Sarcomatoid Neoplasms of the Lung and Pleura

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Sarcomatoid neoplasms of the lung and pleura are rare tumors that present a complex differential diagnosis, making them challenging for surgical pathologists. In the lung, the main tumors are sarcomatoid carcinomas, including pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma. They are characterized by histologic heterogeneity; molecular data support their origin from a pluripotent stem cell that undergoes neoplastic transformation with divergent epithelial and sarcomatous differentiation. Diagnosis is difficult in small biopsy specimens and typically requires a resection specimen. Despite the presence of sarcomatoid features, these tumors are classified as lung carcinomas. Pulmonary blastomas must be distinguished from pleuropulmonary blastomas, which are a unique type of thoracic sarcoma typically occurring in young children. In the pleura, the main tumors to consider are the sarcomatoid and desmoplastic types of malignant mesothelioma, solitary fibrous tumor, and desmoid tumor. While light microscopy is sufficient to diagnose most of these tumors, immunohistochemistry can be useful in selected settings. In particular, it can aid in confirming epithelial differentiation in spindle cell carcinomas and the presence of rhabdomyosarcoma in sarcomatoid carcinomas, mesotheliomas, or pleuropulmonary blastomas. For sarcomatoid and desmoplastic mesothelioma, keratin is the most useful stain because it can highlight invasive growth and mesothelial markers are positive in only the minority of cases. Clinical and radiologic correlation is needed to separate some pleomorphic carcinomas with pleural involvement from sarcomatoid malignant mesothelioma, since these poorly differentiated tumors may not express the usual immunohistochemical markers for carcinoma or mesothelioma.

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Sarcomatoid neoplasms of the lung and pleura are rare tumors that present a complex differential diagnosis, making them challenging for surgical pathologists. Primary pulmonary sarcomatoid carcinomas need to be distinguished from sarcomas and metastatic carcinomas. In the pleura, these tumors include sarcomatoid carcinoma, malignant mesothelioma, fibrous tumor, and desmoid tumor. This review will address the pathologic aspects of some of the more frequent sarcomatoid pulmonary and pleural tumors and their differential diagnosis with other primary sarcomatoid lung tumors. The wide variety of sarcomatoid neoplasms that can metastasize to the lungs are not the focus of this article.

SARCOMATOID NEOPLASMS OF THE LUNG

Sarcomatoid carcinomas of the lung are rare, with giant and spindle cell carcinomas accounting for 0.3% of all invasive lung malignancies. The classification of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements is complex and it is difficult to resolve all of the controversial issues in 1 classification. In the 2004 World Health Organization (WHO) classification, sarcomatoid carcinoma is used as an overall term for a spectrum of tumors that includes pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and blastoma. Most of these tumors can be classified by light microscopy alone, although in certain situations immunohistochemistry can be helpful. These tumors may be suspected on small biopsy specimens, but definitive diagnosis typically requires a resected specimen, largely owing to their histologic heterogeneity and pleomorphism. Overall histologic features and distinguishing characteristics are summarized in Table 1.

Most lung carcinomas with components of spindle cell and/or giant cell carcinoma are histologically heterogeneous. Pure spindle or giant cell carcinomas are rare. Because of the spindle cells and giant cells, these tumors are often mistaken for sarcomas or carcinosarcomas. Immunohistochemistry and electron microscopy have contributed to an improved understanding of this spectrum of tumors. Classification of these tumors is based primarily on light microscopic criteria. Pulmonary blastomas are the rarest of the sarcomatoid carcinomas, accounting for 0.25% to 0.5% of all primary malignant lung tumors.

There is a continuum of differentiation between pleomorphic or spindle/giant cell carcinomas, carcinosarcomas, and blastomas. The mechanisms of carcinogenesis by which these tumors develop have been debated for years. However, molecular evidence supports the concept that these are carcinomas of the lung, with a clonal origin from pluripotent stem cells, that are capable of divergent differentiation into various mixtures of carcinomatous and sarcomatous components.
Clinical Features

All sarcomatoid carcinomas occur in older adults, with a median age of 60 to 70 years (range, 30–85 years), have a strong male predominance, and are associated with a high frequency of smoking. Most clinical data are based on cases from surgical resections, rather than cases involving patients with advanced-stage disease, owing to the requirement for a surgical specimen, rather than a small biopsy or cytology specimen, to make the diagnosis. Presenting symptoms include thoracic pain, cough, and hemoptysis.

Pleomorphic carcinomas have an aggressive clinical course, with mean or median survival of patients ranging from to 5 to 35 months. For pleomorphic carcinoma, some studies, but not all, have shown worse prognosis than for other non–small cell carcinomas. Multivariate analysis in 1 study of pleomorphic carcinomas showed that massive necrosis, lymphatic permeation, and advanced stage were independent prognostic factors. The small bowel is one of the sites that pleomorphic carcinomas tend to metastasize.

For blastomas and carcinosarcomas, surgical resection is the primary therapeutic modality. If the tumor is at an advanced stage, combination chemotherapy or radiation therapy may be used as a palliative approach; however, there is no proven benefit save several anecdotal reports. Recurrence occurs in approximately 43% of biphasic pulmonary blastomas. The prognosis for patients with biphasic blastomas is poor. Survival is 33% at 2 years, 16% at 5 years, and 8% at 10 years. Patients with stage I “blastomas” have a 5-year survival rate of about 25%. Overall, for carcinosarcomas of the lung, the prognosis is poor. Koss et al reported a 5-year survival rate of 23%. A median survival of 9 to 12 months has been reported in patients who underwent curative surgery. Fewer than 10% survive 2 years.

