The Diagnosis of Pleural Tumors Other Than Mesothelioma

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• Context.—Pleural pathology has been dominated by discussions relating to the diagnosis, prognosis, etiology, and management of malignant mesothelioma. However, there exists a diverse group of other neoplasms that involve the pleura; the most common by far is metastatic carcinoma, usually of pulmonary origin. Other metastatic tumors of varied histogenesis do occur but are less common. Primary pleural neoplasms other than diffuse malignant mesothelioma are either uncommon or rare and have received less attention.

Objective.—To provide a review of those diverse tumors that can involve the pleura other than mesothelioma in order to facilitate their accurate diagnosis.

Data Sources.—Review of relevant literature published via PubMed and other search engines.

Conclusions.—A wide variety of tumors can involve the pleura. In most cases, the approach of considering the morphologic features with appropriate immunohistochemistry, in the correct clinical context, allows for a confident diagnosis. For a number of those soft tissue tumors that are well recognized in the pleura, such as solitary fibrous tumor, desmoid-type fibromatosis, synovial sarcoma, and epitheloid hemangioendothelioma, novel markers now exist based on an understanding of the individual tumors' molecular characteristics. Primary pleural lymphomas are rare with poor prognosis. They represent localized specific diffuse large B-cell lymphomas, with either post–germinatal center B-cell or plasma cell lineage, arising in the context of either immunodeficiency or immune sequestration and with viral infection.

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The World Health Organization (WHO) classification of tumors of the pleura recognizes, based on morphology, codes, 3 broad histogenetic classes of neoplasm, namely mesothelial tumors, mesenchymal tumors, and lymphoproliferative disorders.1 Mesothelial tumors are beyond the scope of this review. The primary pleural mesenchymal tumors can be distilled into 3 groups: fibroblastic tumors (solitary fibrous tumor [SFT] and its malignant counterpart, malignant SFT; calcifying fibrous tumor [CFT]; and desmoid-type fibromatosis [DTF]), vascular tumors (epithelioid hemangioendothelioma [EHE] and angiosarcoma [AS]), and tumors of uncertain differentiation (synovial sarcoma [SS] and desmoplastic small round cell tumor). There also exist a number of other tumors that may rarely occur as primary pleural neoplasms, such as pleuropulmonary blastoma (PPB) and undifferentiated sarcoma, and these are discussed.

Primary pleural lymphomas are rare, comprising 2 specific lymphoma entities, namely primary effusion lymphoma (PEL) and diffuse large B-cell lymphoma associated with chronic inflammation (DLBCL-Cl). However, a number of other distinct lymphoma entities may manifest as primary pleural disease, most notably marginal zone B-cell lymphoma. All forms of hematologic malignancy may involve the pleura, usually as secondary involvement from nodal, extranodal, or marrow-based disease.

Secondary tumors are the most common cancer to involve the pleura by far, and metastatic carcinoma, usually of pulmonary origin, manifests with malignant pleural effusions and/or multifocal serosal involvement.2 In some cases, there is diffuse pleurotropic metastatic disease, and these tumors have been termed pseudomesothelioma on account of their close clinical and radiologic mimicry with diffuse malignant mesothelioma.3,4 Pleural metastases from a variety of other extrathoracic carcinomas, as well as from a variety of histogenetically diverse neoplasms, are also well reported.5–12 There has been much focus on the diagnostic distinction between metastatic carcinoma and malignant epithelioid mesothelioma.13–20 Spindle cell tumors of the pleura pose an even greater diagnostic dilemma to the surgical pathologist and have received much less attention in the scientific literature.21–24 In general, particularly in small biopsy specimens, routine markers have had limited use in either confirming or rejecting the diagnosis of sarcomatoid mesothelioma. More recently, novel markers have been identified for a number of nonmesothelial mesenchymal tumors, born of a greater understanding of the individual tumor's molecular characteristics. These novel
molecular and immunohistochemical markers now allow for a confirmatory diagnosis of these pleural tumors, and, by implication, allow the surgical pathologist to exclude sarcomatoid mesothelioma. It is beyond the scope of this review to discuss the diagnosis of the various metastatic tumors that may involve the pleura beyond highlighting their frequency and diversity. In most cases, careful morphologic assessment with considered marker studies and an evaluation of the case in the clinical context allow for an accurate diagnosis. This article provides an overview of the various pleural tumors other than mesothelioma that may be encountered and a practical approach to their diagnosis.

MESENCHYMAL TUMORS

The WHO classification of tumors of the pleura recognizes the following as primary mesenchymal tumors: SFT and its malignant counterpart, malignant SFT; CFT; DT; EHE and AS; and those tumors of uncertain differentiation, SS and desmoplastic small round cell tumor. The Table summarizes the typical morphologic, immunophenotypic, and molecular findings for these neoplasms.

