Primary Pleural Neoplasia

Entities Other Than Diffuse Malignant Mesothelioma

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**Context.**—Overwhelmingly, the most common neoplasm involving the pleura is metastatic carcinoma. In contrast, diffuse malignant mesothelioma occurs relatively rarely; however, it is nonetheless the most common neoplasm primary to the pleura. Metastatic carcinoma and diffuse malignant mesothelioma each have their own prognostic and therapeutic characteristics. Other primary pleural neoplasms occur uncommonly or rarely, with their own prognostic and therapeutic characteristics.

**Objective.**—To review primary pleural neoplasms other than diffuse malignant mesothelioma, to better ensure correct diagnosis and optimal assessment of prognosis and treatment.

**Data Sources.**—Literature review and primary material from the authors’ institutions.

**Conclusions.**—A nonexhaustive group of uncommon to rare benign and malignant primary pleural neoplasms—other than diffuse malignant mesothelioma—are presented, of which one must be aware in order to maintain an appropriate index of suspicion to include them in the differential diagnosis of a pleural tumor.

Arch Pathol Lab Med. 2008;132:1149–1170

By far the most common neoplasm involving the pleura is metastatic carcinoma, causing approximately 200,000 pleural effusions each year in the United States.1 Diffuse malignant mesothelioma (DMM), which in contrast is relatively rare, accounting for approximately 1500 malignant pleural effusions in the United States each year, is nonetheless the most common neoplasm primary to the pleura.2 Differentiation between metastatic carcinoma and other neoplasms involving the pleura, with their variable prognoses and therapeutic options, and pleural DMM, with its prognosis, limited therapeutic options, and frequent relationship to asbestos exposure, is extremely important both medically and legally and has been the subject of numerous articles during many years, a few of which are referenced.3-12 Aside from metastases and DMM, other primary pleural neoplasms, with their individual prognostic and therapeutic characteristics, occasionally are encountered. An understanding of the pathologic features of these uncommon or rare neoplasms is necessary to ensure optimal treatment and prognosis. The following is a nonexhaustive group of the primary pleural neoplasms of which one must be aware in order to maintain an appropriate index of suspicion of them.

**BENIGN PRIMARY PLEURAL NEOPLASMS**

**Solitary Fibrous Tumor**

Solitary fibrous tumor (SFT), also termed localized fibrous tumor, is the most common benign primary pleural neoplasm.13 It may on occasion present with more than 1 tumor mass, and as such, the term localized fibrous tumor may be more descriptively accurate; however, the term SFT is so engrained in the literature that it probably should be retained, especially as pleural SFT already has a history of confusing terminology.

The first report of SFT has been attributed to Wagner in 1870,14 and in 1931 Klemperer and Rabin15 provided the first accurate pathologic description of pleural SFT, dividing primary pleural tumors into diffuse mesotheliomas and localized mesotheliomas. In 1942, Stout and Murray16 introduced the term localized fibrous mesothelioma and proposed a mesothelial cell origin for SFT based on their cell culture findings of tumor growing in mesothelial-like sheets. Three decades later, other authors proposed a mesenchymal origin for SFT.17-21 Currently, these tumors are considered to arise from mesenchymal cells—submesothelial cells or soft tissue fibroblasts.22,23 Their mesenchymal cell origin is supported by immunohistochemical findings including general vimentin positivity and CD34 positivity.24-26 Because of the controversy regarding histogenesis, SFT was in the past given a variety of different names, including benign fibrous mesothelioma, solitary fibrous mesothelioma, localized fibrous mesothelioma, pleural fibroma, benign mesothelioma, and submesothelial fibroma. As SFTs are believed to arise from submesothelial cells, all of these terms should be avoided. The diagnostically inaccurate terms localized mesothelioma and fibrous mesothelioma should not be used in order to avoid confusion with localized malignant mesothelioma (LMM) and sarcomatous DMM, respectively.

Besides their pleural location, SFTs have been recognized in a wide variety of extrapleural sites, including head and neck and nasal cavity, retroperitoneum, soft tissues, orbit, liver, thyroid, salivary glands, kidney, and breast, among others.27-30 Approximately 800 cases of pleural SFT have been reported, and a few series of cases have been published, including those of Briselli et al in 1981, documenting 360 cases from the literature and another 8 of their own, and England et al in 1989, reporting...
Clinically, SFTs occur in people ranging in age from childhood to the eighth decade, with the majority occurring in middle-aged and older adults, with men and women generally equally affected. Most patients with benign SFTs are asymptomatic and found incidentally to have a well-circumscribed, pleural-based mass on radiologic studies. Symptoms such as cough, chest pain, and dyspnea are suggestive of malignancy. Approximately 10% to 20% of patients with SFT exhibit digital clubbing and hypertrophic pulmonary osteoarthropathy— Pierre-Marie-Bamberg syndrome; however, these features generally resolve within 2 to 5 months after surgical resection. The syndrome has been hypothesized to occur due to abnormal hepatocyte growth factor production or tumor release of hyaluronic acid. Less than 5% of SFT patients develop Doege-Potter syndrome—refractory hypoglycemia due to secretion of insulin-like growth factor. Blood glucose levels typically return to normal within 2 or 3 days after surgical resection.

Solitary fibrous tumor is not associated with asbestos exposure. Approximately three fourths of SFTs are attached to the visceral pleura, with the remaining tumors attached to the parietal pleura, the fissural pleura, or the diaphragm. Most tumors are about 5 to 10 cm in greatest dimension, but rare tumors ranging up to about 40 cm have been reported. Grossly, SFTs are off-white to light grey or light tan and may have a whorled appearance on cut section (Figure 1, A). Although small foci of hemorrhage may be present in benign SFTs, extensive hemorrhage or necrosis suggests malignancy. About half are sessile and half pedunculated, often with a fibrous stalk (Figure 1, B). Most SFTs are benign; malignant SFTs are discussed below. If SFT is suspected, multiple sections from the lesion are necessary to facilitate proper diagnosis.

The microscopic features of benign SFT include a variety of histologic patterns, one or all of which may be present in an individual tumor. The “patternless pattern of Stout” is characterized by relatively hypocellular areas composed of thick, ropey collagen with associated slitlike spaces and bland, sometimes inconspicuous spindle cells. A hemangiopericytoma-like pattern may also be identified, with variable cellularity and characteristic “staghorn” vascular structures. Also, a cellular pattern may be present, with spindle cells forming loose sheets, fascicles, or storiform or “herringbone” arrangements. Focal areas of myxoid change and focal calcification may occur. Any or all patterns may be found in a SFT, and the patterns may blend gradually with each other or may have an abrupt transition. Cytologic atypia and mitotic figures are absent or minimal; and increased cellularity, hemorrhage, and necrosis are absent or very focal in benign SFT. Benign SFTs that are sessile, frequently attached to the visceral pleura, generally have a pushing pattern of growth, which may include a peglike pattern of growth that should not be confused with invasive tumor. Inclusions of benign pulmonary epithelial cells may be found adjacent to the peglike growing edge and should not be confused with epithelial malignancy. Epithelial-like areas that are immunohistochemically not truly epithelial and are not prognostically important may occasionally be found within SFTs; these areas must not be confused with the true pulmonary epithelial cell inclusions described above.