Carcinosarcomas arising in the peripheral parenchyma tend to spread into the pleura and chest wall. Central endobronchial tumors without parenchymal extension tend not to involve hilar lymph nodes. However, if there is parenchymal invasion, approximately 50% may have lymph node metastases at the time of initial surgery. Recurrences are often in the lung, but metastases to the hilar and mediastinal lymph nodes are also frequent. Metastases can contain both histologic components of the primary tumor; carcinoma is the most common type encountered if only 1 component is found.

Gross Features

Sarcomatoid carcinomas are frequently large tumors with a mean size of 5 to 8 cm (range, 1–28 cm). Pleomorphic carcinomas and blastomas are most often situated in the peripheral lung, but chest wall involvement is more characteristic of pleomorphic carcinomas and may be seen in up to 25% of cases. A central location, sometimes with endobronchial involvement, can be seen in all sarcomatoid carcinomas, but it is seen more often in carcinosarcomas and least often in pleomorphic carcinomas. They are circumscribed and unencapsulated, with a variegated, white, tan, or gray, or hemorrhagic cut surface. Hemorrhage and necrosis are frequent.

Microscopic Features

Pleomorphic (Spindle/Giant Cell) Carcinoma.—Pleomorphic carcinoma is defined as a poorly differentiated, non–small cell lung carcinoma, namely squamous cell carcinoma, adenocarcinoma, or large cell carcinoma that contains at least 10% spindle cells and/or giant cells, or more commonly a mixture of these cell types.

In addition to the spindle and/or giant cell carcinoma patterns, when a component of adenocarcinoma or squamous cell carcinoma is present in a pleomorphic carcinoma, it should be documented (for example, pleomorphic carcinoma with squamous cell carcinoma, spindle cell and giant cell carcinoma). Although commonly present, foci of large cell carcinoma do not need to be included in the diagnosis. If a component of small cell carcinoma is identified, the tumor is classified as a combined small cell carcinoma, with mention of the specific non–small cell lung carcinoma components present. Rare cases of pleomorphic carcinoma, mostly with a squamous cell component, may show a pseudo-vascular pattern (Figure 3). Vascular invasion is common in pleomorphic carcinomas (Figure 4, A and B). Necrosis is common and often extensive.
Because pleomorphic carcinomas are frequently large tumors, at least 1 section per centimeter of the tumor mass should be submitted for initial evaluation. If there is some question about the diagnosis of carcinoma in a sarcomatoid tumor, owing to lack of frank carcinomatous areas and/or keratin expression, more extensive sampling may aid in achieving a diagnosis if areas of adenocarcinoma or squamous carcinoma are identified. In small biopsy specimens, the diagnosis of pleomorphic carcinoma may be suspected, but it cannot be diagnosed owing to the requirement that spindle and/or giant cells be identified in 10% of the tumor.

**Spindle Cell Carcinoma.**—Spindle cell carcinoma is defined as a carcinoma consisting only of spindle-shaped tumor cells. The pure form of spindle cell carcinoma is rare. Since it represents a histologic continuum with pleomorphic carcinoma and shares the same aggressive behavior, it is classified in this general group of tumors. Spindle cell carcinoma displays a sarcoma-like growth pattern often exhibiting marked cellular pleomorphism and abnormal mitoses (Figure 5, A and B). Epithelioid morphology of the tumor cells may be a clue to carcinomatous differentiation. It is frequently admixed with nonneoplastic connective tissue elements and may be combined with giant cell carcinoma. Rare cases may show a prominent inflammatory stroma, often leading to confusion with other inflammatory lesions, such as necrotizing granulomas or inflammatory myofibroblastic tumors (Figure 4, B). In inflammatory cases, vascular invasion can be a helpful clue for malignancy (Figure 4, B).

**Giant Cell Carcinoma.**—Giant cell carcinoma is defined as a carcinoma consisting only of highly pleomorphic tumor giant cells (Figure 6, A). Pure giant cell carcinoma is very rare. More often, the pattern of giant cell carcinoma is associated with a spindle or large cell component. If a differentiated component such as adenocarcinoma is present, the case is classified as pleomorphic carcinoma. Giant cell carcinoma consists of multinucleated or mononucleated, large, polygonal cells, often discohesive, with hyperchromatic, coarsely granular chromatin, and distinct nucleoli. Marked stromal infiltration or emperipolesis by polymorphonuclear leukocytes or lymphocytes may occur.

Giant cell carcinoma is reported to account for 0.3% to 2% of all invasive lung malignancies. The giant tumor cells may stain immunohistochemically for human chorionic gonadotropin but should not be confused with a primary choriocarcinoma of the lung. Lung cancers can ectopically produce any of the placental glycoproteins. Most reported cases of primary pulmonary choriocarcinoma actually are giant cell carcinomas ectopically producing human chorionic gonadotropin. Rarely, lung carcinomas can demonstrate osteoclast-like giant cells that mimic malignant fibrous histiocytoma (Figure 6, B).