SOLITARY FIBROUS TUMOR

Solitary fibrous tumor is the most common benign neoplasm of the pleura, although it accounts for less than 5% of pleural tumors. Solitary fibrous tumor is a fibroblastic mesenchymal tumor arising in ubiquitous anatomic locations within a wide age range with no sex preponderance. Most cases are identified in middle-aged adults as occult findings, although a variety of nonspecific general and thoracic symptoms have been reported. Uncommonly, finger clubbing, hypertrophic pulmonary osteoarthropathy, and refractory hypoglycemia related to the production of an insulin-like growth factor have been reported. There is no known etiologic agent and no link with tobacco or asbestos. Most SFTs are well-circumscribed, partially encapsulated, firm, tan-colored masses around 5 to 10 cm, although rare giant SFTs are reported. Most SFTs with typical morphology are indolent benign neoplasms; about 10% to 15% show local recurrence and unpredictable clinical behavior. Aggressive behavior is associated with positive symptomatology, large size (>10 cm), and infiltrative borders. By light microscopy, high mitotic rate (more than 4 mitoses per 2 mm²), hypercellularity, cellular atypia, and necrosis have been determined as morphologic criteria for malignant SFT, although mitotic rate is the most reliable criterion of aggressive behavior. Frankly sarcomatous elements or dedifferentiation may be observed and are associated with a poor prognosis. In comparison with benign-spectrum SFT, the more aggressive SFTs show higher Ki-67 expression and overexpress p53 with variable CD34. However, in small biopsy specimens, these markers are not reliable to determine aggressive behavior in SFT.

The main morphologic differential diagnoses with SFT in the pleural setting is wide and includes malignant mesothelioma, sarcomatoid type; SS; thymoma WHO type A; schwannoma; and DT. Immunohistochemistry plays an important role and is discussed.

CALCIFYING FIBROUS TUMOR

This is a rare fibroblastic proliferation in the pleura characterized by paucicellular fibrocollagenous stroma with psammomatous or dystrophic calcification. Infrathoracic CFT is usually localized to the visceral pleura without invasion of the underlying lung parenchyma. There are no known etiologic factors. Calcifying fibrous tumor is now regarded as a distinct neoplastic entity. It has been postulated that CFT may fall within the spectrum of IgG4-related disease. However, this is not widely accepted. Pleural CFT occurs predominantly in adult women. The mean age at diagnosis is 34 years. The tumor is commonly identified as an incidental finding. However, symptomatic presentations include chest pain and a nonproductive cough. Imaging shows single or multiple well-defined pleural-based lesions, with areas of high attenuation on computed tomography scanning reflecting the intratumoral calcification. Resection specimens show a well-circumscribed but unencapsulated lesion. The tumor morphology is characteristic with abundant collagenous stroma and scant fibroblasts, variable lymphocytic aggregates, and focal dystrophic or psammomatous calcification. On immunohistochemistry, the lesional spindle cells show reactivity to vimentin, CD34, and factor XIIa antibodies. Smooth muscle actin, desmin, S100, and CD31 are usually negative. No specific molecular genetic aberrations have been associated with pleural CFT.

Approximately 10% to 15% of patients have recurrent disease, although there are no reliable morphologic indicators to determine this. Calcifying fibrous tumor does not metastasize and overall prognosis is excellent.

Calcifying fibrous tumor can usually be distinguished from the myriad of other spindle cell proliferations in the pleura on account of its morphologic features in conjunction with the characteristic clinical and radiologic findings. Histologic overlap with other benign entities such as chronic fibrous pleuritis, calcified pleural plaque, silicotic nodule, and hyalinizing granuloma can be problematic in small biopsies.
| Morphologic Features | Cytokeratin | Calretinin | CK 5/6 | WT-1 | SMA | Desmin | S100 | CD34 | CD31 | ERG | FLI-1 | CD99 | BCL-2 | STAT6 | β-Catenin | TLE1 | CAMTA-1 | Molecular Marker |
|----------------------|-------------|------------|--------|------|-----|--------|------|------|------|------|-------|------|-------|-------|-----------|------|---------|-----------------|
| SFT                  | -           | -          | -      | -    | -   | ±      | -    | +    | -    | -    | -     | +    | +     | +     | ±         | -   | -       | NAB2-STAT6 fusion |
| CFT                  | -           | -          | -      | -    | -   | ±      | -    | -    | -    | -    | -     | +    | -     | -     | -         | -   | NA      |
| DTF                  | -           | ±          | -      | -    | -   | -     | -    | -    | -    | -    | -     | -    | +     | -     | -         | +   | CTNNB1 mutation |
| EHE                  | ±           | -          | ±      | -    | -   | -     | +    | +    | +    | -    | -     | -    | -     | +     | -         | -   | WWTR1-CAMTA1 fusion |
| AS                   | ±           | -          | ±      | -    | -   | -     | -    | -    | -    | -    | -     | -    | -     | -     | -         | -   | NA      |
| SS                   | +           | +          | +      | -    | -   | ±     | -    | -    | -    | -    | -     | -    | -     | +     | -         | +   | t(X;18) SYT-SSX fusion |
| PPB                  | -           | -          | -      | -    | -   | ±     | -    | -    | -    | -    | -     | -    | -     | -     | -         | -   | DICER-1 mutation |
| DSRCT                | +           | -          | -      | +    | -   | +    | -    | -    | -    | -    | -     | ±    | -     | -     | -         | +   | EWSR1-WT1 fusion |
| Ca                   | +           | ±          | -      | -    | -   | -     | +    | -    | -    | -    | -     | +    | -     | -     | -         | +   | NA      |
| MM                   | +           | ±          | ±      | +    | -   | -    | ±    | -    | -    | -    | -     | -    | ±     | -     | ±         | -   | NA      |