Studies have shown that between 80% and 100% of SFTs stain positively with CD34, Tumor cells generally stain positively with vimentin, Bcl-2, and CD99 as well. Solitary fibrous tumors are typically immunonegative with keratin, factor VIII, smooth muscle actin, muscle-specific actin, desmin, CD31, and S100. CD34 immunopositivity is not a specific feature of SFTs and may be found in other tumors such as neurofibromas, smooth muscle tumors, and schwannomas. Immunostains are of benefit in differentiating SFT from various other differential diagnoses. Sarcomatous DMMs are, in contrast to SFT, generally immunopositive with actin and pankeratin, and immunonegative with Bcl-2 and CD34. Pleuropulmonary synovial sarcomas are generally immunonegative with CD34 and immunopositive with AE1 and collagen IV. Smooth muscle tumors are typically immunonegative with CD34 and immunopositive with actin, desmin, and h-caldesmon. Undifferentiated carcinomas are generally immunopositive with pankeratin, AE1/AE3, and epithelial membrane antigen (EMA) and immunonegative with CD99.

**Adenomatoid Tumor**

Adenomatoid tumors are rare benign neoplasms of mesothelial differentiation. Although these tumors occur most often in the male or female genital tract, 3 cases have been described in the pleura. The tumors described have consisted of 0.5- to 3.0-cm pleural nodules identified at the time of thoracic surgery for other processes. Histologically, adenomatoid tumors within the pleura are similar to adenomatoid tumors within the genital tract. They consist of nodular expansile proliferations of plump to flattened vacuolated epithelioid cells often arranged as tubular or glandlike spaces within a fibromuscular stroma sometimes containing smooth muscle. Vacuolated epithelioid cells may appear similar to signet rings. However, special stains for mucin (mucicarmine and periodic acid–Schiff with diastase) are negative. The epithelioid cells within adenomatoid tumors stain positively with markers of mesothelial origin including calretinin, HBME-1, and cytokeratin and lack expression of vascular markers or pulmonary adenocarcinoma including carcinoembryonic antigen, BER-EP4, B72.3, and CD15. The cells lack staining for vascular markers such as CD34, factor VIII, or Qbend.

The differential diagnosis of pleural adenomatoid tumors includes reactive mesothelial hyperplasia, DMM, metastatic adenocarcinoma, and vascular neoplasms. The distinct nodular proliferation of cells and unremarkable underlying pulmonary parenchyma helps to separate adenomatoid tumor from a reactive process, whereas the solitary nature of the tumor, overall circumscription, and absence of invasion distinguishes it from DMM. Adenomatoid tumors may prompt consideration of metastatic signet ring cell adenocarcinomas. However, the cells lack mucin on special stains (mucicarmine or periodic acid–Schiff with diastase), stain positively with mesothelial markers (eg, calretinin), and do not express markers identified preferentially in pulmonary adenocarcinomas such as carcinoembryonic antigen, B72.3, BER-EP4, or CD15. Likewise, epithelioid hemangioendothelioma or other vascular...
neoplasms can be excluded by the lack of staining for vascular markers such as CD34, factor VIII, or Qbend.53

**Calcifying Fibrous Pseudotumor**

Calcifying fibrous pseudotumor is a rare, distinct soft tissue lesion most commonly found in the extremities, trunk, scrotum, groin, or axilla. Rare cases of calcifying fibrous pseudotumor have been described within the pleura.56,57 The reported cases have usually been found incidentally during investigation of other disorders. Imaging studies show single to multiple lobular pleural-based masses with areas of calcification.56–58

Resected specimens have consisted of one to several well-demarcated but unencapsulated white to tan masses ranging from 1.5 to 12.5 cm (Figure 3, A). These usually have a gritty cut surface. Histologically, the masses are well circumscribed and consist of hyalinized connective tissue admixed with benign-appearing spindle cells (Figure 3, B). A distinctive feature is the presence of scattered psammomatous microcalcifications (Figure 3, C). Some areas of dystrophic calcification may also be present. There is a sparse perivascular chronic inflammatory infiltrate consisting of lymphocytes, histiocytes, and plasma cells.58 Follow-up of these lesions so far indicates they are benign. Local excision appears to be adequate therapy.56–58

The differential diagnosis includes SFT, old calcified granulomas, pleural plaques, inflammatory pseudotumor, and hyalinizing granuloma. These can be distinguished based on their clinical and histologic features. The presence of a “patternless pattern” and absence of calcification and inflammatory infiltrate help to distinguish SFT from calcifying fibrous pseudotumor. In contrast to calcifying fibrous pseudotumor, hyalinizing granuloma and inflammatory pseudotumor usually occur within pulmonary parenchyma. Hyalinizing granuloma may contain areas of dystrophic calcification but lacks psammomatous calcification typical of this disorder. Inflammatory pseudotumor is more cellular than calcifying fibrous pseudotumor and lacks any kind of calcification.58

**Miscellaneous Benign Mesenchymal Neoplasms**

Lipomas and schwannomas may occasionally present within the pleura. Their gross and histologic features are similar to those reported in soft tissue59–61 (Figure 4, A through C).

**Reactive Eosinophilic Pleuritis**

Although a reactive process, reactive eosinophilic pleuritis may mimic other forms of pleural neoplasia. Reactive eosinophilic pleuritis refers to a nonneoplastic nodular to diffuse proliferation of eosinophils, histiocytes, giant cells, and other inflammatory cells62,63 (Figure 5, A and B). This reaction occurs commonly along the visceral pleura as a reaction to spontaneous pneumothorax. Its chief importance lies in its distinction from pleural involvement by pulmonary Langerhans cell histiocytosis. The distinction can be facilitated by consideration of the clinical setting (pneumothorax in the absence of radiographic features of pulmonary Langerhans cell histiocytosis as well as the absence of collections of Langerhans cells on immunohistochemical stains for S100 and CD1a.62,63

**MALIGNANT PLEURAL NEOPLASMS OTHER THAN DMM OCCURRING PRINCIPALLY IN THE PLEURA**

**Localized Malignant Mesothelioma**

By definition, DMM of the pleura grows widely over the pleural surface with a pattern of diffuse spread that is a key feature for both the radiologist and the pathologist to appreciate in order to make a correct diagnosis.64,65 Early DMMs exhibit nodular studding of the pleura (Figure 6, A and B), and with time tumor encases the lung and may extend to surrounding areas such as the mediastinum and may metastasize to distant sites, with most patients dead generally within 2 years of diagnosis. However, a small number of localized tumors with histopathologic, histochemical, immunohistochemical, and ultrastructural features identical to those of DMM, termed localized malignant mesothelioma, have been described in the pleura and other serosal membranes such as pericardium and peritoneum.64,65 In 1994, Crotty et al64 described a series of 6 LMMs, and in 2005 the United States–Canadian Mesothelioma Reference Panel reported on 23 cases collected by the panel.65 Other LMMs have been reported in the English language literature, primarily as case reports.65,67,68–70 Most tumors are identified incidentally, and some patients present with nonspecific symptoms. The median age of patients is 62 years, and almost all are older than 40 years of age.65 The male-female ratio is approximately 3:2, in contrast to DMM, in which the vast majority of cases occur in men.64 No defined role of occupational asbestos exposure has been identified in the causation of LMM.

