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Sarcomatoid Mesothelioma with Bland Histologic Features: A Potential Pitfall in Diagnosis

Allen P. Burke,
University of Maryland, Baltimore, MD UNITED STATES

Naomi Hardy, M.D.,
University of Maryland Medical Center. 22 S. Greene St., Baltimore, MD 21201

Rachel Fanaroff, M.D.,
University of Maryland Medical Center, 22 S. Greene St., Baltimore MD 21201

Teklu Legesse, M.D.
University of Maryland School of Medicine, 22 S. Greene St., Baltimore, MD 21201

Abstract

Sarcomatoid mesotheliomas can be challenging to diagnose on small biopsy specimens, where limited material may preclude definitive assessment of invasion and lesional cells can have relatively bland cytology with no mesothelial marker expression. We report a case of a patient who presented with a pleural effusion and had subsequent pleural biopsy that showed a bland, uniform spindle cell proliferation in a mildly myxoid background. There was little if any collagen; no chest wall, soft tissue, or fat; and mesothelial markers were negative. The cells were positive for pancytokeratin and GATA3 by immunohistochemistry, and in situ hybridization showed a "negative" result for homozygous loss of CDKN2A; however, there was partial (heterozygous) loss of one allele. A diagnosis of atypical spindle cell proliferation was made based on these findings. Several months later, the patient had a repeat pleural biopsy that showed spindled cells with more pleomorphism, areas of invasion into the chest wall, and the same partial loss of CDKN2A, consistent with a sarcomatoid mesothelioma. This case underscores the challenges present on small biopsy specimens, the fact that sarcomatoid mesotheliomas can be relatively bland appearing with focal pleomorphism, and that heterozygous loss of CDKN2A should be considered a positive result indicative of a neoplastic process.

Case report.

A 68-year-old man presented with dyspnea and cough. As a teenager he had worked in a factory with direct contact with asbestos for about a month. A chest X-ray demonstrated a left pleural effusion. A chest CT performed several months later after a syncopal episode demonstrate a large left-sided effusion, which was drained, with negative cytologic results. A limited biopsy was performed which showed a spindle cell proliferation that was positive for pancytokeratin, weakly positive for GATA3 and essentially negative for calretinin by

Corresponding Author: Allen Burke, University of Maryland Author, Baltimore, MD UNITED STATES, allen.burke@gmail.com.

immunohistochemistry (Figures 1–2.) A diagnosis of atypical spindle cell proliferation was made at this time. Fluorescent in situ hybridization (FISH) showed heterozygous loss of p16 cyclin-dependent kinase inhibitor 2A (CDKN2A)($p16^{INK4A}$) at 9p21.3. A definitive VATS biopsy three months later showed a more pleomorphic spindle cell tumor infiltrating the chest wall (Figure 3). Immunostains showed similar results to the initial biopsy, with diffuse pan-cytokeratin positivity; negativity for calretinin, WT-1, mesothelin, HBME, and D2–40; and weak staining for GATA3. BAP-1 was retained immunohistochemically, and MTAP expression was difficult to evaluate, but appeared mostly retained. FISH for CDKN2A again showed heterozygous allelic loss. With a diagnosis of sarcomatoid mesothelioma, the patient was placed with a pleural catheter, and staging CT showed unilateral pleural disease without evidence of lymph node or distant metastasis. The patient received systemic and localized radiation therapy without a tumor response. He died three years later with progressive disease in the thorax and metastasis to the brain.

Classification of pleural mesotheliomas.

Mesotheliomas of the pleura are classified in two ways. “Diffuse” malignant mesothelioma is the most common form and is a poorly circumscribed parietal pleural-based mass that secondarily involves the visceral pleura and encases the lung. “Localized mesothelioma” is not particularly well defined, but is a term used for more nodular tumors that are relatively circumscribed, are based on the visceral pleura, and may project into the lung parenchyma. Localized mesotheliomas range from low-grade, circumscribed, essentially benign tumors, to high-grade neoplasms that invade local structures.(1)

Both diffuse and localized mesotheliomas are classified as either epithelioid or sarcomatoid. Biphasic tumors with both elements are typically treated as sarcomatoid mesotheliomas, which have a worse prognosis and are generally not treated surgically. Because some clinical treatment trials require the proportion of a biphasic mesothelioma that is sarcomatoid for enrollment, it is important for the pathologist to at least attempt quantitation in reporting biphasic tumors.

Histologic features of sarcomatoid malignant mesothelioma of the pleura.

Sarcomatoid mesothelioma is similar histologically to sarcomatoid carcinomas of various sites. Tumor cells are usually pleomorphic and spindled, almost always with some degree of collagen deposition. Necrosis is often present (Figure 4). Sarcomatoid mesothelioma is a disordered proliferation, growing into fat, without linear arrays of reactive spindled mesothelial cells. (2)

When scarring is extensive, the term “desmoplastic” is used. Desmoplastic mesotheliomas typically have various degrees of fibrosis from one area of tumor to another and are typically described by surgeons as “rock hard” and difficult to excise. Desmoplastic mesotheliomas are well known to be difficult to diagnose, because the amount of fibrotic reaction is excessive and tumor cells are infrequent (Figure 5). Therefore, it is often said that invasion of fat is required to diagnose desmoplastic malignant mesothelioma, although the diagnosis

can be favored if there is cytokeratin expression and can be confirmed if there is loss of CDKN2A by FISH.

Immunohistochemical findings in sarcomatoid mesothelioma.