Abbreviations: AS, angiosarcoma; Ca, carcinoma; CFT, calcifying fibrous tumor; DSRCT, desmoplastic small round cell tumor; DTF, desmoid-type fibromatosis; EHE, epithelioid hemangioendothelioma; MM, malignant mesothelioma; NA, not applicable; PPB, pleuropulmonary blastoma; SFT, solitary fibrous tumor; SS, synovial sarcoma; - , typically absent; +, typically positive; ±, variably positive.

It is recognized that in exceptional cases the typical immunophenotype as detailed in the table may be supplemented by the expression of other markers discussed in the text.

Focal.

Dot positivity.
of extra-abdominal DTF. Aneuploidy has also been associated with DTF, with trisomy 8 and trisomy 20 detected in 31% and 23% of cases, respectively.\(^{59,60}\) Sporadic APC mutations have been found in a very small subset of DTF. Interestingly, the APC gene is responsible for breakdown of β-catenin; thus, β-catenin is overexpressed, albeit through a different mechanism than that of tumors with CTNNB1 mutations. Unlike its intra-abdominal counterpart, DTF of the pleura has not previously been linked with germline APC mutations in the context of familial adenomatous polyposis.\(^1\)

Although DTF shows no metastatic tendency, aggressive localized infiltrative disease is common. Around 25% will recur locally, which can pose management difficulties, often leading to suboptimal clinical outcomes.\(^{61,62}\) Predicting behavior is problematic, as excision margin status and histologic features do not correlate with local recurrence. Tumor size and young age at presentation have been linked with a more aggressive course.\(^{53}\) Several studies have concluded that CTNNB1 mutation is predictive for recurrence; however, some conflicting reports have also been published.\(^{64-67}\) Nonphospho β-catenin has shown favorable prognostic power in comparison with conventional β-catenin immunohistochemistry in predicting response to COX-2 inhibitors, highlighting a potential role for targeted treatment in these pleural tumors.\(^{68}\) The presence of trisomy 8 defines a subgroup of DTF with a high rate of recurrence.\(^{59}\)

The differential diagnoses with pleural DTF are primarily with the various aforementioned benign spindle cell tumors of the pleura (most notably SFT), although various sarcomas, sarcomatoid mesothelioma, and sarcomatoid carcinoma should be considered. The morphologic features are important. Nuclear atypia and necrosis are typically absent in DTF compared with cases of sarcoma, sarcomatoid carcinoma, and sarcomatoid mesothelioma. Desmoplastic mesothelioma can be more problematic, with paucicellularity and less marked atypia, although necrosis is not uncommon in this tumor. The marker panel combining broad-spectrum cytokeratins (for sarcomatoid mesothelioma and sarcomatoid carcinoma) with β-catenin (nuclear expression in DTF), CD34, and STAT6 (for SFT) has utility and can aid in the differential diagnosis for most pleural spindle cell tumors.

It should be noted that potential pitfalls can occur, as it is recognized no marker is either 100% specific or 100% sensitive. First, cytokeratin expression, albeit rare, has been reported in SFT.\(^{69,70}\) The distribution of staining is often localized compared with mesothelioma and carcinoma. Second, nuclear β-catenin expression has been reported in a variety of non-DTF cases, including 22% of 23 SFTs. Third, DTF commonly expresses calretinin typically with no or minimal cytokeratin.\(^71\) The authors place greater reliance on the distinguishing morphology between sarcomatoid mesothelioma and DTF, the strong expression of broad-spectrum cytokeratins in the former, and the clinical context (diffuse in malignant mesothelioma versus localized tumor distribution in DTF).

