows Arch 2008;453(6): 627–35.
84. Chiosea S, Krasinskas A, Cagle PT, et al. Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas. Mod Pathol 2008; 21(6):742–7.
85. Kinoshita Y, Hamasaki M, Yoshimura M, et al. Hemizygous loss of NF2 detected by fluorescence in situ hybridization is useful for the diagnosis of malignant pleural mesothelioma. Mod Pathol 2020; 33(2):235–44.
86. Tochigi N, Attanoos R, Chirieac LR, et al. p16 Deletion in sarcomatoid tumors of the lung and pleura. Arch Pathol Lab Med 2013;137(5):632–6.
87. Hmeljak J, Sanchez-Vega F, Hoadley KA, et al. Integrative molecular characterization of malignant pleural mesothelioma. Cancer Discov 2018;8(12): 1548–65.
88. Guo G, Chmielecki J, Goparaju C, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. Cancer Res 2015; 75(2):264–9.
89. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48(4):407–16.
90. Blum Y, Meiller C, Quetel L, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. Nat Commun 2019;10(1):1333.
91. Quetel L, Meiller C, Assie JB, et al. Genetic alterations of malignant pleural mesothelioma: association to tumor heterogeneity and overall survival. Mol Oncol 2020. https://doi.org/10.1002/1878-0261.12651.

92. Bott M, Brevet M, Taylor BS, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma. Nat Genet 2011;43(7):668–72.
93. Lo Iacono M, Monica V, Righi L, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. J Thorac Oncol 2015;10(3):492–9.
94. Yoshikawa Y, Emi M, Hashimoto-Tamaoki T, et al. High-density array-CGH with targeted NGS unmask multiple noncontiguous minute deletions on chromosome 3p21 in mesothelioma. Proc Natl Acad Sci U S A 2016;113(47):13432–7.
95. Desmeules P, Joubert P, Zhang L, et al. A subset of malignant mesotheliomas in young adults are associated with recurrent EWSR1/FUS-ATF1 fusions. Am J Surg Pathol 2017;41(7):980–8.
96. Hung YP, Dong F, Watkins JC, et al. Identification of ALK rearrangements in malignant peritoneal mesothelioma. JAMA Oncol 2018;4(2):235–8.
97. Loharamtaweethong K, Puripat N, Aoonjai N, et al. Anaplastic lymphoma kinase (ALK) translocation in paediatric malignant peritoneal mesothelioma: a case report of novel ALK-related tumour spectrum. Histopathology 2016;68(4):603–7.
98. Mian I, Abdullaev Z, Morrow B, et al. Anaplastic lymphoma kinase gene rearrangement in children and young adults with mesothelioma. J Thorac Oncol 2020;15(3):457–61.
99. Panou V, Gadiraju M, Wolin A, et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. J Clin Oncol 2018;36(28):2863–71.
100. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. Proc Natl Acad Sci U S A 2019;116(18):9008–13.
101. Ohar JA, Cheung M, Talarchek J, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. Cancer Res 2016;76(2):206–15.
102. Pastorino S, Yoshikawa Y, Pass HI, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. J Clin Oncol 2018;36. JCO2018790352.
103. de Reynies A, Jaurand MC, Renier A, et al. Molecular classification of malignant pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition. Clin Cancer Res 2014;20(5):1323–34.
104. Gordon GJ, Rockwell GN, Jensen RV, et al. Identification of novel candidate oncogenes and tumor suppressors in malignant pleural mesothelioma using large-scale transcriptional profiling. Am J Pathol 2005;166(6):1827–40.
105. Lopez-Rios F, Chuai S, Flores R, et al. Global gene expression profiling of pleural mesotheliomas: overexpression of aurora kinases and P16/CDKN2A deletion as prognostic factors and critical evaluation of microarray-based prognostic prediction. Cancer Res 2006;66(6):2970–9.
106. Galateau-Salle F, Vignaud JM, Burke L, et al. Well-differentiated papillary mesothelioma of the pleura: a series of 24 cases. Am J Surg Pathol 2004;28(4):534–40.
107. Stevers M, Rabban JT, Garg K, et al. Well-differentiated papillary mesothelioma of the peritoneum is genetically defined by mutually exclusive mutations in TRAF7 and CDC42. Mod Pathol 2019;32(1):88–99.
108. Churg A, Allen T, Borczuk AC, et al. Well-differentiated papillary mesothelioma with invasive foci. Am J Surg Pathol 2014;38(7):990–8.
109. Goode B, Joseph NM, Stevers M, et al. Adenomatoid tumors of the male and female genital tract are defined by TRAF7 mutations that drive aberrant NF-kB pathway activation. Mod Pathol 2018;31(4):660–73.
110. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. J Thorac Cardiovasc Surg 1999;117(1):54–63 [discussion: 63–5].
111. Verma V, Ahern CA, Berlind CG, et al. Survival by histologic subtype of malignant pleural mesothelioma and the impact of surgical resection on overall survival. Clin Lung Cancer 2018;19(6):e901–12.
112. Rosen LE, Karrison T, Ananthanarayanan V, et al. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. Mod Pathol 2018;31(4):598–606.
