Chapter 4
Histology

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Introduction

Diffuse malignant mesothelioma (DMM) is a relatively rare but unique neoplasm of the pleura and other serosal surfaces. In the last half century, DMM has been the subject of numerous epidemiologic, clinical, experimental, and pathologic studies. Enormous medical and legal interest has been generated by rising DMM incidence, particularly after the recognition of asbestos as a causative agent [1, 2, 3]. DMM diagnosis can be accomplished at several levels during the pathologic evaluation, beginning with gross and microscopic examination and extending through immunohistochemical, molecular, and occasionally even electron microscopic confirmation.

Gross and Microscopic Features

The gross features of DMM are often of paramount importance in rendering accurate diagnoses. Pleural DMM is more common on the right than on the left, in a ratio of 3:2 [1]. Early stages of pleural involvement by mesothelioma usually consist of parietal pleural involvement by small numerous nodules. Visceral pleura less frequently may develop similar features as well [4, 5]. Subsequent growth of the neoplastic nodules leads to its coalescence; overtime progression of the lesion occurs with extensive involvement of the pleural surface resulting in fusion of visceral and parietal pleura with encasement and contraction of the lung (Fig. 4.1). Tumor growth follows the distribution on the pleural surface. The circumferential rind of tumor at late stage is typically lobulated, firm, and white (Fig. 4.2). The tumor tracks along the pleural reflections into the lung fissures with a finger-like extension

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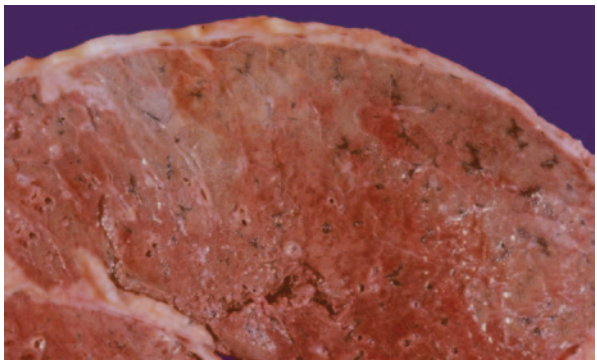

Fig. 4.1 Diffuse malignant mesothelioma: The tumor completely encases the lung and extends along the fissure

Fig. 4.2 Diffuse malignant mesothelioma: The tumor at the *lower right* corner envelop the lung and on the *upper* field encases the bronchvascular bundle and invade the lung

into interlobular septa and underlying lung. The tumor may reach several centimeters in thickness and range from firm to gelatinous in consistency. Mediastinal involvement with invasion of the pericardium, chest wall fat, and muscle involvement is characteristic. Pleural DMM may grow along needle tracts or biopsy incisions, and then manifest as a subcutaneous tumor nodule [6]. Metastases to mediastinal and hilar lymph nodes and lungs are usually evident of advanced-stage disease.

Microscopically, DMM features a wide range of histopathologic variants. The World Health Organization [7] recognizes three broad basic histologic variants of DMM: epithelial, sarcomatous, and biphasic.

Epithelial Diffuse Malignant Mesothelioma

Epithelial DMM is the most common histologic variant [7], a wide range of morphologic patterns are seen. The most frequent patterns are tubulopapillary, the solid patterns [8, 9, 10], and adenomatoid (microglandular). Sometimes, one pattern predominates but several different patterns are commonly seen in the same tumor. Less common patterns include small cell, clear cell, and deciduoid. Most epithelial

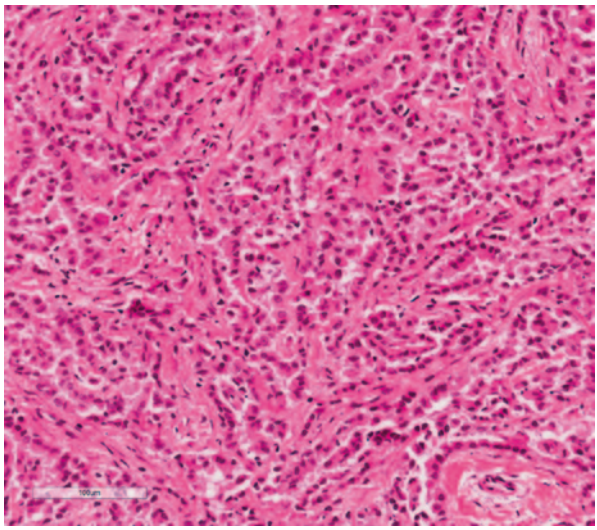

Fig. 4.3 Epithelial malignant mesothelioma showing cuboidal cells with moderate amount of eosinophilic cytoplasm with bland relatively open nuclei and infrequent mitosis

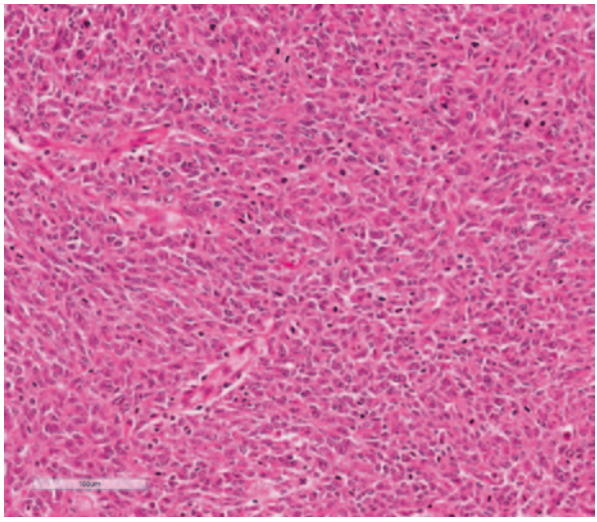

Fig. 4.4 High-grade (pleomorphic) epithelial mesothelioma showing prominent nucleoli with frequent mitosis and considerable cell-to-cell variation

DMM is cytologically monotonous and remarkably bland in appearance. The tumor cells are typically cuboidal with moderate amount of eosinophilic cytoplasm with bland and relatively open nuclei and infrequent mitosis (Fig. 4.3). In the less differentiated area, the nuclei show coarse chromatin and prominent nucleoli with frequent mitosis and considerable cell-to-cell variation of such tumor when that pattern predominate the term high-grade (pleomorphic) epithelial DMM will apply (Fig. 4.4). Such tumor is difficult to distinguish from metastatic carcinoma based on routine hematoxylin–eosin (H&E) histology alone.