**EPITHELIOID HEMANGIOENDOTHELIOMA**

Epithelioid hemangioendothelioma is a malignant vascular neoplasm characterized by distinct angiocentric growth of epithelioid endothelial cells.\(^1\) This rare tumor occurs largely in adults aged 30 to 50 years.\(^{71,72}\) Pleural EHE is more common in males. There is no association with asbestos.
Pleuritic chest pain, pneumothorax, and pleural effusion are typical presenting features.\textsuperscript{73} Diffuse pleural involvement on imaging investigations can mimic diffuse malignant mesothelioma. The disease often shows rapid local progression along with metastases to the lung, liver, and regional lymph nodes.\textsuperscript{71,74}

Microscopic examination reveals an infiltrative lesion composed of cords, strands, and nests of epithelioid cells with glassy eosinophilic cytoplasm set in a myxohyaline or sclerotic stroma.\textsuperscript{75-77} The uniform ovoid nuclei contain vesicular chromatin. Intracytoplasmic neovascular lumina with intraluminal erythrocytes are frequently seen (Figure 2).

**Figure 2.** Solitary fibrous tumor showing nuclear expression of STAT6 (original magnification $\times 400$).

**Figure 3.** Desmoid-type fibromatosis. Long, sweeping fascicles composed of bland, fibroblast-like spindle cells (hematoxylin-eosin, original magnification $\times 40$).

**Figure 4.** $\beta$-Catenin immunohistochemistry showing nuclear expression in desmoid-type fibromatosis. Cytoplasmic expression is not informative (original magnification $\times 200$).

**Figure 5.** Epithelioid hemangioendothelioma. Cords of relatively bland epithelioid cells with intracellular lumina containing erythrocytes (hematoxylin-eosin, original magnification $\times 400$).

**Figure 6.** Epithelioid angiosarcoma. Sheets of atypical epithelioid cells with prominent eosinophilic cytoplasm and occasional intracytoplasmic lumina (hematoxylin-eosin, original magnification $\times 200$).

**Figure 7.** Endothelial marker expression in epithelioid angiosarcoma. Positive membranous CD31 immunostaining (original magnification $\times 200$).
5). More atypical nuclear features can be seen in association with sheetlike growth and necrosis.74

Standard endothelial immunomarkers such as CD34 and CD31 are mostly positive in EHE. ERG is a particularly reliable marker of endothelial differentiation, expressed in 100% of 39 cases.74 Patchy cytokeratin positivity is not unusual.78

In recent years, comprehensive genetic characterization of EHE has provided a greater understanding of the pathobiology of the disease. It is now recognized that approximately 90% of EHEs harbor the t(1;3)(p36;q25) translocation, resulting in a WWTR1-CAMTA1 fusion. This characteristic translocation can be used diagnostically with fluorescent in situ hybridization. Immunohistochemical expression of CAMTA1 shows strong and diffuse nuclear staining in 86% of 59 cases of EHE.79 A subset of EHE contains a YAP1-TFE3 fusion. The 2 translocations are not mutually exclusive.80 Regardless of rearrangement status, tumors that show TFE3 immunohistochemical expression are generally more aggressive neoplasms. Furthermore, pleural EHE has a worse prognosis compared with extrapleural EHE.74

A range of epithelioid vascular and nonvascular neoplasms can mimic EHE, including epithelioid AS, carcinoma, and mesothelioma. Vascular markers can aid in the distinction between the latter 2 entities. CAMTA1 immunohistochemistry is particularly useful in this setting, as this sensitive marker is not expressed in other epithelioid tumors, including epithelioid AS.79 Cytokeratin expression should be interpreted with caution, as patchy expression does not exclude carcinoma or mesothelioma.

ANGIOSARCOMA

Angiosarcoma is an aggressive malignant neoplasm of vascular differentiation. Primary pleural AS is extremely rare. Some cases have been related to pyothorax and radiation. There is no proven association with asbestos.76,81,82

Age at diagnosis ranges from 22 to 79 years, and men are more commonly affected.78 Symptoms at presentation include dyspnea, chest pain, and hemothysis. Imaging studies may reveal pneumothorax or hemothorax, with or without pleural thickening. Aggressive local invasion and dissemination are commonplace for AS.