Grossly, pleural LMMs are solitary, well-circumscribed, pedunculated or sessile, nodular tumors, attached to the visceral or parietal pleura.66 Tumor size averages about 6 cm, but size does not correlate with prognosis. As noted above, a defining characteristic of LMM is that it is histologically, immunohistochemically, and ultrastructurally identical to DMM.64,65 All 3 subtypes—epithelial, biphasic, and sarcomatous—occur, with the epithelial subtype predominating64,65; however, histologic subtype does not correlate with survival, as opposed to DMMs where epithelial forms have a better prognosis65 (Figure 6, C through F).

Localized malignant mesothelioma must be differentiated from DMM. Diffuse malignant mesotheliomas are generally grossly widespread along the pleural surface, often as a ring surrounding the lung or as multiple individual tumor nodules; but in some cases microscopically widespread tumor along the pleural surface is identified histologically. Occasionally, DMM may present with a single, dominant nodule, and this circumstance must be distinguished from LMM, as “even microscopic evidence of tumor away from the main lesion automatically removes the cases from the category of LMM.”65 Tumor recurrence and metastases may occur, ultimately causing patient death; however, diffuse pleural spread of tumor in the manner of DMM does not occur.65

Although many patients diagnosed with LMM ultimately succumb to their disease, “the crucial feature of localized malignant mesothelioma is that many cases can, apparently, be cured by surgical excision.”65 Of the patients studied by the United States–Canadian Mesothelioma Reference Panel in 2005, approximately half of the patients who had follow-up information available were alive, many for several years, in stark contrast to the usual clinical course of DMM patients.65
Well-Differentiated Papillary Mesothelioma

Unlike DMM, a cancer with an almost uniformly poor prognosis generally occurring in the pleura of men in their seventh and eighth decades, well-differentiated papillary mesothelioma (WDPM) is a rare tumor typically considered to be of low malignant potential, usually involving the peritoneum in women of an average age younger than that of the age seen among DMM in men. Well-differentiated papillary mesotheliomas are frequently identified incidentally, often during surgery; however, patients may be symptomatic and present with pleural effusion, ascites, pneumothorax, or abdominal or chest pain. Well-differentiated papillary mesothelioma does occur in men and may arise from various sites besides the peritoneum, including the pleura, pericardium, and tunica vaginalis testis. Well-differentiated papillary mesotheliomas usually occur as diffuse, multifocal lesions, but a WDPM may occasionally arise as a solitary, localized lesion.

Grossly, WDPM is most often diffusely nodular, with small pleural nodules measuring from millimeters to a few centimeters in greatest dimension, giving the serosal surface a velvet-like appearance. A central scar may occur, usually in the solitary form of WDPM. The primary histologic pattern of WDPM is papillae with broad fibrovascular cores covered by a single layer of bland, flattened to cuboidal mesothelial cells, without necrosis, large nucleoli, or mitoses (Figure 7, A through C). The
papillary cores may have a myxoid appearance, and areas of tubular or solid tumor may also occur. Psammoma bodies may be present. Covering cells may contain basal vacuoles. Although invasion is not a characteristic feature of WDPM, some cases show limited invasion (Figure 7, E). Immunohistochemical stains in WDPM are similar to those of epithelial DMM.

Well-differentiated papillary mesothelioma must be distinguished histologically from DMM with a papillary pattern, which has relatively thin fibrovascular cores containing prominent, usually centrally placed blood vessels, and lining mesothelial cells characterized by round, atypical nuclei, frequent prominent nucleoli, and variable numbers of mitotic figures (Figure 7, F). Occasionally, tumors initially diagnosed as WDPM eventually prove fatal, and at least some if not most of these cases represent actually DMMs for which material from a limited biopsy showed only a WDPM-like pattern. As such, care must be used in interpreting small biopsy specimens in this context.

Criteria for diagnosing malignancy in SFTs were developed by England et al in 1989. The criteria include (1) high mitotic activity (>4 mitoses per 10 high-power fields), (2) high cellularity with crowding and overlapping of nuclei, (3) the presence of necrosis, and (4) pleomorphism. Tumors are considered malignant if at least 1 criterion is present. Absence of the 4 criteria for malignancy is necessary to consider a tumor benign; however, the absence of malignant criteria may be difficult to establish due to heterogeneity of tumors or the subjectiveness of criteria. Occasional large bizarre cells or focal areas of high cellularity, without cellular atypia or mitoses, are generally insufficient to categorize the tumors as malignant.

In some cases, malignant SFTs arise from otherwise histologically benign SFTs and have the same basic histopathology of benign SFTs but with areas containing cytologic pleomorphism, hemorrhage, tumor necrosis, or more than 4 mitoses per 10 high-power fields (Figure 8, F and G). In other cases, malignant SFTs have high-grade, frankly sarcomatous areas within otherwise histologically benign SFTs (Figure 8, H). Other malignant SFTs arise de
novo, without obvious areas of histologically benign SFT present adjacent to histologically malignant areas.\textsuperscript{102} The criteria for malignancy established by England et al\textsuperscript{103} remain sound and, along with the gross finding of sessile tumor, have been shown to predict recurrence. In 2000, Cardillo et al\textsuperscript{22} found that recurrent tumors occurred in 63\% of patients with malignant sessile and histologically malignant tumors, 14\% of patients with histologically malignant pedunculated tumors, 8\% or less of patients with sessile SFTs with histologically benign features, and 2\% or less of patients with histologically benign pedunculated tumors.

Malignant SFTs typically show the same immunostaining pattern as benign tumors; however, CD34, while typically showing 80\% to 100\% immunopositivity in benign tumors, has been shown in some studies to exhibit reduced expression in malignant SFTs.\textsuperscript{41,43,104,105} Overexpression of p53 and CD31 and high levels of Ki-67 expression have also been shown in malignant SFTs.\textsuperscript{41,52,104} Caution must be used when attempting to diagnose SFT in cases with atypical features or small biopsy specimens, as the tissue may not be representative of the lesion. Differential diagnosis includes sarcomatous DMM, sarcomatous LMM, synovial sarcoma, and leiomyosarcoma, among others. Immunostains may be helpful in differentiating among these tumors.

As with benign SFTs, resectability of the malignant tumor is considered the single most important prognostic indicator. Wide surgical excision is necessary in these patients because most can be cured by complete resection if done prior to metastasis or extensive local invasion.\textsuperscript{23,39} Tumors with benign histology that recur may represent in-
adequate sampling of a malignant SFT; therefore, the pathologist must widely sample all SFTs. Close follow-up of all patients is necessary to allow for early detection and treatment of any recurrences.102

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) is a rare aggressive malignant tumor that almost always occurs in children under the age of 6 years. The neoplasm commonly presents within the lung but may also occur within the mediastinum or pleura.106–108 Presenting symptoms of affected patients are nonspecific and include cough, respiratory distress, fever, chest or abdominal pain, anorexia, and malaise.106–108 Radiographic studies show a parenchymal or pleural-based mass. On computed tomography (CT), the mass may be extensively multicystic, resembling a congenital cystic adenomatoid malformation. Alternatively, it may be entirely solid or contain solid enhancing nodules within cyst cavities. Pleural effusion is common.109,110

Pathologically, PPB has been subdivided into 3 types based on the degree and extent of cystic change. Type I is predominantly cystic, type II is cystic and solid, and type III is entirely solid. Histologic features vary according to the subtype.108

Type I PPB consists of multiloculated cysts lined by a ciliated columnar epithelium. Within septa there is a variably continuous zone of condensed immature round to spindle-shaped cells with a “cambium layer–like” appearance (Figure 9, A and B). This zone may be focal in

Figure 5.  A, Low-power image of reactive eosinophilic pleuritis showing a nodular aggregate of cells along the pleural surface (arrows). In contrast, the pleural surface appears relatively unremarkable. B, Higher-power image of reactive eosinophilic pleuritis showing acellular aggregate consisting of a mixture of eosinophils, mesothelial cells, and histiocytes, some of which are multinucleated.