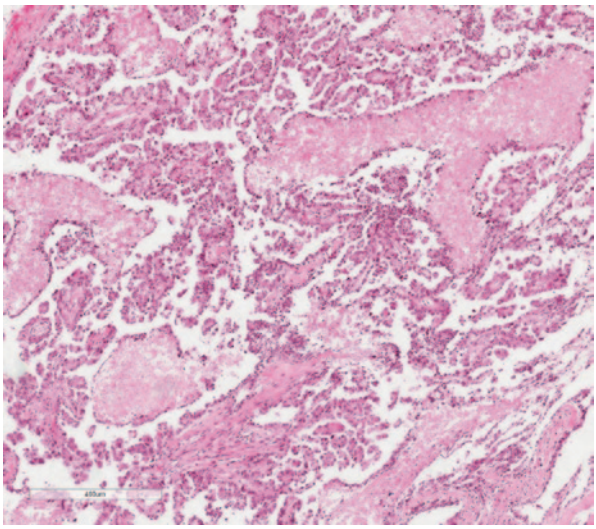

Fig. 4.5 Epithelial mesothelioma showing tubulopapillary pattern with outwards secondary branching

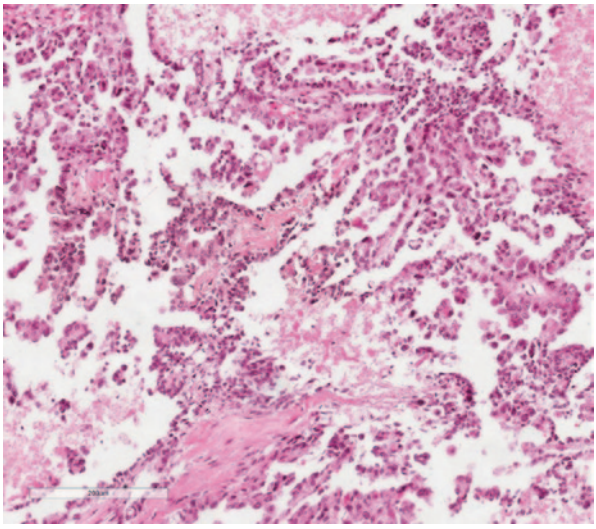

Fig. 4.6 Epithelial mesothelioma with tubopapillary pattern shows the glands and the papillae are covered by single layer of cuboidal to flattened cells

The most frequent pattern is often referred to as tubulopapillary (Fig. 4.5). In this pattern, the glands and the papillae are covered by a single layer of cuboidal to flattened cells (Fig. 4.6). Psammoma bodies may be seen but are usually infrequent [11].

Epithelial DMM may show microcytic (adenomatoid; Fig. 4.7) pattern which is usually composed of flattened bland-looking mesothelial cells; careful examination reveals the presence of some cells with large nuclei and prominent nucleoli and the tumor cells show infiltrative and diffuse pattern [12]. Further examination reveals areas of transition to ordinary patterns of epithelial DMM.

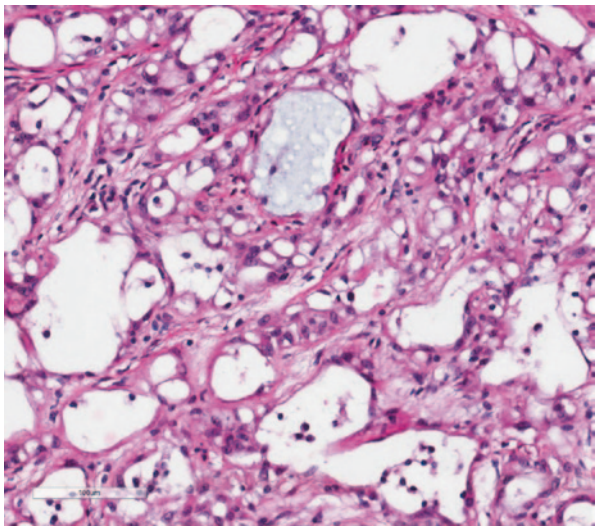

Fig. 4.7 Epithelial mesotheliomas with infiltrative microcytic (adenomatoid) pattern composed of flattened bland looking mesothelial cells

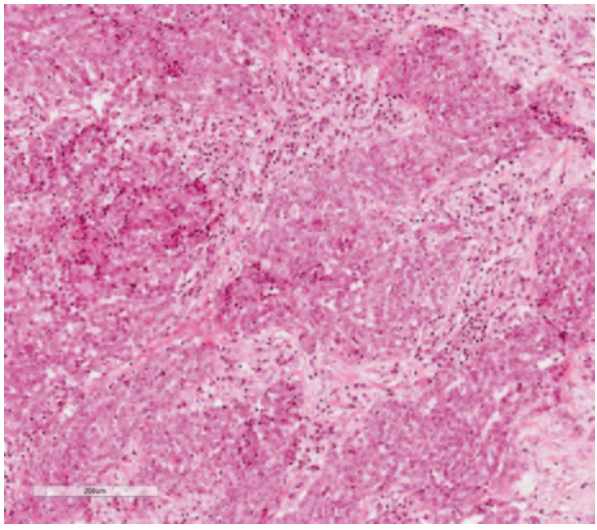

Fig. 4.8 Epithelial mesothelioma with solid infiltrative pattern

Epithelial DMM may also exhibit a predominantly solid sheet-like pattern (Fig. 4.8). In this pattern, the malignant cells form solid sheets of epithelioid cells with abundant eosinophilic cytoplasm with vesicular nuclei and prominent nucleoli; the tumor cells may contain cytoplasmic vacuoles mimicking signet ring carcinoma (Fig. 4.9). The vacuoles are rich in hyaluronate which stain strongly with Alcian blue, pH 2.5, and digested by prior hyalurinidase treatment [13].

The extremely rare small cell pattern [14, 15] of epithelial DMM is composed of fairly small cells mimicking small cell carcinoma of the lung. The mesothelial cells are arranged in monotonous sheets with no crush artifacts or basophilic staining of

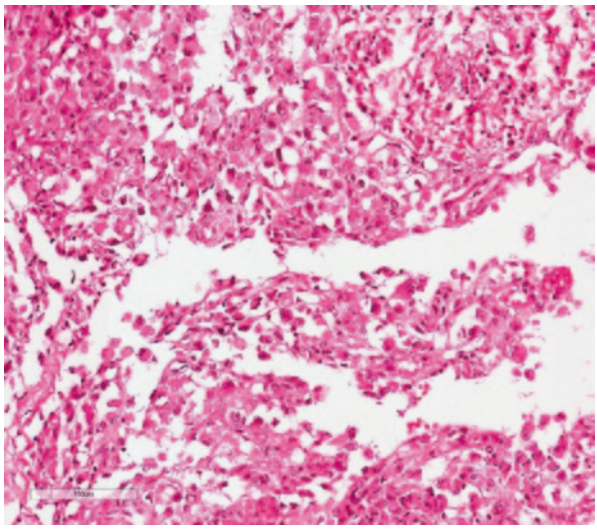

Fig. 4.9 Epithelial mesothelioma showing polygonal cells with dense eosinophilic cytoplasm and some cells with cytoplasmic vacuoles

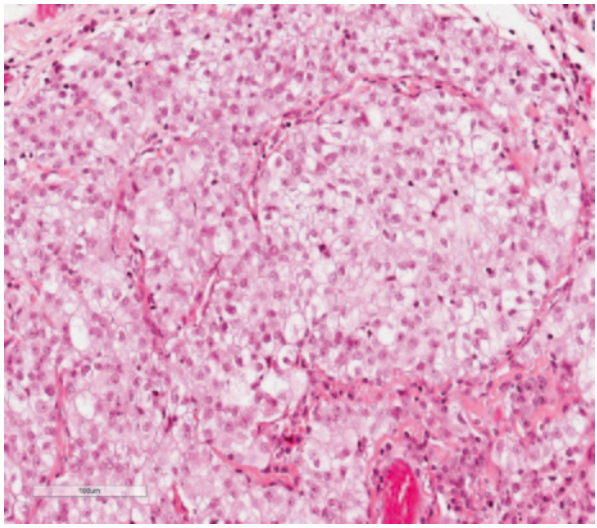

Fig. 4.10 Epithelial mesothelioma with clear cell type, this pattern must be differentiated from metastatic renal cell carcinoma

blood vessels wall. Furthermore, the nuclear chromatin is open with low mitosis. The neuroendocrine markers are usually negative. Further examination of the submitted tissue shows transition to typical patterns of epithelial DMM.