**Pulmonary Blastoma.**—Pulmonary blastoma is a biphasic tumor containing a malignant epithelial component resembling fetal adenocarcinoma and a primitive mesenchymal stroma, which occasionally has foci of osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. Biphasic pulmonary blastomas have both a malignant glandular component and an embryonic or “blastematosus” stroma (Figure 7). The epithelial component is composed of tubules of glycogen-rich, nonciliated cells that resemble fetal lung between 10 and 16 weeks of
Figure 4. Pleomorphic carcinoma with vascular invasion. A, This tumor extensively infiltrates the medium-sized arteriole (center) and its small branch (left top). The tumor consists mostly of spindle cell carcinoma with areas of giant cell carcinoma (bottom right). B, This tumor showed a prominent chronic inflammatory stroma, leading to initial consideration of a reactive process. However, the vascular invasion by cytologically malignant epithelial cells (that were cytokeratin positive) helped establish the diagnosis of carcinoma.

Figure 5. Spindle cell carcinoma. A, This tumor consisted purely of cytologically malignant spindle cells. The presence of some cells with epithelioid morphology is suggestive of carcinoma. B, This spindle cell carcinoma is staining positively with AE1/AE3 (immunohistochemistry for AE1/AE3 pancytokeratin).

Figure 6. Giant cell carcinoma. A, This tumor consists of discohesive sheets of malignant giant cells with abundant eosinophilic cytoplasm. Most cells are uninucleated, but a few multinucleated cells are present. There is prominent emperipolesis with numerous neutrophils within the cytoplasm of multiple tumor cells. B, This tumor had areas with numerous osteoclast-like giant cells. Elsewhere this tumor showed adenocarcinoma.
The embryonic appearance of the stroma of pulmonary blastoma. This malignant tumor consists of a primitive blastematous stroma. The epithelial cells have clear cytoplasm with some subnuclear vacuoles.

gestation, corresponding to the pseudoglandular stage of lung development. Subnuclear and supranuclear glycogen vacuoles give the tumor an endometrioid appearance. The embryonic appearance of the stroma is due to the small size, oval and spindle shape of the cells, and myxoid matrix. In approximately 25% of cases, foci of immature striated muscle and/or cartilage can be found. In 5% of cases osseous differentiation is present. The association of biphasic blastoma mixed with yolk sac tumor has been observed. A single case of a blastoma with a malignant melanoma component has been reported.

Figure 7. Pulmonary blastoma. This malignant tumor consists of a glandular component with endometrioid morphology and a primitive blastematous stroma. The epithelial cells have clear cytoplasm with some subnuclear vacuoles.

Rounded morules of squamous-like cells with abundant eosinophilic cytoplasm are found in 43% of biphasic pulmonary blastomas. These have been compared to neuroepithelial bodies.

Historically, the term pulmonary blastoma has included pure fetal adenocarcinomas as well as the biphasic tumors. In the 1999 WHO classification, fetal adenocarcinomas were separated from the biphasic tumors to become a variant of adenocarcinoma. In the 2004 WHO classification, based on work by Nakatani et al., fetal adenocarcinomas were divided into the low-grade variant and the less common high-grade variant. Because of these changes in diagnostic criteria, the literature reported before the 1999 and 2004 WHO classifications needs to be reviewed critically to determine if fetal adenocarcinomas may have been included in studies of pulmonary blastomas.

Immunohistochemical and Molecular Features

Pleomorphic Carcinoma.—Immunohistochemistry using epithelial markers, including various keratin antibodies or epithelial membrane antigen (EMA), can be useful to confirm carcinomatous differentiation in the spindle cell component of pleomorphic carcinomas (Figure 5, B). This is particularly important because the differential diagnosis of sarcoma is of greater concern if light microscopy does not demonstrate clear carcinomatous components, such as adenocarcinoma or squamous cell carcinoma. In most cases, only a single pancytokeratin antibody, such as AE1/AE3, is needed. The threshold for interpretation as positive may need to be lowered, compared to that of better differentiated tumors, as the staining may be only weak and/or focal. In some poorly differentiated tumors for which the initial pancytokeratin stain results are negative, multiple keratin antibodies such as AE1/AE3, CAM 5.2, and cytokeratin (CK) 7 may need to be tested. CK18 is particularly useful in sarcomatoid neoplasms. Adenocarcinoma components may express thyroid transcription factor 1 (TTF-1), PE10, or Napsin and squamous

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Pleomorphic Carcinoma.
components can stain for p63 or 34βE12. Since carcinomas of the lung are common, and primary sarcomas are very rare, a keratin-negative sarcomatoid tumor is more likely to be a carcinoma than a sarcoma, particularly if the tumor does not readily classify into a known sarcoma type.\textsuperscript{4,6,7,17} β–Human chorionic gonadotropin can stain positively in giant cell carcinomas regardless of whether there are elevated serum levels of this protein.\textsuperscript{39}