Figure 6.  A, Early diffuse malignant mesothelioma showing one of several foci of tumor on the parietal pleural surface. B, Immunostain with cytokeratin (CK) 7 highlights diffuse malignant mesothelioma tumor cells invading subpleural adipose tissue. C, Low-power image of localized malignant mesothelioma showing a tumor nodule containing biphasic pattern tumor. D, Immunostain with CK7 highlights localized malignant mesothelioma tumor cells within the nodular mass. E, Higher-power image of biphasic pattern localized malignant mesothelioma showing epithelial nests of tumor cells with relatively uniform vesicular nuclei containing obvious nucleoli with surrounding dense fibrous stroma. F, Medium-power image of epithelial pattern localized malignant mesothelioma showing histologic features identical to epithelial pattern diffuse malignant mesothelioma.
Figure 7.  A, Low-power image of well-differentiated papillary mesothelioma (WDPM) showing a fibrous central band with surrounding papillae with broad fibrovascular cores without necrosis. B, Medium-power image of WDPM showing multiple papillary fibrovascular cores lined by a single layer of bland, flattened to cuboidal mesothelial cells. C, Higher-power image of WDPM shows papillae lined by mesothelial cells without large nuclei or mitoses. D, High-power image of WDPM papillae showing myxoid change within a papillary core. E, Medium-power image of WDPM showing a focus of superficial invasion. F, High-power image of papillary pattern of epithelial diffuse malignant mesothelioma, showing prominent, centrally laced blood vessels and lining mesothelial cells consisting of round nuclei with prominent nucleoli.
Figure 8.  A, Gross image of malignant solitary fibrous tumor (SFT) showing firm smooth-surfaced mass with areas of hemorrhage.  B, High-power image of malignant SFT showing numerous mitotic figures.  C, High-power image of malignant SFT showing cellular area of tumor with crowding and overlapping nuclei. Scattered mitotic figures are also present.  D, Low-power image of malignant SFT showing a cellular area on the left and a broad area of tumor necrosis on the right.  E, High-power image of malignant SFT showing marked nuclear pleomorphism within tumor cells.  F, Low-power image showing benign-appearing SFT on the left with abrupt transition to very cellular area of malignant SFT on the right.  G, Higher-power image showing benign-appearing SFT with a hemangioendothelioma-like pattern on the left and cellular area of malignant SFT on the right.  H, High-power image showing markedly atypical malignant cell within an area of frank sarcomatous tumor in a malignant SFT.

Solid areas in types II and III PPB have admixtures of cellular islands of blastematous cells with fewer cellular areas of a spindle cell sarcoma. Mitoses are numerous within areas of blastema. Foci of skeletal muscle (eg, rhabdomyoblasts) or cartilaginous differentiation may be present within the sarcomatous areas (Figure 9, C through E). Focal cellular anaplasia with giant, bizarre pleomorphic cells may occur in types II and III PPB. Cystic areas in type II PPB are lined by a ciliated columnar epithelium similar to that observed in type I PPB. True cysts, by definition, do not occur in type III PPB. However, areas of necrosis may cause “cystic degeneration” which, unlike the true cystic areas in types II and III PPB, lacks a ciliated columnar epithelial lining.108

Immunohistochemical studies are not particularly helpful. Cytokeratin stains the overlying ciliated columnar epithelial component but is not expressed in the sarcomatous or blastemal areas. Muscle-specific actin and desmin label areas of skeletal muscle differentiation and may be positive, to a lesser extent, in areas of blastema. S100 stains areas of cartilaginous differentiation.108

Type I PPBs overlap histologically with type IV congenital cystic adenomatoid malformations, and distinction between the entities may be difficult on histologic grounds alone. However, the presence of any area of stromal hypercellularity in a type IV congenital cystic adenomatoid malformation should engender consideration of PPB.111 In this regard, careful sampling of any cystic mass submitted from a child is necessary. Sections from any thickened or plaquelike area may show blastematous or sarcomatous foci and thereby facilitate the diagnosis of this tumor.108

Patients with type I PPB tend to have a better prognosis than patients with types II or III PPB.108 However, recurrences tend to show progression to types II or III over...
Survival varies according to type, but PPB is an aggressive neoplasm. Metastases may occur within the central nervous system (brain and spinal cord), bone, liver, and soft tissue. The overall 5-year survival rate is 45%. Treatment consists of surgical resection, when possible, accompanied by chemotherapy and radiation therapy.108

**Primary Pleural Presentation of Malignant Tumors More Common in Other Locations**

**Synovial Sarcoma**

Synovial sarcoma is a rare, aggressive sarcoma that most commonly arises in periarticular soft tissues. It most commonly occurs in young adults between ages 20 and 40 years but may occur at any age. Synovial sarcoma within the pleura most often represents a metastasis from a soft-tissue primary. However, primary pleural presentation has increasingly been recognized since 1996, when Gaertner et al described a series of 5 biphasic synovial sarcomas originating within the pleural cavity.115,116 Clinically, primary pleural synovial sarcoma occurs in a wide age range of patients. In a study by Bégueret et al117 of 40 patients with intrathoracic synovial sarcoma, the median age was 47 years with a range of 16 to 79 years. Men and women appear affected approximately equally.118
formed glands.115,121 All types of tumors may show areas of differentiation ranging from poorly defined nests to well-defined and stronger in the epithelial component.115,118 Histologically, most pleural synovial sarcomas are either monophasic or poorly differentiated.117 Occasional cases are biphasic. Monophasic tumors are composed entirely of dense but bland spindled cells in intertwining fascicles. Poorly differentiated synovial sarcomas are of higher grade and contain areas of pleomorphic cells distinct from the bland spindled cells of the monophasic variety. They vary from tumors composed of large epithelioid cells, tumors composed of small blue cells resembling peripheral neuroectodermal tumors, and tumors with spindle cells growing in a “herringbone” pattern.120 Biphasic tumors show variable degrees of epithelial differentiation ranging from poorly defined nests to well-formed glands.115,121 All types of tumors may show areas of necrosis, hemorrhage, and frequent mitoses115-117,120,122 (Figure 10, A and B).