The clear cell [16] pattern shows a loosely arranged sheet of clear cells. Further examination of the tumor reveals areas of transition to more typical DMM patterns. Occasionally, clear tumor cells predominate (Fig. 4.10), and the tumor must be distinguished from metastatic renal cell carcinoma. Immunohistochemical and, if necessary, ultrastructure examination will confirm the mesothelial nature of the neoplastic cells.

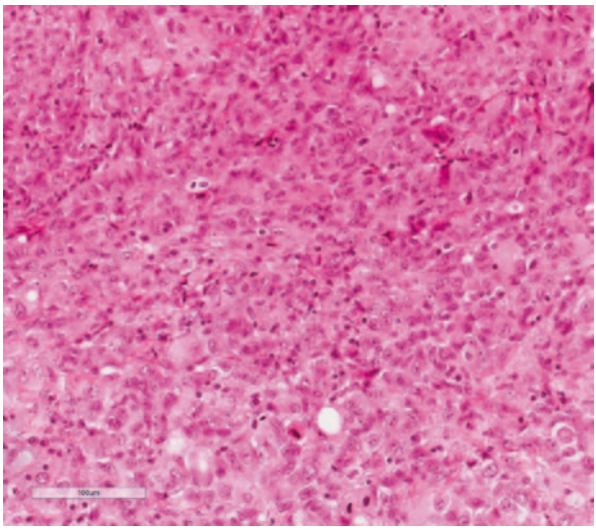

Fig. 4.11 Epithelial mesothelioma. The tumor show some cells with deciduoid pattern with large cells that resemble decidua

The deciduoid pattern [17–19] consists of large polygonal cells with abundant eosinophilic cytoplasm similar to decidual cells (Fig. 4.11). Sometimes, there is transition from deciduoid form to other typical mesothelial patterns. Immunohistochemistry will confirm the mesothelial origin of the tumor cells.

Sarcomatous Diffuse Malignant Mesothelioma

Sarcomatous DMM is an aggressive type of malignant mesothelioma which histologically exhibits a wide range of architectural complexity from hypocellular collections of extremely bland spindle cells to densely cellular areas with obviously high-grade cellular features. The most common pattern consists of closely packed bland-looking spindled cells arranged in fascicles resembling fibrosarcoma (Fig. 4.12) or obviously malignant spindle cells with multinucleated giant cells and a storiform pattern, resembling so-called malignant fibrous histiocytoma (Fig. 4.13). A combination of different patterns may be seen in the same tumor [20–22].

The spindle cells of sarcomatous DMM range from bland spindle cells with a long and thin cytoplasm (Fig. 4.14) to marked anaplasia with bizarre nuclei and increased mitotic figures as shown in Fig. 4.13. In small percentage of cases heterologous elements in the form of malignant cartilage, bone, smooth or skeletal muscles occur, mimicking chondrosarcoma, osteosarcoma, leiomyosarcoma, or rhabdomyosarcoma [3, 23–25]. All these are referred to as sarcomatous DMM. Differentiation of sarcomatoid DMM with heterologous elements from primary sarcoma of pleura may be accomplished by focal or diffuse immunohistochemical staining for broad-spectrum cytokeratin (CK) 5/6 and calretinin or ultrastructure examination. There are two additional morphologic variants of sarcomatoid DMM: lymphohistiocytoid variant of sarcomatoid DMM and desmoplastic DMM.

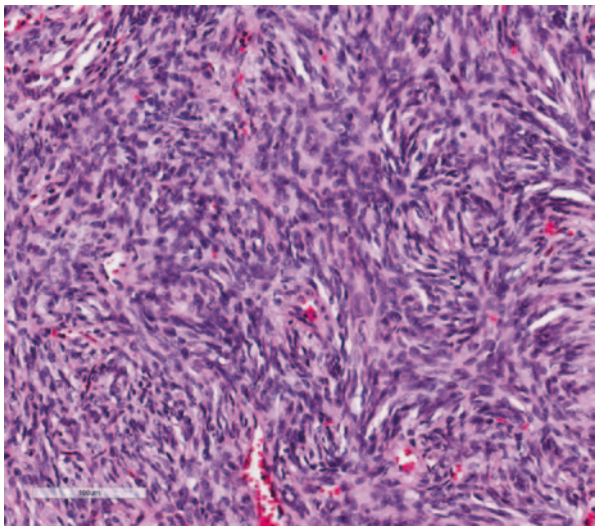

Fig. 4.12 Sarcomatous mesothelioma showing malignant spindle cells with arranged in fascicles resemble fibrosarcoma

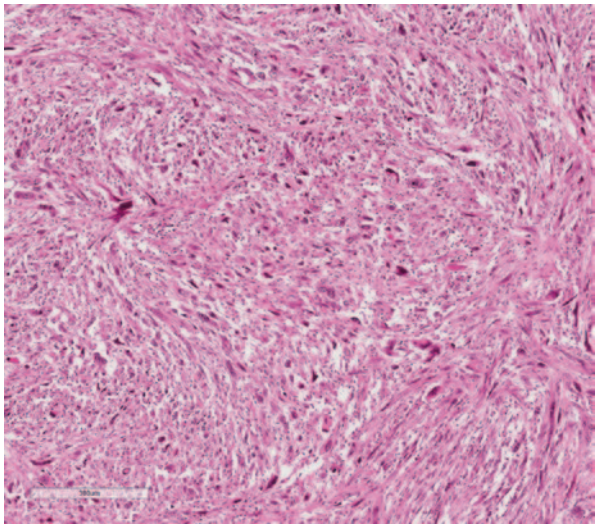

Fig. 4.13 A sarcomatous mesothelioma showing the storiform pattern and the high grade nuclei and occasional multinucleated giant cells a typical features seen in sarcomatous mesothelioma

The lymphohistiocytoid variant was first described by Henderson in 1988. [26] This variant of sarcomatoid DMM is characterized by intense chronic inflammatory cell infiltrate of small lymphocytes, plasma cells, and on occasion, eosinophils intermixed with large polygonal to spindle malignant cells with vesicular nuclei and prominent nucleoli (Figs. 4.15 and 4.16). The malignant cells are positive with (CK)5/6 and Calretinin and negative with lymphoma markers. It is important to recognize this variant due to it similarity to malignant lymphoma [27]. The survival of this neoplasm is similar to those of epithelial DMM.