Only a few studies have explored the molecular features of sarcomatoid carcinomas. Pleomorphic carcinomas are reported to have less frequent KRAS and p53 mutations than adenocarcinomas and squamous cell carcinomas.\textsuperscript{62} One study\textsuperscript{62} demonstrated KRAS mutations in 22% of pleomorphic carcinomas, and in 5 of 6 cases the mutations were in both the epithelial and sarcomatoid components, favoring a clonal origin. All KRAS mutations were transversions found in smokers, supporting the notion that smoking played a carcinogenic role.\textsuperscript{62} In 1 case, an EGFR mutation, consisting of a deletion in exon 19, was found in a pleomorphic carcinoma before gefitinib therapy, and in both the adenocarcinoma and sarcomatoid components at autopsy; however, the sarcomatous component also had a T790M EGFR mutation in exon 20, which is associated with acquired resistance to tyrosine kinase inhibitors.\textsuperscript{63,64} A study using chromosomal comparative genomic hybridization and immunohistochemistry\textsuperscript{65} suggested epithelial-mesenchymal transition played a role in development of the spindle and giant cell carcinomas regardless of whether there are elevated serum levels of this protein.\textsuperscript{39}

Blastomas.—The glands in blastomas stain with antibodies to keratin, TTF-1, carcinoembryonic antigen, surfactant, and EMA.\textsuperscript{28,49,67} Epithelial cells in morules stain positively with antibodies to both TTF-1 and GATA-6 (a fetal lung epithelial differentiation-specific transcription factor).\textsuperscript{67} Stromal cells can express smooth muscle actin

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\caption{Pleuropulmonary blastoma (PPB). A, This type I PPB has multiple cystic spaces with a cellular cambium layer of spindle cells with rhabdomyoblastic differentiation. B, This type III PPB consists of nests of cellular, hyperchromatic, small primitive blastematos cells with scant cytoplasm alternating with less cellular areas of round to oval cells.}
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\begin{figure}[h]
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\caption{Carcinosarcoma. A, This tumor consisted of squamous cell carcinoma (left) and rhabdomyosarcoma (right). The rhabdomyosarcoma component is a mixture of malignant spindle and epithelioid cells, which stain strongly with desmin and myogenin. B, This tumor consisted of adenocarcinoma (left) and rhabdomyosarcoma, which stains strongly with desmin (immunohistochemistry for desmin).}
\end{figure}
and vimentin.\(^\text{26,67}\) If rhabdomyosarcoma is suspected, desmin and myogenin may be helpful.

Neuroendocrine differentiation is found in two-thirds of pulmonary blastomas. Substantial chromogranin and neuron-specific enolase staining can be seen in morules and less prominently in glandular epithelial cells.\(^\text{26}\)

Pulmonary blastomas have been shown to have \(\beta\)-catenin mutations, varying percentages of \(p53\) mutations, but no \(KRAS\) mutations.\(^\text{56,69}\) Natani et al\(^\text{49}\) found mutations in exon 3 of the \(\beta\)-catenin gene in 3 of 4 blastomas, but not in 5 carcinosarcomas with a high-grade fetal adenocarcinoma component. In 2 of these cases, \(\beta\)-catenin mutations were found in both the epithelial and sarcomatous components.\(^\text{68}\) By immunohistochemistry, both nuclear and cytoplasmic staining were found in both the epithelial and sarcomatous components, with less staining in the latter.\(^\text{99}\) Sekine et al\(^\text{26}\) found \(\beta\)-catenin mutations in 3 well-differentiated adenocarcinomas and 2 blastomas with morules, but not in 4 blastomas lacking morules. \(p53\) mutations are reported in 14% to 53% of cases.\(^\text{14,70}\) One case study of the epithelial and mesenchymal components of a primary tumor and a metastatic tumor\(^\text{15}\) used whole genome allelic imbalance scanning and mutations of \(p53\), \(EGFR\), \(KRAS\), and \(\beta\)-catenin. In this study, all tumor components analyzed showed allelic imbalance at chromosome regions 14q24-q32 and 17p11-p13 and \(\beta\)-catenin mutations.\(^\text{15}\) However, additional allelic imbalance in chromosome regions 6p24-p25 and 6q14-2q27 was found in the metastasis as well as the epithelial component, but not the mesenchymal component of the primary tumor. This was interpreted to suggest that the tumor was monoclonal in origin; however, the genetic heterogeneity represented accumulation of genetic changes in the mesenchymal component and the metastases.\(^\text{15}\)

**Carcinosarcoma.**—The diagnosis of carcinosarcoma is based on light microscopy, except for those cases in which the rhabdomyosarcomatous component is poorly differentiated and not recognizable morphologically. In these cases, the myogenous differentiation needs confirmation by immunohistochemistry with muscle markers such as desmin (Figure 9, B) and/or myogenin.\(^\text{71}\) Keratin may be helpful in confirming the carcinoma component.\(^\text{74}\) Adenocarcinoma components may be positive for TTF-1, and squamous cell carcinoma components may express p63. S100 will stain the chondrosarcoma component.\(^\text{74}\)

Dacic et al\(^\text{16}\) analyzed loss of heterozygosity with 12 polymorphic microsatellite markers and found extensive allelic loss in both the epithelial and mesenchymal components, especially for 3p, 5q, and 17p. A greater amount of fractional allelic loss was found in the sarcomatous compared to the epithelial component.\(^\text{15}\) Holst et al\(^\text{16}\) found an identical \(p53\) mutation in both the carcinoma and sarcoma component in 1 of 3 carcinosarcomas (by 2004 WHO criteria).\(^\text{14}\) No \(KRAS\) mutations were found in any of the 3 cases. These studies are consistent with the concept of origin from a pluripotent stem cell, with development of a lung carcinoma that then develops a sarcomatous component.