By light microscopic examination, there are commonly sheets of large anaplastic epithelioid cells with abundant eosinophilic cytoplasm (Figure 6). Vasiformative areas may be seen. Nuclei are large and vesicular with prominent nucleoli. Intranuclear vacuoles may be evident. There may be anastomosing channels lined by plump neoplastic cells, but this is uncommon. Endothelial markers such as CD31, CD34, and Von Willebrand factor are useful in confirming the diagnosis (Figure 7). Newer, more sensitive and specific vascular immunomarkers such as ERG and FLI-1 are helpful where there is diagnostic difficulty. Expression of FLI-1 seen in 90% of AS is of diagnostic value. Expression of lymphatic markers, including D2-40, has been reported in AS.83,84

The prognosis of pleural AS is poor, with rapid progression of the disease.88

Angiosarcoma should be considered in the differential diagnosis of any cytokeratin-negative epithelioid pleural neoplasm, because AS can mimic diffuse malignant mesothelioma with a diffuse serosal growth pattern.72,78,82,88,89 Focal keratin expression can further exacerbate the mimicry of diffuse mesothelioma. Strong expression of 2 endothelial markers is necessary to confirm the diagnosis. Diffuse expression of cytokeratin would favor mesothelioma or metastatic carcinoma. Caution is required in the interpretation of a number of commercial mesothelial markers, such as WT-1 and D2-40, as these can be commonly expressed in normal vessels and neoplastic counterparts EHE and AS.

SYNOVIAL SARCOMA

Synovial sarcoma is an aggressive malignant tumor of uncertain histogenesis that shows variable mesenchymal and epithelial differentiation.1 The tumor is characterized by a t(X;18)(p11.2;q11.2) translocation.90 The anatomic distribution of the tumor is wide; however, pleural-based lesions are rare. There is often concurrent involvement of the underlying lung parenchyma.

Median age at diagnosis is 40 years and there is no sex predilection. Clinical manifestations include chest pain, pleural effusion, and dyspnea. The tumors usually present as a localized solid mass, although rare diffuse pleural lesions have been described. On gross examination, SSs form large masses that can be pedunculated. A pseudocapsule can be present. The macroscopic cut surface shows a tan-gray appearance with variable cystic areas and necrosis. Two broad histologic patterns are seen: monophasic and biphasic. Monophasic SS is the more common in the pleura, and comprises sheets or vague fascicles of spindle cells. The ovoid spindle cells often overlap and show a characteristic uniformity. Atypia, pleomorphism, and necrosis are not common features, and mitotic activity is variable. Variations on the archetypal pattern are numerous, and include herringbone architecture, palisaded growth, foci of wavy collagen, and myxoid-rich areas. Stromal calcifications are seen in approximately one-third of cases (Figure 8, A through C). Staghorn vasculature is frequently observed. Infiltrating mast cells can be abundant. Biphasic SSs show a spindle cell component as in monophasic sarcoma, as well as an epithelial component forming glands, ducts, nests, and cords.91 Squamous cell changes are rarely seen. Poorly differentiated variants of SS are formed of hypercellular, hyperchromatic, small, rounded to oval cells with irregular nuclear membranes and coarse chromatin, frequent mitoses, and often necrosis. Immunohistochemistry shows that SSs are focally cytokeratin positive (Figure 9, A) and are EMA positive. A variety of nonspecific markers are frequently positive, including vimentin, CD99, CD56, and Bcl2.92–94 Transducer like enhancer of split 1 (TLE1) is a new nuclear marker for SS, considered helpful in distinguishing SS from its histologic mimics particularly if moderate or strong nuclear staining is observed (Figure 9, B). However, weak and/or focal expression should be regarded as nonspecific; it has been seen in DTF and a variety of carcinomas.95 Negative markers include CD34, desmin, SMA, synaptophysin, and TTF-1. The characteristic t(X;18)(p11.2;q11.2) translocation seen in most cases of SS is a fusion of one of the SSX genes (SSX1, SSX2, or SSX3) at Xp11 to the SS18 gene at 18q11. The function of the fusion protein has not been definitively defined; however, it is likely that the protein is a transcription regulator.96,97 For soft tissue SS, SYT-SSX1 fusions are more commonly associated with biphasic morphology and aggressive behavior. Conversely, in pleural SS, SYT-SSX2 appears to herald an adverse
The overall prognosis of SS is poor, with a median survival of 2 years. Definitive diagnosis of SS requires a synthesis of the clinical, radiologic, morphologic, immunophenotypic, and molecular findings. Entities with vastly differing prognoses enter the differential diagnosis of SS, including malignant mesothelioma (sarcomatoid and biphasic), sarcomatoid carcinoma, SFT, and WHO type A thymic epithelial tumor. It is emphasized that sarcomatoid mesothelioma is typically a diffuse pleural-based tumor in counterdistinction to those stated differentials. The importance of interpreting cases of diffuse malignant mesothelioma in the appropriate clinical and radiologic context cannot be overstated. From a pathologic perspective, particularly in small biopsies, there can be considerable overlap. The differentiation between sarcomatoid mesothelioma and SS can be problematic, as both may show cytokeratin and calretinin expression (Figure 10). Cytogenetic confirmation of the t(X;18)(p11.2;q11.2) translocation should be performed where there is a suspicion for SS. The precise application of TLE1 in the pleural setting is evolving and has already been observed in sarcomatoid mesothelioma by one of the authors (R.L.A., unpublished data, March 2017). TLE1 has been reported in 82% of 73 SSs, in comparison with 15% of 47 malignant peripheral nerve sheath tumors and 8% of 49 SFTs, so caution is exercised when interpreting this marker in isolation. Ultimately, cytogenetic demonstration of the t(X;18)(p11.2;q11.2) translocation by FISH or reverse transcriptase polymerase chain reaction is the gold standard for the diagnosis of SS.