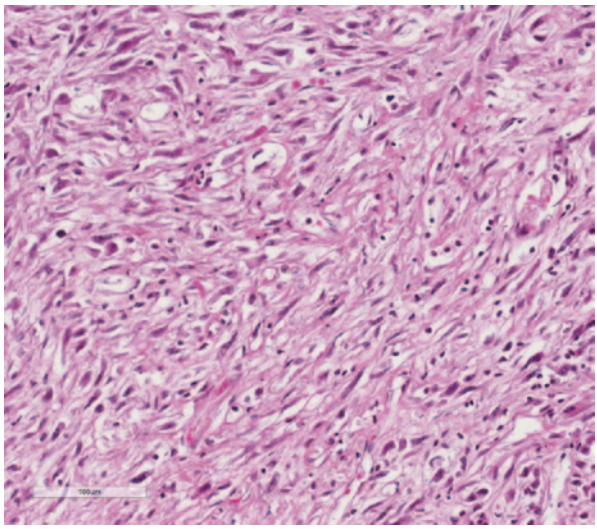

Fig. 4.14 Sarcomatous mesothelioma showing infiltrative relatively bland looking spindle cells with a long and thin cytoplasm

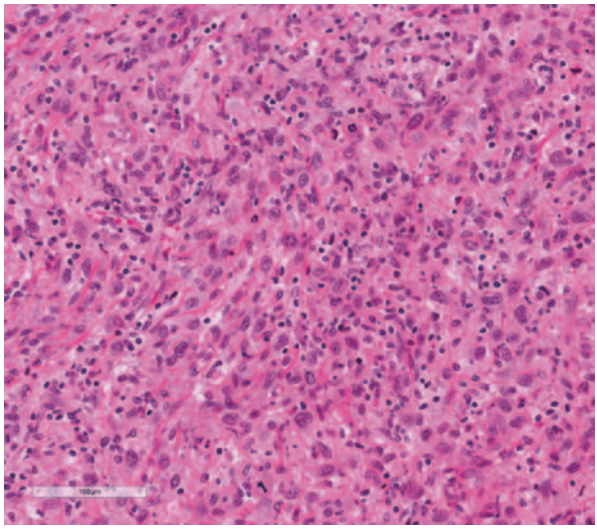

Fig. 4.15 Lymphoepithelioid mesothelioma. The tumor may resemble large cell lymphoma

Desmoplastic DMM is a rare and extremely aggressive variant of sarcomatous DMM [28–30]. This subtype, accounting for approximately 5–10% of DMM, was first described by Kannerstein and Churg in 1980 [31]. Histopathologic evaluation shows a dense paucicellular hyalinized collagen among which spindle or stellate tumor cells, often associated with slit-like spaces (Fig. 4.17), are arranged in a storiform or patternless arrangement. Sarcomatous foci are usually present and epithelioid foci can occasionally be seen. Diagnosis of DMM requires the identification of characteristic paucicellular, densely collagenous tissue in addition to the presence of frankly sarcomatous areas (Fig. 4.18), in conjunction with one or more of the following features that are considered highly specific for DMM:

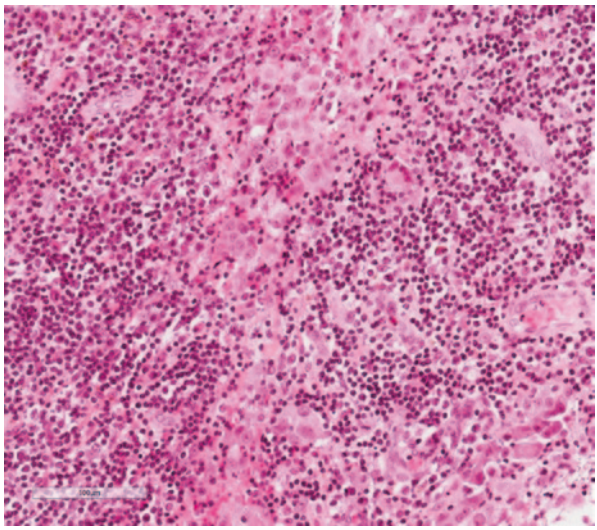

Fig. 4.16 Lymphoepithelioid mesothelioma. High-power view of the histiocytoid tumor cells intermixed with lymphocytes, a feature which may resemble large cell lymphoma

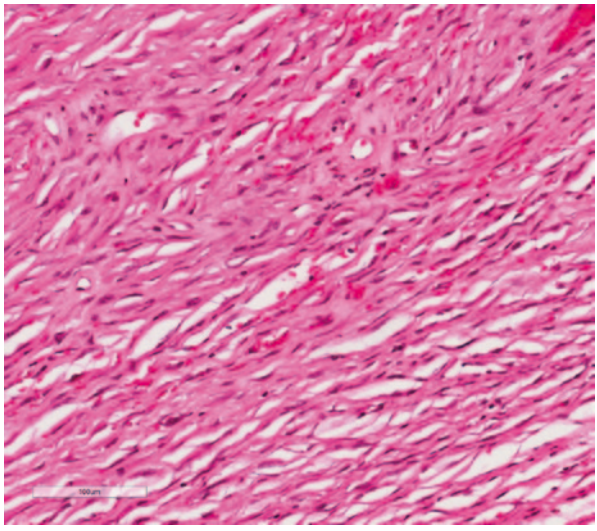

Fig. 4.17 Desmoplastic mesotheliomas. High-power view shows the patterns pattern with a dense paucicellular hyalinized collagen among which spindle or stellate tumor cells

1. Bland infarct-like (no cellular debris or karyorrhexis) sharply demarcated necrosis (Fig. 4.19).
2. Invasion of the chest wall adipose tissue or muscle or the lung (Fig. 4.20).
3. Presence of expansile nodules, (Fig. 4.21).
4. Distant metastasis.

The presence of these features assists in distinguishing desmoplastic DMM from reactive fibrous pleuritis. Infiltration of the underlying chest wall adipose tissue, with isolation of individual adipocytes (Fig. 4.20), is typically confirmed with keratin immunostain. [32, 33].

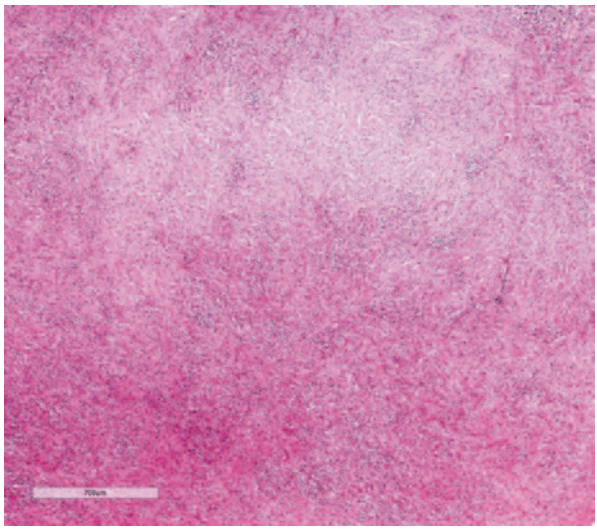

Fig. 4.18 Desmoplastic mesothelioma low-power view showing characteristic paucicellular, densely collagenous tissue upper field in addition to the presence of frankly sarcomatous areas in the lower field