**Differential Diagnosis**

The differential diagnosis for sarcomatoid carcinomas is complicated because these tumors need to be separated not only from each other but also from a variety of other poorly differentiated carcinomas and sarcomas.

The spindle and giant cells of pleomorphic carcinomas usually stain with epithelial markers such as pancytokeratin (ie, AE1/AE3), CAM 5.2, CK18, and EMA, but in a small percentage of cases the staining results can be negative. If a component of frank carcinoma showing clear adenocarcinoma or squamous cell carcinoma is present, the tumor is a pleomorphic carcinoma even if epithelial differentiation cannot be demonstrated by special techniques in the sarcomatoid component. The term carcinosarcoma is reserved for tumors with malignant heterologous mesenchymal elements such as osteosarcoma, chondrosarcoma, or rhabdomyosarcoma. The use of keratin stains is problematic owing to difficulties inherent in variable staining methods, interpretation of staining results, and potential staining of both carcinomas and some sarcomas.

The differential diagnosis for pleomorphic carcinoma includes carcinosarcoma, blastoma, and carcinoma with reactive desmoplastic stroma; for tumors involving the pleura, malignant mesothelioma may be considered. Histologic features that allow for separation of pleomorphic carcinoma from spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and blastoma are summarized in Table 1. Hyalinized or desmoplastic stroma within a lung carcinoma lacks the malignant cytologic characteristics and keratin expression seen in pleomorphic carcinoma.

Giant cell carcinomas can be separated morphologically from choriocarcinomas because they show a size spectrum in the giant cells, while choriocarcinomas show only 2 cell types: syncytiotrophoblasts and cytotrophoblasts.

To diagnose pleomorphic carcinoma with osteoclast-like giant cells, extensive sampling may be required to demonstrate carcinomatous areas.\(^\text{46}\) If an epithelial component cannot be identified, a malignant giant cell tumor with osteoclastic giant cells may be regarded as giant cell malignant fibrous histiocytoma, according to the 2002 WHO classification of soft tissue tumors.\(^\text{72}\)

In the setting of a keratin-negative sarcomatoid and/or epithelioid tumor in the lung, an epithelioid vascular tumor or malignant melanoma should be considered. Since epithelioid hemangioendotheliomas and angiosarcomas may express cytokeratins, even if a vasoformative tumor is keratin positive, the tumor should be stained with vascular markers.

Primary sarcomas of the lung are extremely rare; therefore, if a sarcomatoid neoplasm does not have the characteristic morphologic, immunohistochemical, and/or molecular features of a specific sarcoma, it is likely that the tumor represents a sarcomatoid carcinoma even with negative keratin staining. Synovial sarcoma is discussed below in the differential diagnosis of sarcomatoid malignant mesothelioma.

The differential diagnostic clinical and pathologic features of pulmonary blastoma versus well-differentiated fetal adenocarcinoma and pleuropulmonary blastoma are summarized in Table 2. While both blastomas and carcinoid tumors show neuroendocrine differentiation, carcinoid tumors do not consist of either purely glandular or biphasic glandular and sarcomatous elements. Carcinosarcomas lack the endometrioid glandular pattern and the embryonic stroma seen in biphasic blastomas.

The differential diagnosis of carcinosarcoma includes blastoma, spindle cell carcinoma, carcinoma with osseous metaplasia,\(^\text{73}\) and true sarcoma. Blastomas can be biphasic

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with epithelial and sarcomatous elements; however, carcinosarcomas do not show a primitive blastemal component. Nakatani et al.²⁶ have proposed the term blastomatoid variant of carcinosarcoma to classify carcinosarcomas with a high-grade fetal adenocarcinoma component. They point out that these tumors lack β-catenin mutations and differ from classic pulmonary blastomas that usually show a well-differentiated fetal adenocarcinoma component and express β-catenin mutations. While their article makes a useful point that carcinosarcomas with a high-grade fetal adenocarcinoma component should be distinguished from classic pulmonary blastomas, the term blastomatoid variant of carcinosarcoma is likely to create further confusion with blastoma. It seems more practical to simply classify these tumors as carcinosarcomas and then mention the high-grade fetal adenocarcinoma along with the other carcinomatous and sarcomatous components that are present.

Rarely, benign ossification can be encountered in the stroma of ordinary lung carcinomas.²⁵ Sarcomas differ from carcinosarcomas in that they do not show a component of carcinoma.

**SARCOMATOID NEOPLASMS OF THE PLEURA**

The main sarcomatoid tumors of the pleura addressed in this section are sarcomatoid malignant mesothelioma, solitary fibrous tumor, and desmoid tumor. While solitary fibrous tumor and desmoid tumors are much rarer, their importance exceeds their frequency because they come into the differential diagnosis with sarcomatoid malignant mesothelioma.