PLEUROPULMONARY BLASTOMA

Pleuropulmonary blastoma is an aggressive tumor of infancy and childhood, with no sex predilection. There is usually involvement of both the pleura and lung parenchyma, chest wall, and/or mediastinum. Pleuropulmonary blastoma is subtyped as type I (pure cystic), type II (cystic and solid), and type III (pure solid), with median ages increasing from type I through type III. Subjects can present with a variety of pulmonary symptoms subject to subtype, with acute respiratory failure, pneumothorax, progressive dyspnea, fever, chest pain, and cough all described. Macroscopic features are also dependent on the specific PPB subtype in question. Cystic components are usually multiloculated and thin walled. Purely solid tumors (type III PPB) have variegated cut surfaces with variable hemorrhage and necrosis. Microscopically, type I tumors appear as multiple cysts lined by respiratory-type epithelium. Within the intervening septa there are small immature cells with or without rhabdomyoblastic differentiation, and a cambium layer–like arrangement can be present. Areas with immature cartilage may be seen. Solid sheets of blastomatous and sarcomatoid cells characterize PPB type III tumors (Figure 11). Immunohistochemistry is of limited value in PPB, with vimentin, focal desmin expression (in the rhabdomyoblastic elements and variably within the primitive cells in the cambium–like layer), and focal S100 expression (in areas of chondroid differentiation).

Gains in chromosome 8 and losses of 9p21–24 and 11p14 have been associated with PPB. Around 40% of PPBs are familial and arise in the context of PPB family tumor and dysplasia syndrome, otherwise termed DICER1 syndrome. In this context, tumors are associated with other nonpulmonary tumors including cystic nephroma, Sertoli-Leydig cell ovarian tumors, embryonal rhabdomyosarcoma, Wilms tumor, and multinodular goiter. Some families with this condition harbor a loss-of-function germline mutation of DICER1. This can be demonstrated immunohistochemically with loss of DICER1 staining in the epithelial cells and normal staining in the malignant mesenchymal cells.

Five-year disease-free survival is on the order of 80% to 90% for type 1 disease; however, recurrent tumors occur in 40% of patients. The less favorable types II and III disease harbor a less than 50% 5-year survival rate. Complete resection and absence of invasion are associated with an improved prognosis.
DESMOPLASTIC SMALL ROUND CELL TUMOR

Desmoplastic small round cell tumor of the pleura is a rare manifestation of the more widely recognized intra-abdominal counterpart arising in the retroperitoneum, mesentery, omentum, pelvis, and paratesticular regions. It is an aggressive malignancy of young adult men, with poor prognosis despite multimodality treatment. Chest pain, pleural effusion, and dyspnea are the most common clinical manifestations in pleural cases. By light microscopy, the tumor is characterized by well-defined nests of small round hyperchromatic tumor cells associated with stromal desmoplasia. Epithelial differentiation, glands, rosettes, and spindle cells as well as intracytoplasmic eosinophilic rhabdoid inclusions are recognized. The stromal component is usually prominently vascularized. Mitotic figures and central necrosis within tumor nests are common. Desmoplastic small round cell tumor shows a complex immunophenotype with common coexpression of epithelial

Figure 9. Synovial sarcoma. Immunophenotype. A, Focal cytokeratin. B, Diffuse nuclear TLE1 expression (original magnification ×100).
Figure 10. Synovial sarcoma with focal nuclear and cytoplasmic calretinin expression (original magnification ×100).
Figure 11. Pleuropulmonary blastoma—mixed immature solid epithelial and spindle cell elements imparting a biphasic tumor morphology (hematoxylin-eosin, original magnification ×100).
Figure 12. Undifferentiated sarcoma—pleomorphic cell morphology: numerous bizarre multinucleate giant cells interspersed with patternless distributions of pleomorphic spindle cells (hematoxylin-eosin, original magnification ×200).
Figure 13. Primary effusion lymphoma—discohesive tumor cells, some multinucleate cell forms, some cytolysis (hematoxylin-eosin, original magnification ×200).
(cytokeratins, epithelial membrane antigen, MOC31, Ber EP4), muscle (perinuclear “dot” desmin), and neural (neuron-specific enolase, CD 57) markers. WT-1 is typically positive and both myogenin and Myo-D1 are negative. There may be variable expression with CD99 and synaptophysin. Molecular cytogenetics plays an important role in the diagnosis of desmoplastastic small round cell tumor as distinct from its mimics, as it is characterized by a recurrent chromosomal translocation of t(11;22)(p13;q12) resulting in EWSR1-WT1 gene fusion.