Sarcomatoid mesothelioma is positive for pancytokeratin and usually cytokeratin 7 and CK5,6, in the majority of tumor cells (figure 6). Immunohistochemical stains for epithelioid mesothelial markers are usually negative and are not recommended to be performed. (3) Calretinin, D2–40 and WT-1 are expressed in one-half or less of sarcomatoid malignant mesotheliomas, often only focally. (4) These three markers are all positive in a significant proportion of sarcomatoid carcinomas of the lung, some even a higher proportion than sarcomatoid mesothelioma. Therefore, they are of limited use in differential diagnosis of sarcomatoid mesothelioma. (3–5)

It has been recently suggested that the fact that sarcomatoid mesothelioma usually is negative for mesothelioma markers has been little appreciated and ignored by pathologists and lawyers working for industry. It is sometimes argued that a sarcomatoid mesothelioma that is only cytokeratin positive (and negative for a panel of mesothelial markers, such as the case in this report) should be diagnosed as “sarcomatoid malignant neoplasm.” (6) In consulting for a plaintiff’s attorney, one of the authors encountered a tumor that the defense expert argued was a sarcoma, even though there was strong cytokeratin positivity, the clinical and imaging were typical of mesothelioma, and, after staining several blocks, areas of calretinin and GATA3 positivity were found.

Recently, GATA3 expression, when diffuse, has shown to be fairly sensitive and specific for sarcomatoid mesothelioma, when compared to sarcomatoid carcinoma, which rarely shows diffuse expression. (7) GATA3 expression may also be useful in distinguishing sarcomatoid mesothelioma from reactive spindled mesothelial cells (Figure 7).

Adenocarcinoma markers are negative in sarcomatoid mesothelioma, but most entities in the differential diagnosis are often negative as well. For example, less than one-third of sarcomatoid carcinomas of the lung stain with markers such as TTF-1 and carcinoembryonic antigen. One pitfall to be aware of, is that TTF1 clone SP141 has been shown to be expressed in more than one-third of sarcomatoid mesotheliomas. (8).

Differential diagnosis of sarcomatoid mesothelioma of the pleura.

The two most common problems diagnosing sarcomatoid mesothelioma are distinguishing benign from malignant spindle cell mesothelial proliferations and identifying spindle cell areas in epithelioid mesothelioma as malignant or reactive The distinction between sarcomatoid mesothelioma and sarcomatoid carcinoma is usually not difficult in clinical practice.

Dense fibrosis in chronic pleuritis

Dense fibrosis in chronic pleuritis can be difficult to distinguish from the desmoplastic type of sarcomatoid mesothelioma, especially in small biopsies. Imaging and the operative

note can provide important clues, as chronic fibrinous pleuritis typically involve first the visceral pleural surface, whereas mesotheliomas the parietal pleural surface. Grossly and histologically, fibrous pleuritis is typical of relatively uniform thickness, and the reactive spindled mesothelial cells are generally parallel to the surface (figure 8). In contrast, mesothelioma forms cartwheels and storiform structures, and grow into the chest wall at right angles. The pitfall of the “fake fat” artifact is well known, (2) and acellular scarring in itself (without cytokeratin positive spindle cells) can extend around real fat (Figure 9) Artifactual spaces can be confirmed to be fake fat by immunostaining for S-100 or calretinin but is rarely necessary if other histologic features are considered.

Epithelioid mesothelioma.

The pleomorphic and transitional patterns of epithelioid mesothelioma may be difficult to distinguish from sarcomatoid mesothelioma. Transitional pattern of epithelioid mesothelioma has been described as “sheet-like growth of cohesive, plump, elongated epithelioid cells with well-defined cell borders and a tendency to transition into spindle cells” (9) Another feature of epithelioid mesothelioma that is often difficult to distinguish from sarcomatoid component is the presence reactive fibrous stroma. In contrast to reactive fibroblasts, sarcomatoid neoplastic cells have frequent mitotic figures, atypical mitotic figures, and cytokeratin expression. BAP-1 loss by immunohistochemistry occurs in about one-half of biphasic mesotheliomas, of which a further one half (25% of total) show loss in the sarcomatoid component, which is also helpful in the distinction from reactive fibroblasts. (10,11)

Biphasic mesotheliomas are often treated like sarcomatoid mesotheliomas, depending on the percentage of the sarcomatoid component. Therefore, identifying a malignant spindled area of an epithelioid mesothelioma is important, its presence could prevent a patient from receiving surgical treatment.

Pleomorphic carcinoma of the lung

Pleomorphic carcinoma of the lung is not always distinguishable histologically from sarcomatoid mesothelioma, but based on imaging and location of the tumor, this distinction is easily made in most cases. If there are areas of pleural plaques indicative of asbestos exposure, then desmoplastic mesothelioma is far more likely than pleomorphic carcinoma. As noted above, probably the only immunohistochemical markers that is useful is GATA3, which if diffusely positive points strongly towards mesothelioma. MTAP nuclear loss (see below), and deletion of CDKN2A are not useful in differentiating carcinoma from mesothelioma, as both can occur carcinomas of the lung and other organ sites.

Pleural-based sarcomas.

These are usually straightforward to diagnose and are rarer even than mesothelioma. Malignant solitary fibrous tumor is usually a discrete, well-rounded mass, and projects into the lung parenchyma, and does not spread along pleural surfaces. In distinction to localized sarcomatoid mesothelioma, some areas should have histologic features and immunohistochemical staining patterns that would confirm a diagnosis. These include positivity for stat6, and negativity for pancytokeratin. Synovial sarcoma is the most common

high-grade pleural-based sarcoma, and is readily diagnosed by molecular testing for X;16 translocation. In general, synovial sarcomas do not have a collagenous background, and have a monomorphous, cellular “dark blue” appearance that is quite different from sarcomatoid mesothelioma. Angiosarcomas may occur in the pleura, but are histologic quite distinct from mesothelioma, both in histologic appearance and immunoprofiles. Vascular markers have been shown to be uniformly negative for vascular markers including CD31. (12) An exception to this generalization are rare epithelioid hemangioendotheliomas that may mimic mesothelioma and be associated with asbestos exposure. (12) Undifferentiated sarcomas of the pleura are extremely rare, and if a tumor has the gross growth pattern of mesothelioma and is composed of pleomorphic spindle cells lacking any consistent markers by immunohistochemistry, other than patchy cytokeratin positivity, the tumor should probably be considered a sarcomatoid mesothelioma over a primary pleomorphic sarcoma of the pleura, especially if there is occupational history. Undifferentiated sarcoma of the pleura should be diagnosed only if there is no evidence of epithelial differentiation with negative markers for pancytokeratins.