Most synovial sarcomas (90%) are at least focally positive for one or more epithelial markers, although the degree and distribution of staining vary somewhat according to the type (monophasic, poorly differentiated, or biphasic). Epithelial membrane antigen is most consistently present in all 3 tumor types: present in 90%, 85%, and 100% of monophasic, poorly differentiated, and biphasic synovial sarcomas, respectively.115-117 Broad-spectrum cytokeratins are present less often (100%, 60%, and 58% of biphasic, monophasic, and poorly differentiated synovial sarcomas, respectively).115-117,120 BER-EP4 and CK7 are expressed more often in biphasic synovial sarcomas (76%, 90%, and 100%, respectively) than in monophasic or poorly differentiated synovial sarcomas (7%, 78%, and 6%, 50%, respectively; for monophasic and poorly differentiated synovial sarcoma120). In biphasic tumors, periodic acid-Schiff-positive, diastase-resistant material may be seen in both DMM and synovial sarcoma.123,124

Synovial sarcomas frequently stain positively for some markers also preferentially expressed in DMMs. In a study of soft tissue synovial sarcomas, Miettinen et al123 identified calretinin expression (both nuclear and cytoplasmic) in 71%, 52%, and 56% of biphasic, monophasic, and poorly differentiated synovial sarcomas, respectively. Bégueuet al127 reported a somewhat lower expression of calretinin in synovial sarcomas limited to the thorax (12.8% of monophasic and poorly differentiated synovial sarcomas, combined). Expression of calretinin in synovial sarcomas, when present, varies from focal to diffuse. CK5/6 is present in most biphasic synovial sarcomas (76%) but is less often expressed in monophasic or poorly differentiated tumors (30% and 18%, respectively). In contrast, expression of WTI is not identified in any of the subtypes of synovial sarcoma.123

Expression of other antigens may be helpful in the diagnosis of synovial sarcoma. Both Bcl-2 and CD99 are expressed by most synovial sarcomas. CD34 and CD117 are only rarely expressed.117

Molecular diagnostic techniques have greatly enhanced the diagnosis of synovial sarcoma. Greater than 90% to 95% of synovial sarcomas harbor the t(X;18) translocation (SYT-SSX). This translocation leads to the fusion of SYT (at 18q11) with SSXI or, less commonly, SSX2 or SSX4 (all at Xp11), resulting in fusion protein products thought, through their effect on cell cycle regulation, to be integral to the pathogenesis of this tumor.124,125 Identification of the SYT-SSX translocation through reverse transcriptase polymerase chain reaction (PCR), fluorescence in situ hybridization or conventional cytogenetics is currently regarded as the most sensitive and specific method of diagnosis.122,126-128 This translocation is not found in sarcomatoid DMMs129 or other types of malignancies.130,131

The differential diagnosis of synovial sarcoma in the pleura consists of metastatic synovial sarcoma, sarcomatoid and biphasic variants of DMM, benign and malignant SFTs, metastatic sarcomatoid carcinomas, and metastases or pleural involvement from other types of sarcomas. These entities can usually be distinguished on the basis of their clinical, gross, and histopathologic features.121

Soft tissue synovial sarcomas may commonly metastasize to the lung and pleura. Accordingly, an extrapleural primary should be rigorously excluded clinically before accepting a pleural presentation.115 In contrast to synovial sarcoma, DMMs usually present with diffuse pleural thickening in older individuals with a history of asbestos exposure.115,132 Although the immunohistochemical profiles of synovial sarcoma and DMM overlap,132 DMMs tend to express cytokeratin more diffusely and intensely than synovial sarcomas do.121,133 Expression of the mesothelial markers calretinin and CK5/6 is not useful as they may be seen in both DMM and synovial sarcoma.123,124 Benign and malignant SFTs can usually be distinguished by their histologic and immunohistochemical features. Immunohistochemical staining for CD34 is useful as it has been reported only rarely in synovial sarcoma but is usually present in both benign and malignant SFTs.117,133 Likewise, immunohistochemical staining for epithelial markers such as EMA and cytokeratin is negative in SFTs but positive in most synovial sarcomas.117,133 Positive staining for the epithelioid markers EMA and cytokeratin in synovial sarcoma tends to exclude pleural involvement or metastases from other types of sarcomas. In addition, synovial sarcomas lack staining for neural (S100) and smooth muscle (desmin, smooth muscle actin) markers.123,134 Metastatic sarcomatoid carcinomas can usually be distinguished by consideration of the clinical history as well as differing histopathologic and immunohistochemical features. In all of these cases, assessment of the SYT-SSX translocation by reverse transcriptase PCR, fluorescence in situ hybridization, or cytogenetics is very helpful in confirming or excluding synovial sarcoma.125,126-128

The prognosis of primary pleural synovial sarcoma is poor. In the series published by Gaertner et al,115 4 of 5 patients died within 3 years of initial surgery. Given the rare nature of this presentation, treatment is not standardized but usually consists of surgical resection occasionally accompanied by preoperative or postoperative radiation and chemotherapy.118

Angiosarcoma

Angiosarcoma may rarely present in the pleura and often mimics DMM (“pseudomesotheliomatous angiosar-
The majority of cases have an epithelioid morphology histologically with variable degrees of vascular differentiation. Biopsy specimens show ragged infiltration by sheets or nests of large spindled and polygonal epithelioid cells interspersed with occasional ill-defined, variably sized vascular spaces. Within these spaces there may be micropapillary projections of tumor cells. The cells are cytologically malignant with large, pleomorphic, vesicular nuclei and prominent nucleoli. Mitotic figures are often frequent (Figure 11, A through C). As in angiosarcomas of other areas, cells may contain small intracytoplasmic vacuoles containing intact or degenerating erythrocytes. 

The differential diagnosis includes DMM, metastatic carcinoma, and epithelioid hemangioendothelioma. These entities can be distinguished based on a combination of histopathologic features and expression of epithelial, mesothelial, and vascular immunohistochemical markers.

Unlike DMM and metastatic carcinoma, angiosarcoma lacks expression of calretinin and CK5/6, markers of mesothelial differentiation. Epithelioid angiosarcoma often shows some staining for broad spectrum cytokeratin. If present, however, this staining is usually weaker and more focal than typically seen in DMM. Angiosarcoma should stain for one or more vascular markers including CD34, CD31, or factor VIII. Staining for these markers is not observed in DMM. Although not formally studied in this setting, D2-40, a newly described mesothelial marker, does not appear to be useful, as it is also a lymphatic endothelial marker and stains a subset of angiosarcomas.

Epithelioid hemangioendothelioma is distinguished from angiosarcoma by its generally lower grade histologic appearance. Compared with angiosarcomas, epithelioid hemangioendotheliomas show milder degrees of nuclear atypia, fewer mitoses, and less necrosis. Zhang et al., however, suggest that this distinction may not be prognostically important as the prognoses of both epithelioid hemangioendothelioma and angiosarcoma are similar.

Putative etiologic factors of pleural angiosarcoma are diverse. In Japan, pleural angiosarcoma has been strongly linked to chronic pyothorax. A history of prior radiation therapy is not currently supported, as DMMs showing areas of liposarcomatous, osseous, and cartilaginous differentiation. However, this theory is not currently supported, as DMMs showing areas of angiosarcomatous differentiation have not been described. Moreover, Attanoos et al. found no evidence of endothelial differentiation in a study of 92 cases of DMM studied by immunohistochemistry for CD31, CD34, or von Willebrand factor.

The prognosis of angiosarcoma is generally poor. In the study by Zhang et al., most patients were dead within 6 months despite aggressive surgery including pneumonec- tomy and pleurectomy. Localized cases have occasionally fared better with long-term survival in a few.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma in the lung was first described by Dail et al., who initially termed it intravascular bronchioloalveolar cell tumor. Aside from the lung, the tumor also commonly presents in the soft tissue, liver, and bone. Rare cases of epithelioid hemangioendothelioma have also been reported within the pleura.

The clinical characteristics of epithelioid hemangioendothelioma are similar to those of angiosarcoma. Most patients are male and present with chest pain or discomfort and dyspnea. Chest CT scans show smooth to nodular, localized to diffuse pleural thickening.