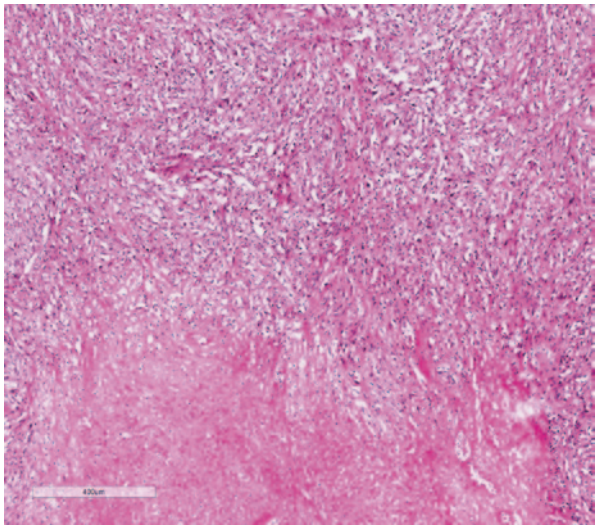

Fig. 4.19 Desmoplastic mesothelioma showing area of bland necrosis in the *lower left* corner

Biphasic Diffuse Malignant Mesothelioma

Approximately 20–35% of DMM are classified as biphasic DMM. This type is frequently identified in pleural DMM patients. Any combination of epithelial or sarcomatous pattern may be present (Fig. 4.22). According to WHO [7], each component must represent at least 10% of the tumor to meet the criteria for the diagnosis of biphasic DMM.

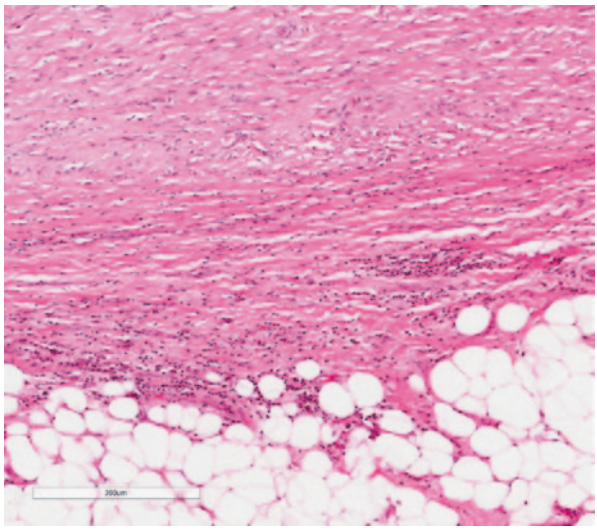

Fig. 4.20 Desmoplastic mesothelioma showing invasion of the chest wall adipose tissue, a feature not seen in fibrosing pleuritis

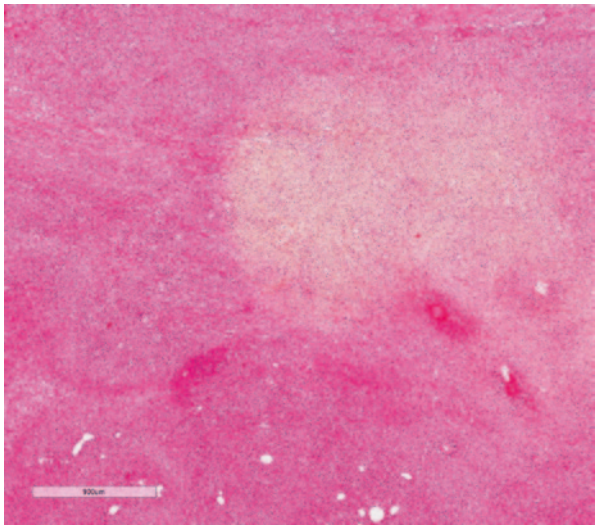

Fig. 4.21 Desmoplastic mesothelioma showing presence of expansile nodule in the *upper right*

Differential Diagnosis of Diffuse Malignant Mesothelioma

The differential diagnosis of DMM includes pleural diffuse or localized neoplastic or nonneoplastic (inflammatory/reactive/infectious) processes. The distinction between these entities almost always requires the correlation of clinical, radiographic, gross, microscopic, and immunohistochemical studies. Some differential diagnoses are common and important to discuss.

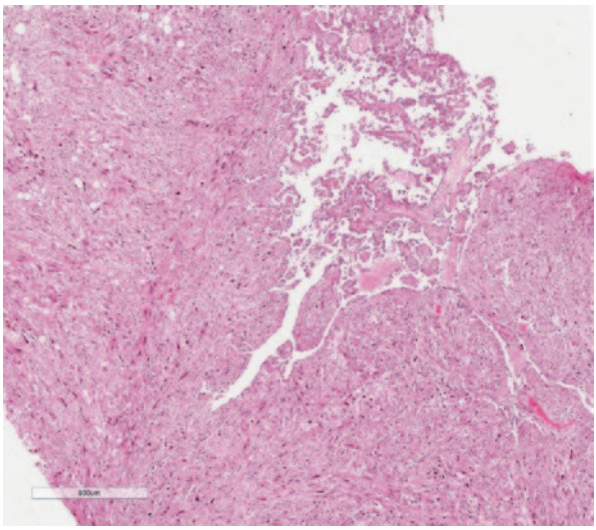

Fig. 4.22 Biphasic malignant mesothelioma showing an area (*upper right*) of epithelial and area (*Left*) of sarcomatous mesothelioma in the same tumor

Epithelial Diffuse Malignant Mesothelioma and Adenocarcinoma

The differential diagnosis between epithelial DMM and lung adenocarcinoma is a well-known diagnostic challenge in surgical pathology, and it is of critical importance for proper medical management. It is also of major importance for legal proceedings that frequently accompany a proposed DMM diagnosis. Both diseases may involve the pleural surfaces and, in most instances, their overlapping histological features preclude a definitive diagnosis based on conventional light microscopic examination. Several ancillary diagnostic techniques, particularly immunohistochemistry, have been employed to assist in rendering accurate diagnoses in these situations [34–36]. The diagnostic utility of conventional histochemical stains alone is limited. Lung adenocarcinomas are not consistently positive for intracytoplasmic mucicarmine and PAS after diastase digestion. Furthermore, false positivity may be observed in a few epithelioid DMM due to technical reasons [14]. The alcian blue-positive, hyalurinidase-sensitive reaction has also been reported in lung adenocarcinomas [15]. Electron microscopy has proven to be useful and is often considered as the gold standard in the diagnosis of epithelial mesothelioma [37, 38]; however, electron microscopic study generally requires great expense and time compared with the other diagnostic techniques, and the morphological ultrastructural features of mesothelial differentiation may not be apparent in the less-differentiated tumors. Furthermore, it may be difficult to obtain. Immunohistochemistry is a generally reliable and typically utilized tool in differentiating DMM from other lesions.