CDKN2a, MTAP, and BAP1 in malignant mesothelioma (emphasis on sarcomatoid).

Genetic loss of two genes are common in malignant mesothelioma. These are tests for malignancy, do not indicate mesothelial origin, so are useful only in distinguishing reactive mesothelial proliferations from mesothelioma. BAP-1 loss is determined by immunohistochemical staining. CDKN2A loss is evaluated by either FISH or immunohistochemical staining for MTAP. Although both immunostains are very useful in the evaluation of epithelioid mesothelioma, they are less useful in sarcomatoid mesothelioma. BAP1 loss is uncommon in epithelioid mesothelioma, and the interpretation of MTAP loss can be difficult on spindle cell proliferations, for which FISH is more reliable and reproducible.

BAP-1 (BRCA associated protein-1}

BAP-1 (BRCA associated protein-1} mutations are detected by loss of nuclear staining by immunohistochemistry. Granular cytoplasmic staining is seen in about one-fourth of tumors that lose nuclear expression. There is abundant information on BAP-1 loss in mesotheliomas of various sites. A series of a large number of pleural mesotheliomas in showed that 22% of sarcomatoid mesothelioma showed loss of BAP-1, (11) although rates as low as 7% have been reported. (13) It is generally accepted that 60% of mesotheliomas overall show loss of BAP-1, with 1–2% of patients demonstrating germline mutations and a predisposition to breast and ovarian cancers. In a young woman with mesothelioma, germline mutations of BRCA1 should be suspected. BAP-1 loss does not have prognostic implications. (3)

Allelic loss of CDKN2A ($p16^{INK4A}$; 9p21.3)

Allelic loss of CDKN2A ($p16^{INK4A}$; 9p21.3) is generally detected by fluorescent in situ hybridization. There are various thresholds for heterozygous loss, homozygous loss, and wild type. In one study, a cut-off of 20% was used as a mean of all nuclei counted, with both alleles absent in >20% of nuclei for homozygous loss, or one absent in >20% of nuclei for

heterozygous loss. (14) In another study, cutoff values for homo- and heterozygous loss were set at 10% and 47%, respectively, based on studies on reactive mesothelial proliferations in their laboratory. (15) FISH interpretation reports generally state these mean percentages and provide the thresholds used in the analysis. (In the case reported here, the value was 38% single allele loss, and 15% double allele loss).

In the largest series, 81% of sarcomatoid mesotheliomas of the pleura had homozygous loss of CKDN2A. In a study of biphasic tumors, 95% showed homozygous loss (in both morphologies in all cases). (16) Up to 15% of malignant mesotheliomas can show heterozygous loss, the actual value depending on the thresholding and length of the probe used. (15) In general, it is stated that p16 deletion (generally indicating homozygous) occurs in 90–100% of sarcomatoid types, and approximately 70% of epithelioid and biphasic type (3,17).

There is some evidence that prognosis of pleural mesothelioma is worse with homozygous loss at the CDKN2A locus compared to wild type, with heterologous loss imparting an intermediate prognosis. (15,18)

Immunohistochemical staining for MTAP

Immunohistochemical staining for MTAP has a high correlation with FISH results, and is a useful adjunct for diagnosis and, with BAP1, an essential immunostain for pathologists who see reasonable numbers of mesotheliomas. A recent large series showed, for all morphologies, a 78% sensitivity and 96% specificity for CDKN2A homozygous deletion for all mesotheliomas, without separation of sarcomatoid tumors. (19) There is little data on MTAP expression loss in sarcomatoid mesothelioma. It would be expected to be similar to FISH results for CDKN2a deletions (i.e., 80–90%). In Kinoshita et al's series, 24 of 30 sarcomatoid mesotheliomas of the pleura showed nuclear loss. (20) In our experience, evaluation of nuclear staining loss is difficult in sarcomatoid and biphasic mesotheliomas, in contrast to BAP-1. (Figure 10)

Patterns of metastatic spread of sarcomatoid mesothelioma.—Sarcomatoid mesothelioma has propensity for distant metastasis. The most common locations are bone, viscera, brain, and peritoneum, in order of decreasing frequency (21). Sarcomatoid mesothelioma are significant less likely to spread to the peritoneum that the epithelioid variant of mesothelioma. (21) Figure 11 demonstrates a sarcomatoid mesothelioma metastatic to bone.