Gross findings on pneumonectomy or pleurectomy mirror those in imaging studies, showing localized to diffuse thickening of the pleura, which can extend along interlobar fissures in a “pseudomesotheliomatous” growth pattern. Histologically, biopsy and resection specimens show strands, cords, or nests of epithelioid cells within a myxoid or hyaline stroma. Epithelioid cells often have intracytoplasmic lumina, which may contain variably degenerated erythrocytes. Nuclear features are generally bland, and mitotic figures are scarce (Figure 12, A through C).

The immunohistochemical profile of epithelioid hemangioendothelioma is similar to that of angiosarcoma. The neoplastic cells stain weakly and/or focally for cytokeratin and also stain for one or more of the vascular markers CD31, CD34, and factor VIII. To our knowledge, expression of the mesothelial markers calretinin and CK5/6 has not been studied in this setting.

The differential diagnosis of epithelioid hemangioendothelioma consists of DMM, metastatic carcinoma, metastases from other sites of origin, and angiosarcoma. Diffuse malignant mesotheliomas and metastatic carcinomas generally show diffuse strong immunohistochemical staining for cytokeratin in contrast to the weak and/or focal staining in epithelioid hemangioendotheliomas. Moreover, expression of vascular markers CD31, CD34 and/or factor VIII is present in epithelioid hemangioendothelioma but not observed in DMM or metastatic carcinoma. Metastases from another soft tissue or visceral origin are generally excluded by appropriate clinical workup.

Epithelioid hemangioendothelioma is distinguished from angiosarcoma by its generally lower grade histologic appearance including blander nuclear cytology, lower frequency of mitoses, and lesser degree of necrosis. Nonetheless, as Lin et al. recognized, the boundary between higher grades of epithelioid hemangioendothelioma and well-differentiated angiosarcoma is not clearly defined and can, in occasional cases, be somewhat arbitrary. In this regard, Zhang et al. argue that because of their invariably fatal outcome all epithelioid vascular tumors of the pleura should be regarded as highly malignant regardless of their distinction as angiosarcoma or epithelioid hemangioendothelioma.

Primary Effusion Lymphoma

Primary effusion lymphoma comprises a subset of large B-cell non-Hodgkin lymphomas recognized in the 1990s due to their unique presentation as pleural, pericardial, or peritoneal lymphomatous effusions in patients with ac-
Figure 11. A, Medium-power image of angiosarcoma showing ragged infiltration of pleura by ill-defined vascular spaces lined by malignant cells. B, High-power image of angiosarcoma showing markedly atypical cells lining the vascular spaces. The cells are enlarged with vesicular nuclei and variably prominent nucleoli. C, High-power image of angiosarcoma showing a less-differentiated area where the cells are more epithelioid and the vascular pattern is more difficult to appreciate. Courtesy of David Dail, MD, Virginia Mason Medical Center, Seattle, Wash.

Figure 12. A, Low-power image of epithelioid hemangioendothelioma showing nests and cords of bland epithelioid cells within a fibromyxoid stroma. B, Medium-power image of epithelioid hemangioendothelioma showing intracytoplasmic lumina and no mitotic figures. C, High-power image of epithelioid hemangioendothelioma showing intracytoplasmic lumina. Courtesy of David Dail, MD, Virginia Mason Medical Center, Seattle, Wash.

Figure 13. A, Wright-Giemsa–stained smear of primary effusion lymphoma showing a uniform population of atypical large lymphoid cells. B, Papanicolaou–stained smear of primary effusion lymphoma showing atypical lymphoid cells.

Figure 14. A, Medium-power image of an Epstein-Barr virus–associated pleural lymphoma showing a collection of large atypical lymphoid cells present adjacent to a pleural plaque (lower right) and necrotic tumor (upper left). B, Higher-power image showing cytologically atypical cells with enlarged, vesicular nuclei, one to several prominent nucleoli, and irregularly thickened and cleaved nuclear membranes. C, CD20 immunostain showing tumor cell immunopositivity. Tumor cells were also positive for Epstein-Barr virus by in situ hybridization.
quired immunodeficiency syndrome. A remarkable finding in these cases was the absence of an associated mass lesion. Subsequent studies showed that the majority of these lymphomas are associated with coinfection by Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8). 153–156

In recent years, the clinical and pathologic spectrum of this disorder has expanded. Cases of primary effusion lymphoma have been reported in patients without acquired immunodeficiency syndrome, 157 and some cases have lacked infection by HHV-8, EBV, or both. 158–164 Reports have also recognized HHV-8-associated solid extrathoracic lymphomas with cytologic features of primary effusion lymphoma either with or without associated serous effusions. 165–169 Although most cases were originally thought to have a B-cell origin, rare cases with a T-cell phenotype have been described. 170,171

Given the absence of an associated mass in most cases, diagnosis of primary effusion lymphoma is usually made on examination of cytologic preparations accompanied by immunohistochemical, flow cytometric, and molecular diagnostic studies. On Wright-Giemsa–stained and Papanicolaou-stained cytospin preparations, cells show highly atypical intermediate to large lymphoid cells with irregular nuclei and one to several prominent nucleoli (Figure 14, A). The overall cytologic features are consistent with a large cell lymphoma. 153–156,170 Flow cytometric and immunohistochemical studies usually show positive staining of the cells for CD45 as well as activation markers such as CD30, CD38, and CD138. In most cases, cells usually have a null cell phenotype and do not express lineage-associated B-cell– or T-cell–associated antigens (eg, CD20, CD79a, CD3). 154–156 Occasional cases, however, may show a B-cell or T-cell phenotype. The cells express the HHV-8/KSHV–associated latent protein by immunohistochemistry. 169,170,171 Despite the association with EBV, however, staining for EBV LMP 1 is negative. 173 Clonal rearrangement of the immunoglobulin genes can be identified in most cases either through Southern blot analysis or by PCR. 154–156 Rare cases have also been reported with rearrangement of the T-cell receptor genes. 150,170 Southern blot or PCR analysis shows HHV-8 present in all cases. 153–156 Epstein-Barr virus can also be detected in most cases on Epstein-Barr virus–encoded RNA in situ hybridization.

The prognosis of primary effusion lymphoma is poor, with a median survival of 6 months. Treatment usually consists of a combination of chemotherapy (CHOP—cyclophosphamide, doxorubicin, vincristine, and prednisone) combined with antiretroviral therapy (if the patient is human immunodeficiency virus positive). 174

**Pyothorax-Associated Lymphoma**

Pyothorax-associated lymphoma refers to the development of a pleural EBV-associated diffuse large B-cell lymphoma in patients with longstanding chronic pyothorax. Pyothorax-associated lymphoma was initially described in 1987 in 3 patients who had developed chronic pyothorax after artificial pneumothorax for tuberculosis. 175–177 Since this original description, many additional cases have been reported.