The International Mesothelioma Panel [39] recommends that, at a minimum, two mesothelial and two carcinoma immunomarkers can be used in addition to a pancytokeratin immunostain in rendering a diagnosis. None of these antibodies are 100 % specific and false positives (which often show less than 10 % staining) can occur in

Table 4.1 Key histologic features in differentiation between reactive mesothelial proliferation and mesothelioma

Mesothelial hyperplasia	Mesothelioma
Reactive mesothelial cells confined to pleural surface (superficial)	Nests of mesothelial cells in and surrounded by stroma or papillary pattern with secondary or tertiary branching
Entrapped uniform linear mesothelial nests	Irregular nests of invasive mesothelial cells in underlining stroma
Abundant inflammatory cells	Minimal inflammatory response
Necrosis if present is usually inflammatory	Bland tumor necrosis usually present
No invasion of underlying tissues	Invasion of chest wall fat or muscle, or invasion of lung parenchyma

any neoplasm. Positive thyroid transcription factor 1 (TTF-1) is considered a valuable immunostain for diagnosing lung adenocarcinoma. DMM are immunonegative with TTF-1. The diagnosis is most straightforward when only DMM or carcinoma markers are positive, but in some cases the staining results are conflicting or ambiguous. In those cases, it is often useful to expand the staining panel to include additional markers. If the result continues to be conflicting, electron microscopy may be considered to assist in accurate diagnosis.

Primary adenocarcinomas in other organs—including tumors from the breast, kidney, and ovary, thyroid, pancreas, and kidney—often metastasize to the pleura. Most breast carcinomas will express estrogen receptor, progesterone receptor, and/or mammaglobin. Ovarian serous carcinoma will stain for WT-1, ER, and PR.

Epithelial Diffuse Malignant Mesothelioma and Reactive Mesothelial Cell Hyperplasia

Reactive mesothelial cell hyperplasia may mimic DMM or metastatic carcinoma. Some of the causes of reactive mesothelial cell hyperplasia in the pleural space include infections, pulmonary infarcts, drug reactions, pneumothorax, collagen vascular diseases, lung carcinomas, surgery, trauma, and nonspecific inflammation.

The cytologic features of a reactive mesothelial proliferation that may mimic a neoplasm include high cellularity, the presence of numerous mitotic figures and cytologic atypia, the presence of inflammatory type of necrosis, the formation of papillary groups, and entrapment of reactive mesothelial cells within fibrous tissue of pleural biopsy mimicking invasion [39–42]. Features distinguishing reactive mesothelial hyperplasia from DMM are summarized in Table 4.1.

Stromal or fat invasion is considered an important feature in the diagnosis of DMM (Fig. 4.20). Invasion may involve the visceral and/or parietal pleura and may extend to other adjacent structures; the extent of invasion can be highlighted by pancytokeratin or calretinin immunostain. Invasive mesothelial cells may appear deceptively bland, completely lack a desmoplastic reaction, and involve only a few

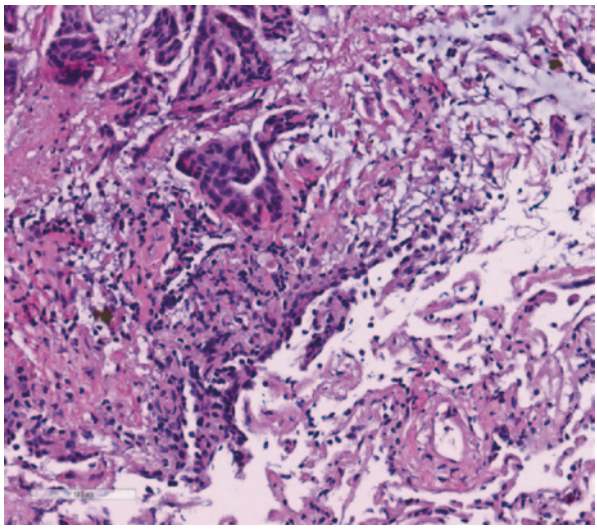

Fig. 4.23 Epithelial mesothelioma. Showing a deep area of the tumor that invades the lung parenchyma, right lower corner

layers of submesothelial collagenous tissue. However, identification of invasion is not absolutely necessary for the diagnosis of DMM. For example, in cases where there is a large solid piece of malignant tumor with histologic features of DMM, invasion may not be absolutely required for diagnosis [39].

Invasion of the fat, muscle, or lung parenchyma continues to be by far the most reliable criterion for separating benign from malignant mesothelial proliferations. Fat is the stroma most frequently encountered and the finding of mesothelial cells growing between fat cells is a strong evidence of the malignant mesothelial cell proliferation unless there is an extraordinarily good reason to believe otherwise. The same comment applies to invasion of muscle or invasion of lung (Fig. 4.23) or distant metastasis. Pankeratin stains are extremely helpful in showing the distribution of mesothelial cells. They are particularly valuable for detecting subtle invasion of fat by a few cells that may not be readily apparent on H&E staining.

Reactive mesothelial proliferations tend to show uniformity of growth with linear arrangements of mesothelial cells, tubules, or small nests (Fig. 4.24), and this uniformity may be confirmed with pancytokeratin immunostain, which will highlight the regular sheets and fascicles of mesothelial cells that respect mesothelial boundaries in contrast to the irregular disorganized growth of DMM.

Mesothelial cell proliferations that are confined to the surface can be benign or malignant; proliferations that reach from the free surface of the thickened pleura to invade the fat or forming papillary architecture with secondary or tertiary branching are almost always malignant (Figs. 4.20 and 4.5). Linear arrangements of mesothelial cells or simple gland-like structures arrayed parallel to the pleural surface and located deep in a thickened pleura are usually benign (Fig. 4.25); they typically represent the original surface of the pleura, which has been buried by organization of an overlying effusion. A more florid example of the same process is layered lines of mesothelial cells aligned parallel to the pleural surface. These represent repeated

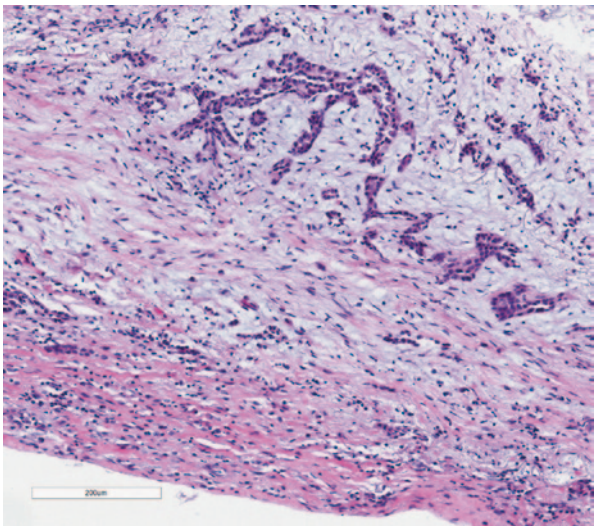

Fig. 4.24 Reactive mesothelial proliferations tend to show a uniformity of growth with entrapment rather than invasive pattern

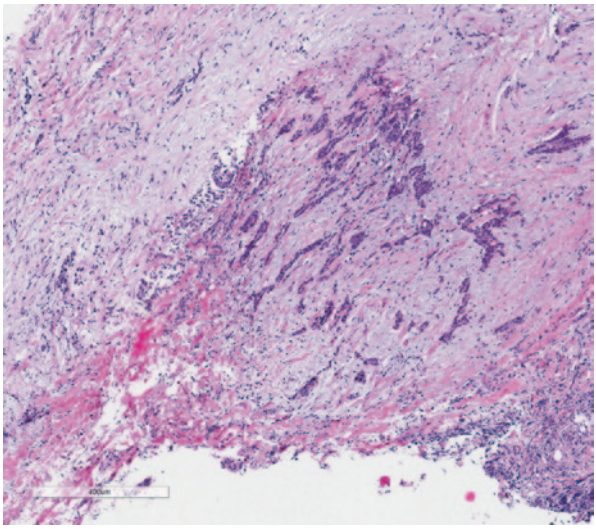

Fig. 4.25 Chronic pleuritis showing lines of mesothelial cells or simple glands arrayed parallel to the pleural surface and located deep in a thickened pleura are usually benign linear layers of entrapment of reactive mesothelial cells

cycles of organization, followed by growth of a new mesothelial layer, followed by further surface organization.