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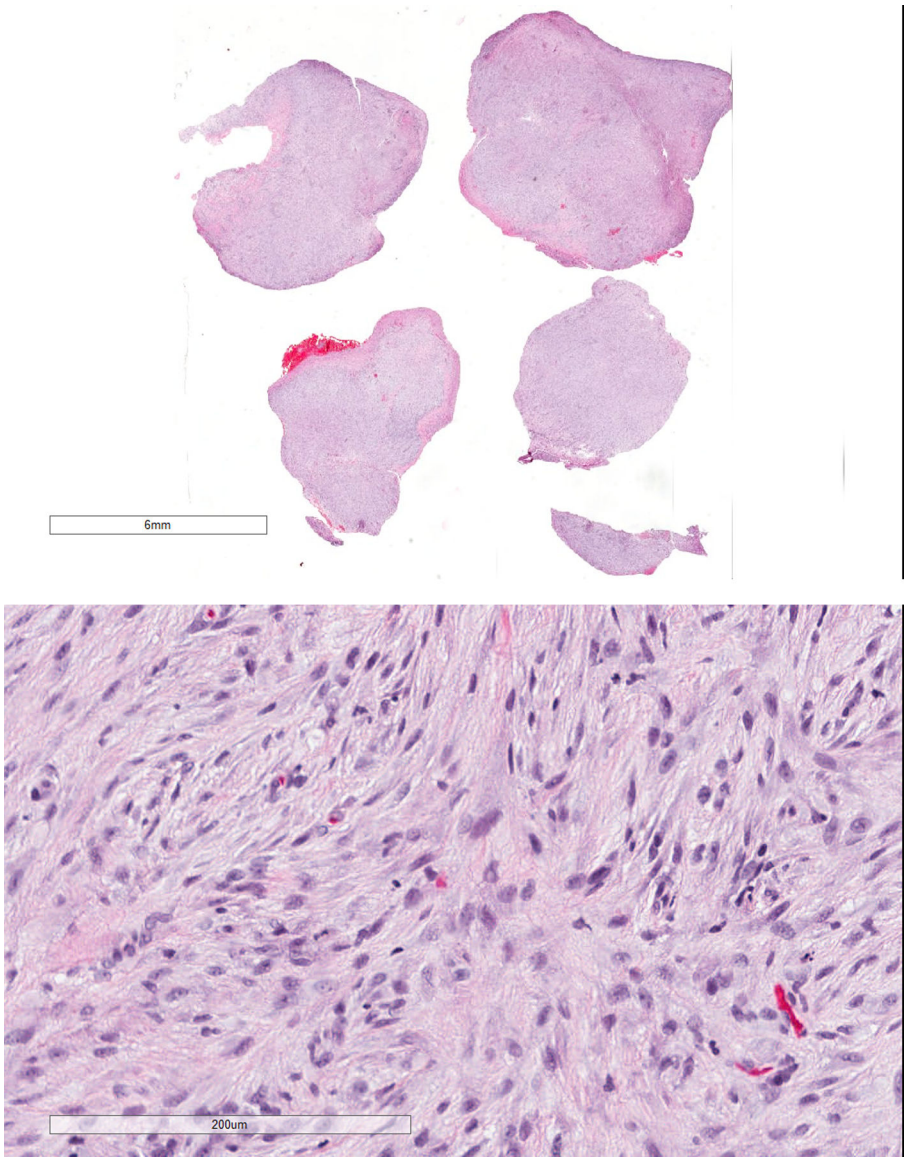

Figure 1.

Pleural biopsy of atypical spindle cell proliferation. Above: Low magnification, the entire sample was embedded, cut into four pieces. No chest wall soft tissue is present. A haphazard proliferation of bland spindle cells is seen.

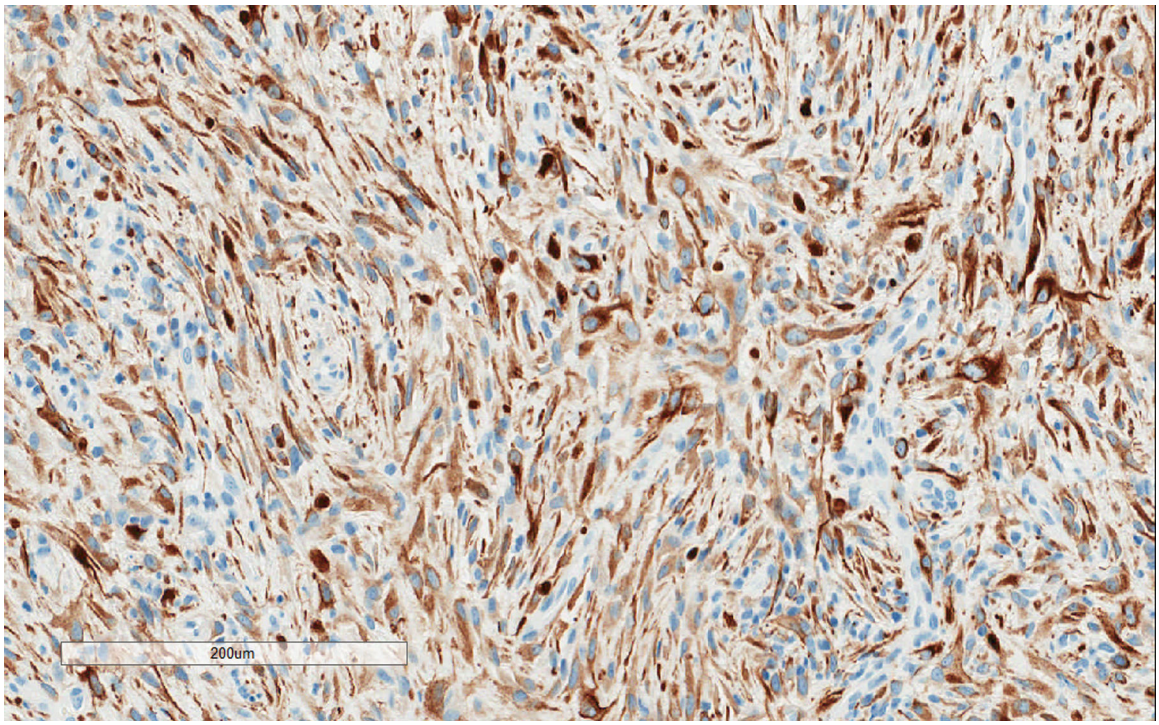

Figure 2.

Pleural biopsy. A pancytokeratin stain shows diffuse positivity. The diffuseness and haphazardness of the proliferation is worrisome for mesothelioma. In the absence of invasion, the diagnosis was “atypical spindle cell proliferation.”