**MISCELLANEOUS SOFT TISSUE TUMORS**

The pleura has been reported as the site of a wide number of soft tissue tumors, including smooth muscle tumors, nerve sheath tumors, adipocytic tumors, and undifferentiated sarcoma. They are histologically identical to their extrapleural counterparts. These are all rare localized neoplasms. Undifferentiated sarcomas are reported to occur within a wide age range with no sex predilection. They are morphologically and immunophenotypically heterogeneous tumors, composed of round, spindle, epithelioid, or pleomorphic cell morphology. Round cell morphology is more commonly observed in younger subjects, and associated with a variety of EWSR1 fusions. Pleomorphic morphology (Figure 12) is more common in older subjects and is associated with complex karyotypic abnormalities. A significant proportion of postradiation-associated soft tissue tumors are undifferentiated pleomorphic sarcomas. There is insufficient information available to comment on survival in the pleural setting.

**LYMPHOPROLIFERATIVE DISORDERS**

All forms of hematologic malignancy may involve the pleura, usually as secondary involvement from known nodal, extranodal, or marrow-based disease. Primary pleural lymphomas are rare, representing specific localized anatomic manifestations of diffuse large B-cell lymphoma of post–germinal center or plasma cell phenotype, with associations with immunodeficiency or immune sequestration and viral infection. The pathogenesis of these primary pleural lymphomas is not fully understood but likely involves a complex interrelationship among chronic serosal inflammation, host immune factors, and viral infection as a catalyst for lymphomagenesis.

**PRIMARY PLEURAL LYMPHOMAS**

There are 2 distinct types of primary pleural lymphomas as recognized entities in the 2016 WHO classification: the PEL associated with human herpesvirus 8 (HHV-8) infection and the DLBCL-CI associated with Epstein-Barr virus (EBV) infection.

**PRIMARY EFFUSION LYMPHOMA**

This neoplasm is consistently associated with HHV-8 infection. It presents with serous effusions without lymphadenopathy, organomegaly, or solid tumor masses. Primary effusion lymphoma predominantly involves the pleura (75%), although it can also involve the peritoneum or pericardium, or may appear as multicentric disease, in circulating blood or cerebrospinal fluid, or around implant sites. Extracavitary HHV-8 solid lymphomas represent a variant of PEL and are described in lymph nodes, spleen, gastrointestinal tract, liver, lung, brain, soft tissue/bone, and testis. The vast majority of PELs and variant extracavitary solid HHV-8 lymphomas are seen in 1 of 3 settings: first, most cases (70%–80%) arise in young adult males (median 44 years) with HIV infection (associated with low CD4+ counts, <200/µL) and often concomitant EBV infection; second, in immunosuppressed solid organ transplant recipients; third, in elderly subjects with age-induced immunosenescence.

The morphologic features are best appreciated in cytologic preparations (Figure 13). The tumor cells are typically either immunoblastic in nature (large cells with prominent vesicular nuclei and distinct nucleoli), plasmablastic (in which cells have more abundant basophilic cytoplasm), or anaplastic (composed of multinucleated and polylobated nuclear cell forms). Reed-Sternberg–like cells may be seen. Mitoses are variable. It is not uncommon to see cytolysis and apoptosis. It is important to highlight that bona fide primary pleural Hodgkin lymphoma is exceptional.

The lymphoma immunophenotype usually expresses leukocyte common antigen (CD45), plasma cell markers (CD138, CD38, IRF4/MUM-1, and PRDM1/BLIMP1), and activation-associated markers (CD30, CD38, human leukocyte antigen—antigen D related, and EMA). The proliferation marker Ki-67 is high. In contrast, it is important to appreciate that the pan–B-cell markers are rarely expressed (CD19, 8%; CD20, 15%; CD79a, 12%), surface immunoglobulin is negative, and cytoplasmic immunoglobulin is detectable in only about one-fifth of cases. Aberrant pan–T-cell antigens (CD2, CD3, CD5, CD7) are expressed in around one-quarter of cases. The lymphoma cells are positive for HHV-8, and most HIV+ most cases are coinfected with EBV. The EBV antibody LMP1 is negative. The B-cell origin of PEL is confirmed by the demonstration of clonal rearrangements of immunoglobulin genes with somatic hypermutations indicating origin from post–germinal center B cells. Gene profiling has identified that PEL has a plasmablastic differentiation pattern, intermediate between immunoblastic diffuse large B-cell lymphoma and myeloma. The disease course is poor (median 6-month survival) irrespective of treatment.