113. Ordonez NG. Pleomorphic mesothelioma: report of 10 cases. Mod Pathol 2012;25(7):1011–22.
114. Kadota K, Suzuki K, Sima CS, et al. Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or sarcomatoid mesothelioma. J Thorac Oncol 2011;6(5):896–904.
115. Salle FG, Le Stang N, Tirode F, et al. Comprehensive molecular and pathological evaluation of transitional mesothelioma assisted by deep learning approach: a multi institutional study of the International Mesothelioma Panel from MESOPATH Reference Center. J Thorac Oncol 2020. https://doi.org/10.1016/j.jtho.2020.01.025.
116. Beer TW, Carr NJ, Whittaker MA, et al. Mitotic and in situ end-labeling apoptotic indices as prognostic markers in malignant mesothelioma. Ann Diagn Pathol 2000;4(3):143–8.

117. Borczuk AC, Taub RN, Hesdorffer M, et al. P16 loss and mitotic activity predict poor survival in patients with peritoneal malignant mesothelioma. Clin Cancer Res 2005;11(9):3303–8.
118. Demirag F, Unsal E, Yilmaz A, et al. Prognostic significance of vascular endothelial growth factor, tumor necrosis, and mitotic activity index in malignant pleural mesothelioma. Chest 2005; 128(5):3382–7.
119. Kadota K, Suzuki K, Colovos C, et al. A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma. Mod Pathol 2012;25(2):260–71.
120. Pelosi G, Papotti M, Righi L, et al. Pathologic grading of malignant pleural mesothelioma: an evidence-based proposal. J Thorac Oncol 2018; 13(11):1750–61.
121. Zhang YZ, Brambilla C, Molyneaux PL, et al. Utility of nuclear grading system in epithelioid malignant pleural mesothelioma in biopsy-heavy setting: an external validation study of 563 cases. Am J Surg Pathol 2020;44(3):347–56.
122. Nicholson AG, Sauter JL, Nowak AK, et al. EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach. J Thorac Oncol 2020;15(1):29–49.
123. Chou A, Toon CW, Clarkson A, et al. The epithelioid BAP1-negative and p16-positive phenotype predicts prolonged survival in pleural mesothelioma. Histopathology 2018;72(3):509–15.
124. Baumann F, Flores E, Napolitano A, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis 2015;36(1):76–81.
125. Ruschoff JH, Gradhand E, Kahraman A, et al. STRN-ALK rearranged malignant peritoneal mesothelioma with dramatic response following ceritinib treatment. JCO Precis Oncol 2019;3:1–6.
126. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015;33(17):1974–82.
127. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. J Thorac Oncol 2014;9(7):1036–40.
128. Cedres S, Ponce-Aix S, Zugazagoitia J, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PLoS One 2015;10(3):e0121071.
129. Combaz-Lair C, Galateau-Salle F, McLeer-Florin A, et al. Immune biomarkers PD-1/PD-L1 and TLR3 in malignant pleural mesotheliomas. Hum Pathol 2016;52:9–18.
130. Thapa B, Salcedo A, Lin X, et al. The immune microenvironment, genome-wide copy number aberrations, and survival in mesothelioma. J Thorac Oncol 2017;12(5):850–9.
131. Derakhshan F, Ionescu D, Cheung S, et al. Use of programmed death ligand-1 (PD-L1) staining to separate sarcomatoid malignant mesotheliomas from benign mesothelial reactions. Arch Pathol Lab Med 2020;144(2):185–8.
132. Chung YS, Kim M, Cha YJ, et al. Expression of V-set immunoregulatory receptor in malignant mesothelioma. Mod Pathol 2020;33(2):263–70.
133. Muller S, Victoria Lai W, Adusumilli PS, et al. V-domain Ig-containing suppressor of T-cell activation (VISTA), a potentially targetable immune checkpoint molecule, is highly expressed in epithelioid malignant pleural mesothelioma. Mod Pathol 2020;33(2):303–11.
134. Doyle LA, Fletcher CD, Hornick JL. Nuclear expression of CAMTA1 distinguishes epithelioid hemangioendothelioma from histologic mimics. Am J Surg Pathol 2016;40(1):94–102.
135. Antonescu CR, Le Loarer F, Mosquera JM, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. Genes Chromosomes Cancer 2013;52(8):775–84.
136. Errani C, Zhang L, Sung YS, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer 2011;50(8):644–53.
137. Clark J, Rocques PJ, Crew AJ, et al. Identification of novel genes, SYT and SSX, involved in the t(X; 18)(p11.2;q11.2) translocation found in human synovial sarcoma. Nat Genet 1994;7(4):502–8.
138. Matsuyama A, Hisaoka M, Iwasaki M, et al. TLE1 expression in malignant mesothelioma. Virchows Arch 2010;457(5):577–83.
139. Chmielecki J, Crago AM, Rosenberg M, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. Nat Genet 2013;45(2):131–2.
140. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013;45(2):180–5.
141. Doyle LA, Vivero M, Fletcher CD, et al. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol 2014; 27(3):390–5.