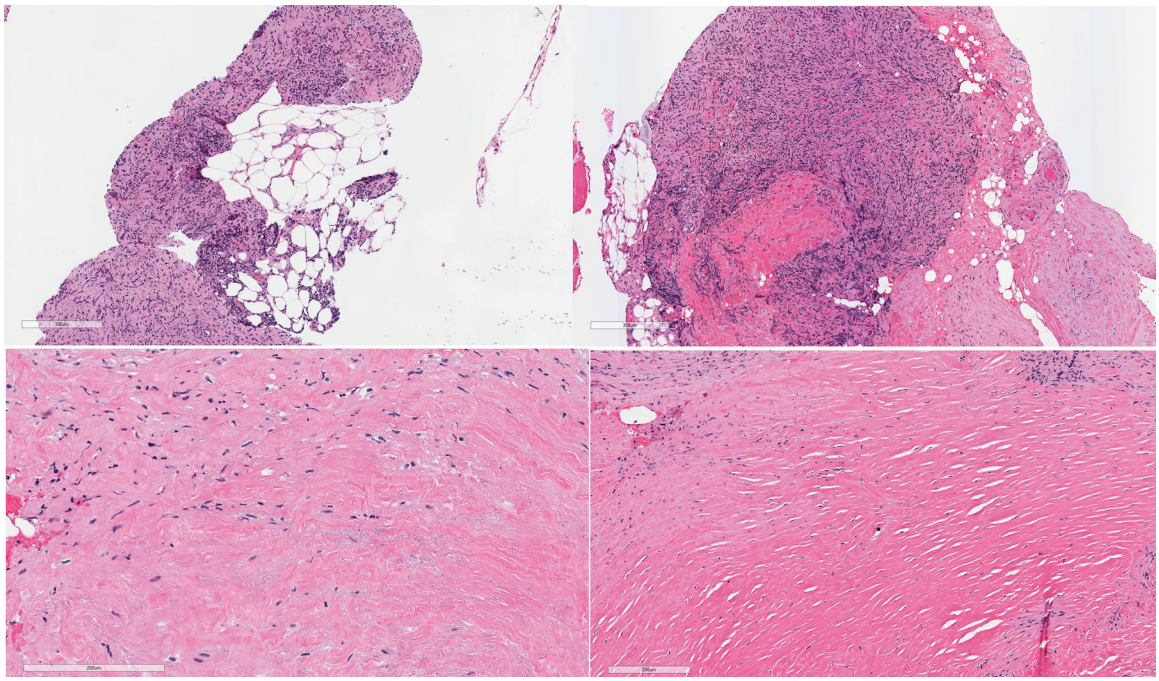

Figure 3.

Open VATS pleural biopsy, 3 months later. Above left: there is invasion into fat by a highly cellular sarcomatoid neoplasm. Above right: There is invasion into fascia. Below left: There were areas of dense fibrosis (desmoplastic mesothelioma). Below right: The basket weave pattern of asbestos plaque was present in some areas, indicative of occupational exposure.

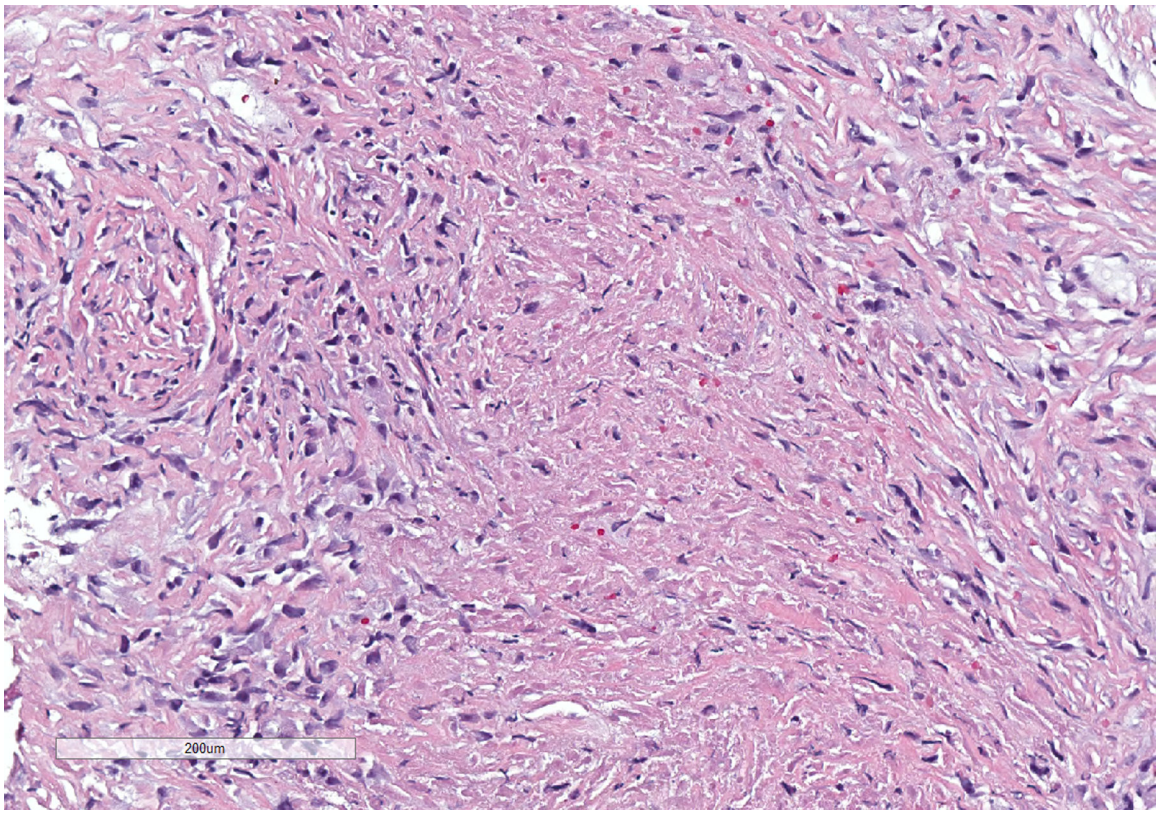

Figure 4.
Sarcomatoid mesothelioma, with necrosis. If there is necrosis, a reactive spindled cell process in fibrosing pleuritis is excluded.