Diffuse large B-cell lymphomas may present as pleural effusions; be immunoblastic, plasmablastic or anaplastic in morphology; and/or be HHV-8 negative. These should not be designated as PEL. Most will have discernible nodal or marrow-based disease, some will represent EBV-associated DLBCL-CI (see below), and some will be variants thereof. Alexanian et al reported 5 cases of HHV-8–negative effusion lymphoma; most arose in the setting of fluid overload states such as heart failure and liver cirrhosis. Compared with PEL, the HHV-8–negative DLBCL subjects were older with less male preponderance, and usually were HIV negative. Most have been described in Japanese populations. Some are associated with hepatitis C infection. Human herpesvirus 8–negative effusion lymphoma may be positive or negative for EBV. It is thought there are pathogenetic overlaps with DLBCL-CI.

**DIFFUSE LARGE B-CELL LYMPHOMA ASSOCIATED WITH CHRONIC INFLAMMATION**

Diffuse large B-cell lymphoma associated with chronic inflammation is an EBV-associated B-cell neoplasm that occurs in the context of long-standing chronic inflammation, usually in a confined anatomic location. This tumor entity was first reported in the pleura in 1987 by luchi and colleagues in 3 Japanese subjects. Since that time the
tumor entity has been reported in Western subjects in the peritoneum, in the pericardium, and in association with fibrin thrombi, chronic osteomyelitis, venous ulceration, surgical mesh implants, and hepatitis C infection.\textsuperscript{110} Diffuse large B-cell lymphoma associated with chronic inflammation is more frequently reported in adults, with a median age of 65 years, and there is a strong male preponderance of at least 10:1.\textsuperscript{111,112} There is a clear latent interval between the initial inflammatory event and the presentation of lymphoma that typically exceeds 10 years. Most cases arise in anatomic sites with limited vascularization (immune-sequestered sites). It is considered that local factors related to chronic inflammation in confined locations facilitate EBV-infected B-cell proliferation and the development of a neoplastic clone.\textsuperscript{111} The most common site remains the pleural cavity, where the lymphoma develops in persons with a history of pyothorax resulting from artificial pneumothorax for the treatment of tuberculosis or arises de novo following chronic tuberculous pleuritis.\textsuperscript{112} Subjects with this disease typically present with chest wall pain and swelling together with fever and respiratory symptoms.

On macroscopic inspection, the tumor shows marked serosal thickening with firm consistency and tan discoloration. Necrosis is common. Invasion into the lung, mediastinum, pericardium, diaphragm, and liver occurs, although dissemination of DLBCL-CI is uncommon.

—On microscopic examination the tumor shows features consistent with other forms of diffuse large B-cell lymphoma, comprising rich mixtures of centroblastic or immunoblastic morphology. Apoptosis may be a prominent feature particularly in areas of extensive necrosis. The tumor immunophenotype is positive for common leukocyte antigen (CD45) and pan-B–cell antigens (CD19, CD20, and CD79a). Most cases have been known to show a post–germinal center phenotype (CD10\textsuperscript{+}, CD20\textsuperscript{+}, and CD79a\textsuperscript{+}). CD30 is often expressed and CD138 may be expressed in cases exhibiting plasmacytic differentiation. Immunohistochemical expression of B–cell markers (CD19, CD20, and CD79a) and pan–B-cell antigens (CD19, CD20, and CD79a) is observed in counterpart nodal or marrow-based disease.

Pleural DLBCL-CI is an aggressive lymphoma with median survival less than one year. The 5-year overall survival is approximately 20%.

**OTHER HEMATOLOGIC NEOPLASMS**

Lymphomatous or leukemic infiltrates involving the pleura are relatively common, observed in approximately 15% of patients with non–Hodgkin lymphoma.\textsuperscript{124} The morphologic, immunophenotypic, and molecular genetic features of these lymphomas are identical to those observed in counterpart nodal or marrow–based disease. Diffuse large B-cell lymphoma, follicular lymphoma, and small lymphocytic lymphoma/chronic lymphocytic leukemia are the most commonly reported lymphomas involving the pleura.\textsuperscript{125} Primary marginal zone lymphoma of the pleura is well described and recapitulates the findings in other extranodal sites.\textsuperscript{126} Clinical assessment is essential to determine if this is a primary or secondary manifestation of disease.

**CONCLUSIONS**

Pleural tumors other than mesothelioma have hitherto received little attention. However, they represent a small but significant group of heterogeneous neoplasms, many of which may mimic each other as spindle cell neoplasms and importantly may pose pitfalls in the diagnosis of sarcomatoid mesothelioma and its desmoplastic variant, particularly in small biopsy specimens. The identification of characteristic molecular markers for a number of these tumors, such as SS, SFT, DTF, and EHE, has greatly facilitated their accurate diagnosis and potentially forms the basis for future targeted therapies.

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