### Sarcomatoid Malignant Mesothelioma

Compared to lung cancer, malignant mesothelioma is a rare neoplasm, with only approximately 3000 new cases diagnosed in the United States each year.²⁴

**Clinical Features.**—The average age of patients with mesothelioma is 60 years, although rarely, cases may occur in childhood²⁵ and young adults.²⁶ The frequency of asbestos exposure in patients with malignant mesothelioma varies, depending on the population studied; however, approximately 80% or more of patients have documented exposure.²⁷⁻²⁹ The latency period for malignant mesothelioma averages 30 to 40 years, with a range from 15 to 60 years.²⁷⁻²⁹ Other potential risk factors for mesothelioma include radiation, chronic inflammation, viral infection (including SV40), and diethylstilbestrol.²⁷⁻²⁹

Multiple studies³⁰⁻³² demonstrate that sarcomatoid mesotheliomas have a significantly worse prognosis than epithelioid mesotheliomas, with a 6-month median survival compared to 10 months for biphasic and 16 months for epithelioid mesotheliomas. Klebe et al.³³ reported 10% and 5% survival at 12 and 18 months, respectively. Pleural mesotheliomas tend to spread locally within the chest cavity, invading and compressing major structures, but metastases can occur to the lung parenchyma and mediastinal lymph nodes as well as to extrathoracic sites such as the liver, bones, peritoneum, and adrenal glands.³⁴

**Gross Features.**—The classic gross appearance of malignant mesothelioma is that of diffuse pleural thickening by a firm, tan-white mass.²⁹,³⁴⁻³⁶ The presence of an intrapulmonary mass suggests the diagnosis of bronchogenic carcinoma rather than mesothelioma. Rarely, malignant mesothelioma may present as a localized mass.²⁸,³⁷,³⁸

**Histologic Features.**—Histologically, malignant mesothelioma can have a variety of patterns including epithelioid, sarcomatoid, and biphasic or mixed epithelioid and sarcomatoid patterns (Table 3).²⁷,²⁹ Biphasic mesothelioma should have at least 10% of both epithelioid and sarcomatoid components. In addition, one can encounter unusual features such as decidual, lipid-rich, clear cell or glycogen-rich, and lymphohistiocytoid features.²⁸

**Sarcomatoid/Desmoplastic Mesothelioma.**—Sarcomatoid mesotheliomas consist of more than 90% spindle-shaped tumor cells (Figure 10, A).³³ Klebe et al.³³ recently reported 324 cases, of which 145 (44%) were conventional, 70 (21%) were sarcomatoid with desmoplastic areas, 110 (34%)
were desmoplastic, 8 (1%) had heterologous elements (osteosarcomatous and/or chondrosarcomatous), and 2 (<1%) were lymphohistiocytoid. These tumors can have heterologous elements including chondrosarcoma, osteosarcoma, or rhabdomyosarcoma.

Desmoplastic malignant mesothelioma is diagnosed when more than 50% of the tumor shows this pattern. It is observed in 8% to 12% of malignant mesotheliomas. Histologically, it consists of dense bands of collagenous tissue separated by scattered, plump spindle cells with oval, sometimes hyperchromatic, nuclei (Figure 10, B). These tumors are characterized by hyalinized bundles of collagen arranged in a storiform pattern and separated by plump hyperchromatic spindle cell nuclei. Invasion of adipose tissue or skeletal muscle of the chest wall and foci of bland necrosis are helpful in establishing a diagnosis of malignancy.

**Immunohistochemical Features.**—Sarcomatoid malignant mesotheliomas are usually keratin positive, although Klebe et al reported keratin-negative findings in 7% of cases. Calretinin staining was positive in only 31% of cases and it usually showed focal labeling of fewer than 10% of the tumor cells. Tumors with heterologous elements for some reason are more likely to be keratin negative. Rhabdomyosarcomatous differentiation may be confirmed by positively staining muscle markers, such as desmin or myogenin.

Immunohistochemistry is of little value in the differential diagnosis between chronic fibrous pleuritis and malignant mesothelioma, except for keratin stains helping to identify the presence of invasive growth (Figure 10, C). The spindle cells stain for low-molecular-weight cytokeratins in virtually all cases, but this finding does not distinguish sarcomatoid or desmoplastic mesothelioma from reactive processes, since reactive mesothelial cells and reactive submesothelial fibroblasts are also keratin positive.

**Differential Diagnosis.**—The differential diagnosis for sarcomatoid and biphasic diffuse malignant mesothelioma is summarized in Table 4. The distinction between desmoplastic malignant mesothelioma and chronic fibrous pleuritis is one of the most difficult problems faced by experts in mesothelioma diagnosis. Mangano et al reported the following diagnostic criteria for desmoplastic malignant mesothelioma: a paucicellular fibrotic lesion with a storiform pattern or the “patternless pattern” of Stout and 1 or more of the following 4 characteristics, namely, (1) frankly sarcomatoid areas; (2) foci of bland necrosis; (3) invasion of chest wall or lung parenchyma; and (4) distant metastases. These criteria correlated well with outcome in a series of 24 patients with desmoplastic malignant mesothelioma and 7 patients with fibrous pleuritis. Furthermore, there was excellent interobserver agreement among 3 panelists using the criteria, with a κ statistic of 0.73.