Pyothorax-associated lymphoma occurs predominantly in elderly men (mean age in the seventh decade with marked male predominance). 175,178 Most patients have a history of chronic pyothorax subsequent to artificial pneumothorax performed in the management of tuberculosis. However, pyothorax-associated lymphoma or similar EBV-associated pleural lymphomas have rarely been reported in other conditions associated with chronic pleural inflammation such as prior exposure to asbestos or following pneumonectomy. 179,180

The duration of chronic pyothorax preceding diagnosis ranges from 20 to 64 years (median, 37 years). 181–183 Patients present most commonly with chest and/or back pain sometimes accompanied by a chest wall mass. Chest x-ray films identify a pleural-based mass in approximately half of patients, although CT scan is more sensitive (85%). The mass is usually 10 cm or larger and may involve the lung or chest wall. Ancillary studies may demonstrate extrapleural dissemination to lymph nodes, liver, bone, bone marrow, and other organs. 183

Biopsy specimens show a diffuse proliferation of large cytologically atypical lymphoid cells associated with a background of chronic fibrous pleuritis. The lymphoid cells often have immunoblastic features consisting of round nuclei with prominent and sometimes multiple nucleoli (Figure 14, A). Many cases show plasmacytoid differentiation. Mitoses are frequent and often associated with apoptotic bodies. 175,181,182 On immunohistochemistry, most cases are of B-cell phenotype and express CD20 and/or CD79a, sometimes associated with expression of CD138 (Figure 14, B). The neoplastic cells generally lack expression of CD10 and Bcl-6 but are positive for MUM1, consistent with derivation from late germinal center/post–germinal center B cells. In some cases, there may be dual or aberrant expression of T-cell markers (CD2, CD3, and CD4). 173,181 Rare cases stain only with T-cell markers, although it is unclear whether these represent pyothorax associated peripheral T-cell lymphomas or loss of B-cell antigens with aberrant T-cell antigen expression. Rare cases express no lineage specific antigens. 173,181,183

In situ or PCR studies for EBV are positive in the majority of cases. Petitjean et al 181 found that most cases show expression of EBV LMP 1 and EBNA-2 consistent with a type III latency profile. Immunohistochemical or in situ studies for HHV-8 are negative. 181,184 Of the cases studied, most show light-chain restriction on immunohistochemistry or clonal rearrangements of the immunoglobulin heavy chain gene by PCR. 184

Prognosis of patients with pyothorax associated lymphoma is poor. In a clinicopathologic review of 98 patients, Narimatsu et al 183 reported a 35% 5-year survival rate. Treatment consists of adjuvant radiation, chemotherapy, or chemoradiotherapy with response rates of 56%, 71%, and 83%, respectively. Pleuropneumonectomy has been reported as successful in some cases. 185

**Malignant Small Cell Tumor of Thoracopulmonary Region (Primitive Neuroectodermal Tumor or “Askin Tumor”)**

In 1979, Askin et al 186 described a rare malignant neoplasm composed of undifferentiated small cells involving the chest wall, lung, and/or pleura of children (Askin tumor). This tumor appeared distinct from Ewing sarcoma, malignant lymphoma, embryonal rhabdomyosarcoma, and neuroblastoma. Based on the presence of occasional rosettelike structures on light microscopy combined with ultrastructural observations of rare neurosecretory-like granules, they postulated a primitive neuroectodermal origin. 186

Since the original description by Askin et al 186 the application of immunophenotypic and molecular genetic techniques has shown that these tumors, along with Ew-
ing sarcoma and primitive neuroectodermal tumors of soft tissue are a common neoplastic entity collectively termed Ewing sarcoma family of tumors (ESFT). All of these tumors are defined by a chromosomal translocation that leads to the fusion of the Ewing sarcoma gene (EWS) with one of the ETS family of transcription factors (including FLI1, ERG, EIAF, FEV, and ZSG). The most common translocation, t(11;22)(q24;q12), leads to in-frame fusion of EWS to FLI1, which results in an oncoprotein consisting of the N-terminal domain of EWS and the DNA-binding domain of FLI-I.

In the original article by Askin et al, patients were generally younger than 20 years old (range, 4 months to 20 years; median, 11 years) and most commonly presented with a mass (either solitary or multiple nodules) involving the chest wall, lung, or pleura. Other clinical symptoms included dyspnea or fever.

Pathologically, round, ovoid, multinodular gray-white masses are present in the chest wall or bulging through the parietal pleura. Histologically, the tumors consist of homogeneous cells with small round to oval nuclei and only a small amount of cytoplasm. The cells are arranged in sheets or in a vaguely lobular pattern. There is variable neural differentiation manifest as Homer-Wright rosettes or pseudorosettes (Figure 15, A). Variable amounts of glycogen are present in a minority of tumors on perls iron stain.

On immunohistochemistry, CD99 (the protein product of the MIC2 gene) is expressed by nearly all ESFTs. Strong and diffuse staining for this marker is characteristic of this entity such that the diagnosis of ESFT in a tumor lacking expression of CD99 should only be accepted if the characteristic translocation can be documented with molecular techniques. CD99 expression, however, is not specific as it may be present in lymphoblastic lymphoma, rhabdomyosarcoma, neuroblastoma, and others. Thus a panel of markers including terminal deoxynucleotidyl transferase, myogenin, myo-D1, and synaptophysin should be applied to any tumor suspected of ESFT to exclude these other entities. More recently, Folpe and others have shown that FLI-1 protein can be detected in most ESFTs and may also be helpful in characterizing these tumors.

In addition to immunohistochemistry, molecular techniques are helpful in confirming the diagnosis of ESFT. Translocations involving EWS may be detected by reverse transcriptase PCR or fluorescence in situ hybridization techniques. Up to one third of patients with ESFT have metastases at presentation, and their prognosis is poor (5-year survival rate of 35%). Common metastatic sites include lung, bone, and bone marrow. The prognosis of patients with localized disease is better (5-year survival rate of 73%).

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a recently described aggressive malignancy of adolescent and young adult males. Although it was originally reported in a predominantly or exclusively intra-abdominal location, more recent studies have noted that it may rarely occur in the pleura, lung, and other extrabdominal locations. At a molecular level, DSRCT is defined by a unique chromosomal translocation, t(11;22)(p13;q12), which results in a fusion protein combining the EWS gene with the DNA binding area of WT1 (EWS/WT1). With the addition of several other fusion partners of WT1, this entity was termed Ewing sarcoma family of tumors (ESFT). All soft tissue are a common neoplastic entity collectively termed Ewing sarcoma family of tumors (ESFT).

Within the abdomen, a DSRCT usually consists of a large intra-abdominal mass accompanied by widespread peritoneal and omental implants and without a clear visceral origin. Tumors occurring within the pleura have a similar presentation and may grossly mimic DMNs.

Histologically, DSRCTs are characterized by irregular, angulated nests of small cells embedded within a cellular fibromyxoid stroma (Figure 16, A). Necrosis is variably present within the centers of nests (Figure 16, B). The small cells within nests are generally uniform, with scanty, eosinophilic cytoplasm (Figure 16, C). In some areas, cells may have a “rhabdoid” appearance with a deeply eosinophilic inclusion-like cytoplasm which indents the nucleus. Mitotic figures are numerous.

Desmoplastic small round cell tumors have a complex, but distinctive, immunohistochemical profile with coexpression of epithelial, muscle, and neural markers. This immunohistochemical profile helps to distinguish them from other small round blue cell tumors of childhood. Desmin is perhaps the most useful marker, as it is expressed in most cases (81% to 100%). Expression is usually strong and diffuse, in many cases (75%) with a “globoïd” or “dotlike” pattern of reactivity. In contrast, other muscle specific markers such as muscle specific actin or α smooth muscle actin are expressed less often (16% and 19%, respectively). Cytokeratin (AE1/AE3, CAM 5.2) can be found in most cases (95%), although it may rarely be absent. Most cases also stain positively for other epithelial markers including EMA (96%), MOC-31 (90%), and BEREP4 (71%). Expression of neural markers including neuron-specific enolase, CD57 (Leu-7), and synaptophysin is more variable (72%, 67%, and 16%, respectively). Approximately one third of tumors stain positively with CD99.