A mesothelial proliferation extending through the whole thickness of a greatly thickened pleura is considered malignant and represents a form of stromal invasion (Fig. 4.26). Another variant is the formation of expansile nodules of stroma, and these can be found within both epithelial and sarcomatous DMM (Fig. 4.21). They may contain relatively few mesothelial cells, but benign processes do not make stromal nodules. Entrapment of mesothelial cells is common and can occur with any type of inflammatory reaction. The inflammation in turn appears to drive

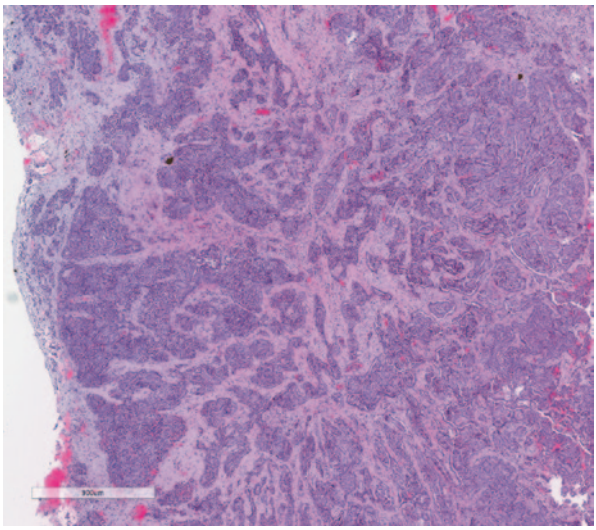

Fig. 4.26 Epithelial mesothelioma showing a complex invasive pattern of solid sheets of tumor cells extending through the whole thickness of a greatly thickened pleura, is really a form of stromal invasion

mesothelial cell proliferations and these can be cytologically quite atypical, a good rule of thumb is to be exceedingly cautious in diagnosing a mesothelioma in the midst of an active inflammatory process especially in small pleural biopsies.

The linear arrays and layered arrays as shown in (Fig. 4.25) are a form of entrapment in which the inflammatory process is usually no longer evident. A helpful hint in circumstances in which there are proliferating mesothelial cells but no inflammation is the distribution of mesothelial cells as mentioned above. Benign processes tend to be sharply circumscribed, with a few glands evident beneath the pleural surface, or with a sharp line beyond which no mesothelial cells are found, whereas mesotheliomas are always invasive with no respect to boundaries.

In summary, separating invasive mesothelial cells of DMM from reactive mesothelial entrapment requires caution. The presence of a significant inflammatory reaction, linear arrays of mesothelial cells, or sharply circumscribed mesothelial proliferations favor entrapped mesothelial cells [39].

Chronic Fibrous Pleuritis Versus Desmoplastic Variant of Sarcomatoid Diffuse Malignant Mesothelioma

Mango et al. [33], studying spindle cell proliferations in the pleura, proposed the key pathologic features important in making the distinction of chronic fibrous pleuritis from desmoplastic DMM, and those features were re-emphasized by others [43]. Identifying one or more of the following features will assist with differentiation: Invasive growth, bland necrosis, frankly sarcomatous areas, and metastatic disease.

Stromal invasion is often more difficult to recognize in spindle cell proliferations of the pleura than in epithelial proliferations. The invasive malignant cells are often

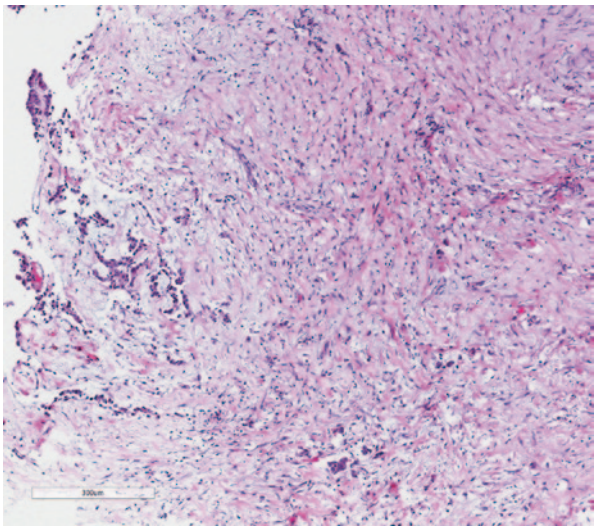

Fig. 4.27 Chronic pleuritis showing zonation phenomenon and entrapped mesothelial cells and the perpendicular capillary arrangements in the fibrous tissue of inflamed pleura

deceptively bland, resembling fibroblasts, and pancytokeratin staining is invaluable in highlighting the presence of cytokeratin-positive malignant cells in regions where they should not normally be present: in the connective tissue, adipose tissue, or skeletal muscle deep to the parietal pleura or invading the visceral pleura and lung tissue as illustrated above. The bland necrosis of paucicellular fibrous tissue by itself may be subtle and one may be reluctant to base a diagnosis of malignancy solely on its presence. Fortunately, most cases that show bland necrosis also show invasive growth. Similarly, the presence of "frankly sarcomatous foci" is a distinctly subjective determination and one would be reluctant to base a diagnosis of malignancy on its presence alone because reactive processes may show marked cytologic atypia, especially at the surface of the process.

Uniformity of growth and the superficial nature of the process with surface atypia and the deep stromal maturation, with perpendicular thin-walled vessels (Figs. 4.27 and 4.28) are typical of chronic fibrous pleuritis in contrast to the disorganized growth pattern and the variable thickness of desmoplastic DMM. A helpful clue in desmoplastic DMM is the presence of expansile nodules of varying sizes with abrupt changes in cellularity between nodules and their surrounding tissue [39].