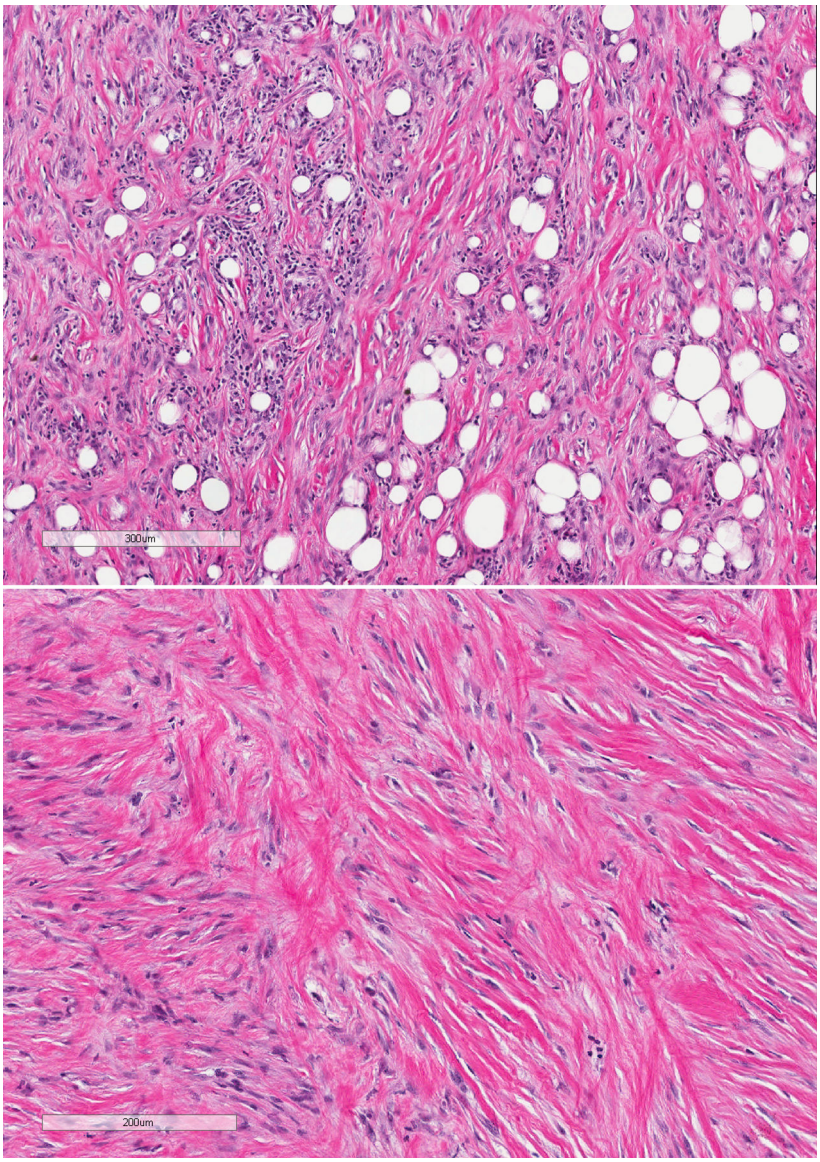

Figure 5.

Desmoplastic mesothelioma. If there is invasion into fat (above), the diagnosis is established. Typical appearance of desmoplastic type of sarcomatoid malignant mesothelioma (below).

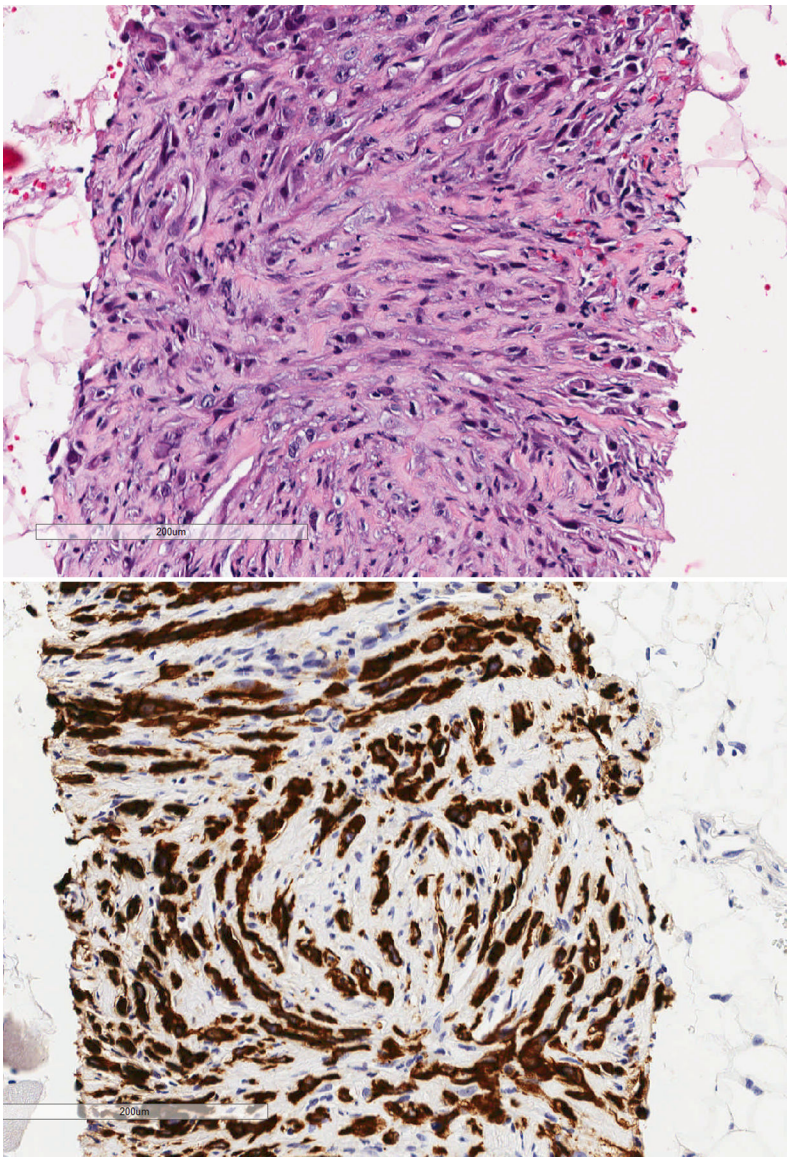

Figure 6.