Recently, WT1 has been reported as helpful in the diagnosis of DSRCT. Nuclear staining for WT1 is present in almost all cases, but is not expressed in ESFT or neuroblastomas.

Molecular techniques may also be helpful in the diagnosis of DSRCT, particularly in cases with atypical features. The chimeric EWS/WT1 gene fusion transcript may be detected by reverse transcriptase PCR. Fluorescence in situ hybridization techniques have also been used.

The prognosis of patients with pleural presentation of DSRCT is poor, similar to that of patients with an abdominal presentation. In the study by Parkash et al., there was an incomplete response to chemotherapy in all patients, and 2 of 3 patients died within 2 years.

Pleural Liposarcoma

Liposarcomas may rarely present within the pleura. Histologic types are similar to those found in soft tissue including well-differentiated/sclerosing, myxoid, and round cell. Radiographically, the tumors present with pleural-based masses. Histologic features are similar to those in soft tissue. Well-differentiated/sclerosing liposar-
Figure 15. A, Low-power image of a primitive neuroectodermal tumor (Ewing sarcoma family of tumors or Askin tumor) showing sheets of small blue cells in a vaguely lobular pattern effacing the normal pleural parenchyma. B, Medium-power image of primitive neuroectodermal tumor (Ewing sarcoma family of tumors or Askin tumor) showing monotonous small blue cells with scant cytoplasm. There is a suggestion of pseudorosette formation.

Figure 16. A, Medium-power image of desmoplastic small round cell tumor showing irregular angulated nests of small cells within a fibrous stroma. B, Medium-power image of desmoplastic small round cell tumor showing areas of necrosis within some nests. C, High-power image of desmoplastic small round cell tumor showing nests of uniform cells with scant eosinophilic cytoplasm.

Figure 17. A, Low-power image of pleural liposarcoma showing irregular areas of sclerosis admixed with mature adipose tissue. Arrows denote interface with adjacent lung. B, Medium-power image of pleural liposarcoma showing scattered atypical hyperchromatic cells within areas of sclerosis (arrows). C, High-power image of pleural liposarcoma showing hyperchromatic atypical nucleus. Courtesy of Joseph Holden, MD, University of Utah Medical Center, Salt Lake City.

Figure 18. Thymoma. Nests of thymoma (arrows) within a thickened pleura.

Thymoma consists of mature adipose tissue with scattered atypical more hyperchromatic cells, some with the appearance of lipoblasts. There are variable amounts of intervening sclerotic/fibrous tissue (Figure 17, A through C). Myxoid/round cell types are more cellular with elongated spindled to round cells with hyperchromatic nuclei within a myxoid stroma containing a delicate capillary network.225–227

**Pleural Presentation of Thymoma**

Thymomas typically involve the pleura by direct extension from the mediastinum. Rarely, however, they may present as pleural-based masses. The described cases have occurred across a broad age range from 38 to 75 years. Affected patients are either asymptomatic or have nonspecific respiratory complaints. Radiographic studies typically show diffuse, often nodular pleural thickening, sometimes accompanied by encasement of the associated lung.228

Histologically, the thymomas reported show a similar histologic spectrum as present in mediastinal lymphomas (types A, B, and C by World Health Organization criteria). They consist of lobules separated by dense fibrous bands (Figure 18). The lobules contain small round lymphocytes admixed with variable numbers of scattered larger epithelial cells. Mitotic activity is not prominent. Hassall cor-
Figure 19. A, Gross image of desmoid tumor showing an off-white to tan nodular mass resembling a solitary fibrous tumor. B, Medium-power image of desmoid tumor showing a modestly cellular proliferation of spindle cells within a collagenous background with scattered small blood vessels. C, High-power image of desmoid tumor showing overall bland cytologic features of the spindle cells. Courtesy of Bruno Murri, MD, Ospedale Umberto I-ASL, Venice, Italy.

Figure 20. A, Low-power image of pleural Rosai-Dorfman disease showing a cellular pleural inflammatory infiltrate. B, High-power image of pleural Rosai-Dorfman disease showing characteristic large pale histiocytic cells admixed with lymphocytes, plasma cells, and neutrophils in a background of fibrosis. Emperipolesis is present. Courtesy of Paul Ohori, MD, University of Pittsburgh Medical Center, Pittsburgh, Pa.

Pleural Desmoid Tumor

Desmoid tumors (fibromatosis) may also rarely present within the pleura. Immunohistochemical stains for cytokeratin (CK5/6 and p63. Background lymphocytes are positive for terminal deoxynucleotidyl transferase, CD99, and CD1a. The differential diagnosis of pleural thymoma consists chiefly of pleural involvement by a mediastinal thymoma, malignant lymphoma, and DMM. Pleural extension of a mediastinal thymoma should be excluded with appropriate radiographic studies. In contrast to thymoma, lymphoma does not contain admixed epithelial cells. Pleural thymoma may mimic DMM clinically and radiographically. However, on histologic examination DMM usually shows areas of tubular and papillary growth and does not show the typical lobulation and fibrous bands of thymoma. Diffuse malignant mesothelioma also usually lacks the conspicuous lymphoid infiltrate present in most thymomas. Immunohistochemical stains for mesothelial markers such as calretinin and CK5/6 are generally not helpful, as they may stain the epithelial cells in both thymoma and DMM. The prognosis of pleural thymoma is unclear from the limited data available. In the study of 8 patients by Moran et al., 1 died, 1 recurred, 4 were lost to follow-up, and 2 patients were free of disease at 2 and 10 years after diagnosis.

Plural Presentation of Rosai-Dorfman Disease

Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is a rare disease of uncertain histogenesis. It most commonly presents as lymphadenopathy due to effacement of affected nodes by a proliferation of large, pale, histiocytic-appearing cells admixed with neutrophils, lymphocytes, and plasma cells, with a background of variable fibrosis. The large pale histiocytes with associated emperipolesis of other inflammatory cells are a distinctive feature of this disease. Positive immunohistochemical staining of these cells for S100 helps to facilitate their distinction from more typical reactive histiocytes. However, the cells lack staining for CD1a and are thus also distinct from Langerhans cells.

Although this disorder usually presents with lymphadenopathy, extranodal presentation may rarely occur. Pulmonary parenchymal involvement occurs in 3% of extranodal cases. Ohori et al reported a single case: an 81-
year-old man who presented primarily with pleural involvement with a pleural effusion associated with parietal pleural thickening. The histologic features in this case were typical of Rosai-Dorfman disease at other extranodal sites (Figure 20, A and B).

CONCLUSION

Compared with metastatic malignancy to the pleura, DMM is uncommon; nonetheless it is the most common malignant primary pleural neoplasm. Relatively uncommon in relation to DMM are a variety of benign and malignant pleural neoplasms. The pathologist needs to maintain an appropriate index of suspicion of these uncommon to rare primary pleural neoplasms in order to render an optimal diagnosis.

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Primary Pleural Neoplasia—Guinee & Allen


Arch Pathol Lab Med—Vol 132, July 2008

Primary Pleural Neoplasm—Guinee & Allen 1169