In summary, the key histopathologic features in separation of chronic fibrous pleuritis from desmoplastic DMM are:

1. Zonation: Chronic fibrous pleuritis exhibits increased cellularity sometime with marked reactive atypia immediately under the pleural effusion and progressively less cellular to paucicellular fibrosis as you move away from the surface (Fig. 4.29). DMM, on the other hand, shows diffuse infiltration of the fibrotic pleura usually by looking bland or sometime by pleomorphic malignant cells with no changes diagnostic of zonation.
2. Invasion: Stromal invasion is the most useful single criterion for separating benign from malignant. In chronic fibrous pleuritis, the fibrosing process is usu-

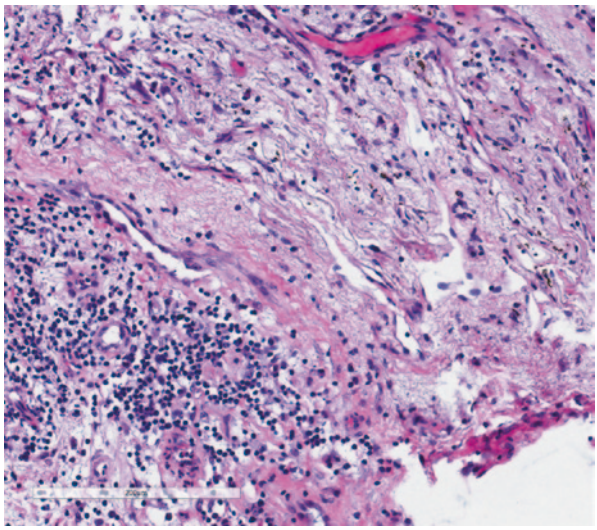

Fig. 4.28 Closer view of the same case showing the perpendicular capillaries arrangements in chronic pleuritis

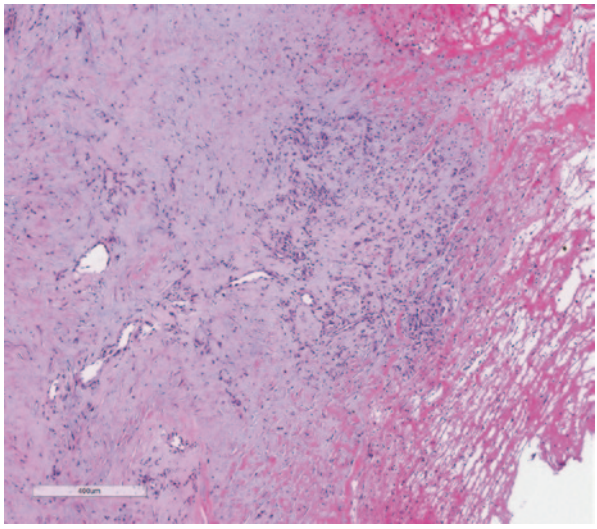

Fig. 4.29 Chronic pleuritis showing the characteristic zonation phenomenon surface fibrin, granulation tissue with capillaries and dense collagen

ally limited to the pleura; whereas in DMM the spindle cells invade the adipose tissue resulting in isolation of individual adipocytes (Fig. 4.20), the spindle cells may also invade muscle and lung parenchyma (Fig. 4.30).

3. Capillaries: The capillaries arising in chronic fibrous pleuritis are typically obvious and usually arranged perpendicular to the surface. With DMM, the capillaries are difficult to see within dense fibrous tissue.
4. Necrosis: Necrosis is usually an indicator of malignancy; however, necrosis may also be seen in benign inflammatory process such as chronic fibrous pleuritis. The necrosis occurring in chronic fibrous pleuritis is rich in inflammatory cells,

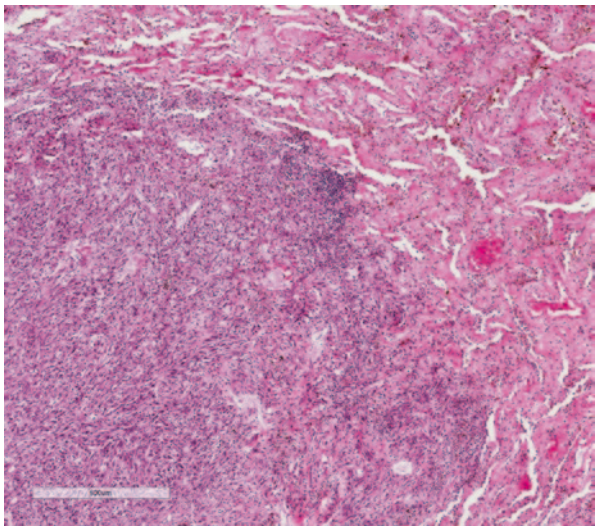

Fig. 4.30 High-power view of the of sarcomatous mesothelioma invading the lung tissue (*right*)

cellular debris, and usually contains few reactive mesothelial cells. The necrosis occurring in DMM is usually sharply demarcated, bland, and infarct-like, with little or no associated cellular reaction and no karyorrhexis or cellular debris (Fig. 4.19), extending into the chest wall adipose tissue or muscle.

5. Nodular stromal expansion: These are expansile nodules of varying sizes with pushing borders and abrupt changes in cellularity between nodules and their surrounding tissue. These expansile nodules if present are diagnostic of DMM and are not a characteristic of chronic fibrous pleuritis.

Sarcomatous Diffuse Malignant Mesothelioma Versus Sarcomatoid Carcinoma or Metastatic Sarcoma

The accurate diagnosis of metastatic sarcoma requires correlation of clinical, radiologic, gross, microscopic, and immunohistochemical information. When possible, the histopathologic and the immunohistochemical studies of the pleural tumor should be compared to those of the primary tumor. Pleural involvement by metastatic sarcoma is typically a late manifestation of the disease, and in most cases a diagnosis of primary sarcoma in the primary location has been established.

Localized Malignant Mesothelioma

Crotty et al. [44] first described a series of six localized malignant mesotheliomas in 1994. Over the years, additional rare cases of localized pleural neoplasms with histopathologic, histochemical, immunohistochemical, and ultrastructural features

identical to those of DMM were identified for which the term "localized malignant mesothelioma" is applicable [45–46].

Localized malignant mesotheliomas are extremely rare; grossly the tumor grows out of the visceral or parietal pleural surface as solitary localized pleural masses in a sessile or pedunculated pattern. Most localized malignant mesotheliomas present clinically with nonspecific symptoms. The median age is 62 years. Most reported cases of localized malignant mesotheliomas have been epithelial and biphasic (mixed) type in addition to a rare case of sarcomatous type [45–47]. The differential diagnosis may be problematic, especially if the tumor is histologically composed of predominantly spindle cells. The sarcomatous variant should be differentiated from solitary fibrous tumor (SFT) of the pleura, because SFT are the most common solitary pleural neoplasms, and some have malignant behavior. SFT, histologically, may mimic sarcomatous DMM. Most immunohistochemical studies of SFT have noted that the tumor cells are consistently negative for cytokeratin and positive for CD34 and vimentin. In contrast, sarcomatous DMM is nearly always immunopositive for cytokeratin and vimentin, but not for CD34. It is clinically and prognostically crucial to recognize and separate localized malignant mesotheliomas from diffuse malignant mesotheliomas. DMM always shows gross and/or microscopic evidence of widespread tumor on the pleural surface, which makes its surgical management extremely difficult or impossible. On the other hand, localized malignant mesothelioma in some cases has apparently been cured by surgical excision. Close to 50% of the patients with follow-up in one series [46] were alive, many with follow-up of several years.

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