Frankly sarcomatoid areas are recognized as foci of increased cellularity and atypical nuclei within the tumor, often with an abrupt transition from less cellular zones. Areas of bland necrosis are deep within the tumor and may be related to vascular invasion. Such areas should not be confused with superficial fibrinous exudates, which can be seen in reactive processes. Invasion of chest wall usually manifests as spindle cells surrounding and invading adipose tissue, but infiltration of skeletal muscle

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**Figure 10. Sarcomatoid malignant mesothelioma.** A, This tumor consists of malignant spindle cells arranged in a storiform pattern. B, This desmoplastic malignant mesothelioma shows an acellular pattern (top) with haphazardly arranged slitlike spaces. The tumor shows a cellular pattern of spindle cells invading the parietal pleural fat (bottom), supporting a malignant rather than a reactive diagnosis. C, This cytokeratin 18 stain highlights invasion of the sarcomatoid tumor cells into parietal pleural fat.
fibers may also be observed. Invasion of lung may appear as tumor tracking along secondary lobular septa or invading alveolar spaces. The latter often has a superficial resemblance to organizing pneumonia. For obscure reasons, hematogenous metastases of these tumors often manifest in bone.77

Pleomorphic carcinoma involving the pleura usually must be distinguished from mesothelioma on the basis of gross and/or radiologic findings in some cases, owing to the potential for overlapping histologic and immunohistochemical features. Mesotheliomas typically cause diffuse pleural thickening and most often do not show destructive invasion of the chest wall, while pleomorphic carcinomas present as a localized peripheral intrapulmonary mass and can invade into the chest wall. A variety of sarcomas must be considered, but synovial sarcoma is the most important. Both biphasic and monophasic synovial sarcomas can present a problem in the differential diagnosis of malignant mesothelioma.98–100 However, they usually occur in younger patients (4–50 years) and are localized masses without diffuse pleural thickening. Histologically, these tumors are more cellular than most mesotheliomas with hemangiopericytoma-like areas and the stroma may be densely hyalinized or myxoid in appearance. An X;18 translocation can be demonstrated from paraffin-embedded tissue in approximately 90% to 100% of cases.98,101 In the biphasic tumors, the glandular components may express mucin or carcino- ma markers such as BER-EP4 or carcinoembryonic antigen.99

If keratin markers are negative in an epithelioid pleural tumor, one should consider the possibility of an epithelioid vascular tumor101,102 or malignant melanoma.

**Solitary Fibrous Tumor of Pleura**

Solitary fibrous tumors of the pleura are uncommon localized neoplasms arising in association with the pleura.78,103,104 Most are benign, but 13% to 36% may be malignant.103,105,106 These tumors were previously called fibrous mesotheliomas.105 They are often mistaken for other mesenchymal neoplasms including hamartoma, neurofibroma, leiomyoma, fibrosarcoma, and hemangiopericytoma.105

Once regarded to be mesothelial tumors, immunohistochemical and ultrastructural studies support an origin from submesothelial fibroblasts.105,107,108 Recent immunohistochemical studies and observation of fibrous tumors in a variety of nonmesothelial sites provides support for the concept that these tumors are derived from fibroblasts or primitive mesenchymal cells with potential for multidirectional differentiation.109

**Clinical Features.**—There is no sex predominance. The median age at presentation is 57 years (range, 9–86 years). Greater than 50% of cases occur in the sixth and seventh decades of life.

Approximately 50% of patients with fibrous tumors of pleura are asymptomatic at presentation.105 Two-thirds of patients with benign tumors are asymptomatic in contrast to only 25% of patients with malignant tumors.105 The most common presenting symptom is chest pain followed by shortness of breath, cough, hypoglycemia, weight loss, hemoptysis, fever, and night sweats.105 Hypoglycemia has been reported in association with insulin-like growth factor 1.110,111

**Gross Features.**—Two-thirds of fibrous tumors of pleura are attached to the visceral pleura and more than half of these have a pedicle often measuring 1 cm in length. The remaining one-third of cases are attached to the parietal pleura.105 Most tumors consist of a solitary mass (Figure 11, A), although rare cases appear as a large conglomerate.105 Most tumors are round or ovoid and circumscribed. The tumors range from 1 to 39 cm and more than 60% of these are greater than 10 cm in size. The weight ranges from 12 to 3800 g.

The cut surface is most often gray-white with a nodular, whorled, or lobulated appearance. Cysts may be present in 10% of cases, especially at the base near the pleural attachment. Rarely, these tumors may occur as intrapulmonary tumors in a subpleural location.112

Features that are found more commonly in malignant tumors are lack of a pedicle, atypical location (attached to parietal pleura, a tissue, mediastinum, or inverted into the peripheral lung), size greater than 10 cm, and necrosis and/or hemorrhage.105

Patients with benign fibrous tumors of pleura have an excellent prognosis.113–116 Rarely will these tumors recur and usually only if the tumor is incompletely removed. Slightly fewer than half of pathologically malignant tumors may be cured if completely resected. Slightly more than half of patients with malignant tumors are not responsive to chemotherapy.113–116 Many of the malignant tumors arise on the parietal pleura and are unresectable at presentation. Recurrences are single in most cases but may consist of multiple masses. The tumors can invade into the chest wall, by contiguity into intrathoracic organs, or compress vital mediastinal structures.