Sarcomatoid mesothelioma, transthoracic core needle biopsy. Spindle cell neoplasm (above); pancytokeratin immunostain (below). The degree of atypia, together with imaging and history, led to a definitive diagnosis of sarcomatoid mesothelioma. Confirmatory CDKN2A FISH results were obtained subsequent to the final diagnostic report.

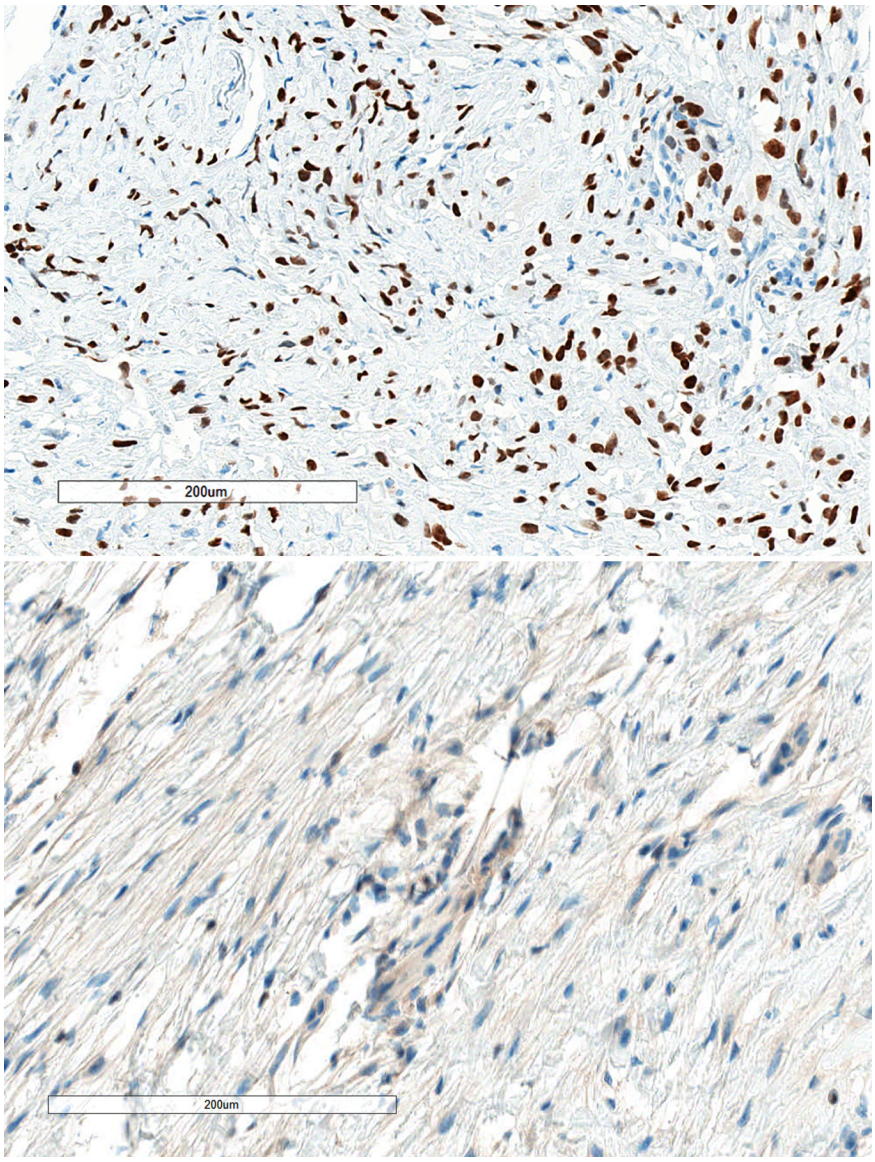

Figure 7.

GATA3 immunohistochemical staining in spindle mesothelial proliferations. There is diffuse positivity above, in a case of sarcomatoid mesothelioma. Staining is negative, below, in a case of fibrous pleuritis. GATA3 immunostaining can also be useful in the distinction with sarcomatoid carcinoma. If FISH and BAP1 staining are available, GATA3 does not add significantly to the sensitivity of diagnosis sarcomatoid mesothelioma from fibrous pleuritis (see table 2) but is very useful in the distinction with sarcomatoid carcinoma.