**Table 4. Differential Diagnosis of Sarcomatoid and Biphasic Diffuse Malignant Mesothelioma**

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Biphasic mesothelioma</td>
</tr>
<tr>
<td>Other biphasic tumors, eg, synovial sarcoma, pleomorphic carcinoma, carcinosarcoma, epithelioid hemangioendothelioma</td>
</tr>
<tr>
<td>Carcinoma with cellular stromal reaction</td>
</tr>
<tr>
<td>Mesothelial hyperplasia with cellular serosal fibrosis</td>
</tr>
<tr>
<td>Metaplasia of alveolar epithelium incorporated in the substance of tumors infiltrating the lung, eg, localized fibrous tumors of pleura</td>
</tr>
<tr>
<td>Sarcomatoid mesothelioma</td>
</tr>
<tr>
<td>Sarcoma, primary or metastatic</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma, primary or metastatic</td>
</tr>
<tr>
<td>Metastatic sarcoma</td>
</tr>
<tr>
<td>Cellular serosal fibrosis</td>
</tr>
<tr>
<td>Desmoplastic mesothelioma</td>
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<tr>
<td>Reactive serosal fibrosis</td>
</tr>
<tr>
<td>Reactive serosal fibrosis</td>
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</tbody>
</table>

Data derived from Travis et al.2 Churg et al.78 Roggli et al.79 Battifora and McCaughhey,80 and Galateau-Salle et al.91

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Sarcomatoid Carcinoma and Mesothelioma—Travis
Shirosi et al\textsuperscript{116} recently reported a series of 88 cases and found that 59\% had at least 1 clinicopathologic feature related to malignancy. However, mortality and recurrence occurred in 10.2\% and 18.2\% of cases, respectively. Survival correlates with the de Perrot staging (Table 5) as well as with sessile appearance, high mitotic rate, tumor cellularity and pleomorphism, necrosis, size greater than 10 cm, and high p53 expression.\textsuperscript{117} Multivariate analysis showed that high p53 expression and tumor necrosis were significantly associated with overall and disease-free survival.\textsuperscript{117}

Metastases may occur to extrathoracic sites such as the liver, central nervous system, spleen, adrenal gland, gastrointestinal tract, lymph nodes, or bone.\textsuperscript{103} The 5- and 10-year survival rate for patients with malignant tumors with invasion are both 15\%; for malignant tumors without invasion, 80\% and 25\%, respectively; and for benign tumors, 90\% and 85\%, respectively.\textsuperscript{103}

Histologic Features.—Fibrous tumors of pleura have distinctive histologic features. The most common histologic pattern is the “patternless pattern” followed by hemangiopericytoma-like, storiform, herringbone, leiomyoma-like, or neurofibroma-like (Figure 11, B). The patternless pattern consists of fibroblast-like cells and connective tissue arranged in a random or disorderly pattern. Alternating cellular and collagen-rich areas are

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Stage 0 & Tumor with pedicle without features of malignancy at histology \\
\hline
Stage 1 & Tumor with sessile or “inverted” appearance without features of malignancy at histology \\
\hline
Stage 2 & Tumor with pedicle with features of malignancy at histology \\
\hline
Stage 3 & Tumor with sessile or “inverted” appearance with features of malignancy at histology \\
\hline
Stage 4 & Multiple metastatic tumor \\
\hline
\end{tabular}
\caption{Staging of Pleuropulmonary Solitary Fibrous Tumor\textsuperscript{a}}
\end{table}

Data derived from de Perrot et al\textsuperscript{117} and modified with permission from Schirosi et al.\textsuperscript{116}

\textsuperscript{a} Malignancy according to criteria of England et al.\textsuperscript{103}
often seen. The tumor cells are spindle-shaped to oval, often with a fibroblast-like appearance. The nuclei are thin and elongate in transverse section and round to oval in cross section. The chromatins are evenly distributed with inconspicuous nucleoli. The collagen may be compressed between the cells in a lacylike network or it may form dense, wirelike bands (Figure 11, C). Occasionally, near the site of pleural attachment, the tumor may entrap lung parenchyma, giving a tubular, cleftlike appearance with spaces lined by bronchial or alveolar epithelium.

Features that favor malignancy include increased cellularity, pleomorphism, tumor necrosis, high p53 expression, and more than 4 mitoses per 10 high-power fields. Malignant tumors may have tumor cells with an increased nuclear to cytoplasmatic ratio and less prominent collagen, and the nuclei may be hyperchromatic with prominent nucleoli. Some malignant cases demonstrate a histologically typical, benign-appearing, solitary fibrous tumor component with an abrupt transition to a high-grade spindle cell sarcoma (‘‘dedifferentiation’’). Immunohistochemical Features.—By immunohistochemistry, most fibrous tumors do not stain for keratin, unlike diffuse malignant mesotheliomas. Rarely, keratin staining may be encountered, but it is usually focal, weak, and is seen more often in malignant tumors. In most cases, tumors stain with vimentin, while a few may stain with desmin, α-anti-chymotrypsin, or actin. CD34 (Figure 11, D), BCL2, and CD99 stain positively in most fibrous tumors of pleura; however, these markers also stain a variety of other tumors. Positive staining for CD34, BCL2, and CD99 with negative keratin staining can be useful to distinguish fibrous tumors from desmoplastic malignant mesothelioma, as well as other spindle cell tumors of the pleura. Synovial sarcomas will stain with BCL2 and CD99 but should be negative for CD34 and focally positive for keratin and EMA.

Differential Diagnosis.—The differential diagnosis for fibrous tumors of pleura includes a variety of mesenchymal neoplasms including synovial sarcoma, leiomyoma, schwannoma or neurofibroma, hemangiopericytoma, desmoid tumor, and thymoma. Key to the diagnosis is recognition of the characteristic histologic patterns and cytologic features. Neurogenic tumors express S100 protein and the epithelial cells of thymomas will stain with keratin. Synovial sarcoma is addressed in the World Health Organization Classification of Tumours in soft tissue.

References