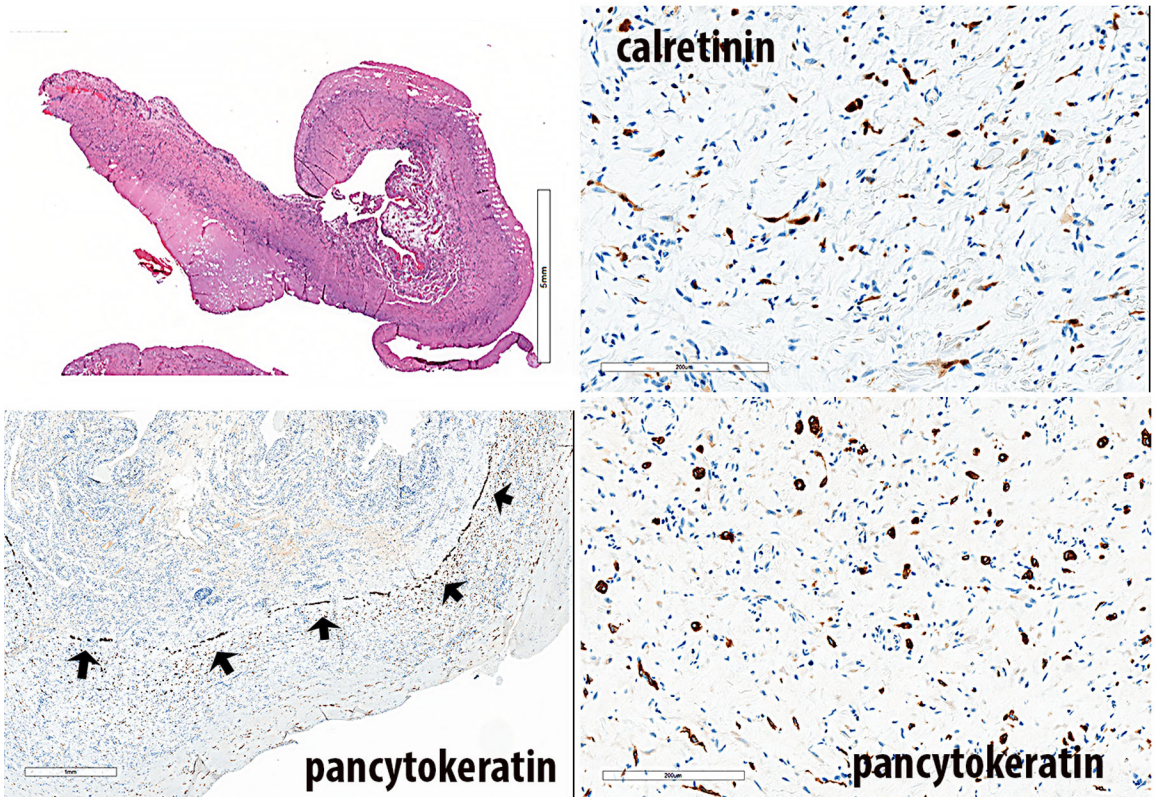

Figure 8.

Fibrous pleuritis. The process is relatively uniform in thickness (upper left). Pancytokeratin shows a linear array of reactive mesothelium, indicative of a benign process (lower left). On the right, there are scattered reactive spindle mesothelial cells that stain with calretinin and pancytokeratin, but there are no whorls or storiform areas (compare with figure 2).

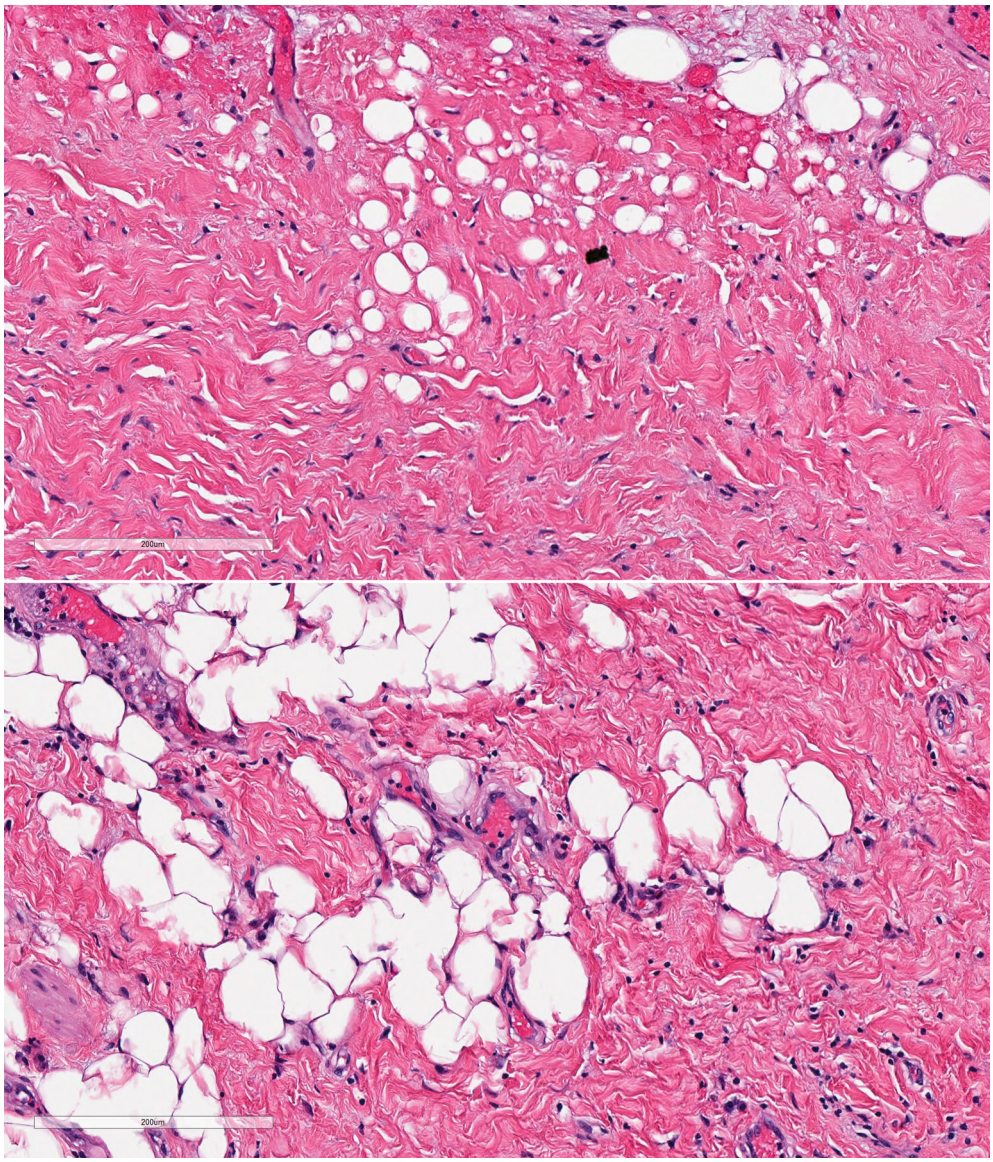

Figure 9.

Fake fat and real fat in fibrous pleuritis. Above, there are artifactual spaces that mimic fat cells; if in doubt, S-100 staining can be done. Below, fibrous pleuritis can extend around layers of fat, usually in an orderly fashion, but there are no spindle cell mesothelial cells in this area (could be confirmed by pancytokeratin staining), excluding sarcomatoid mesothelioma.

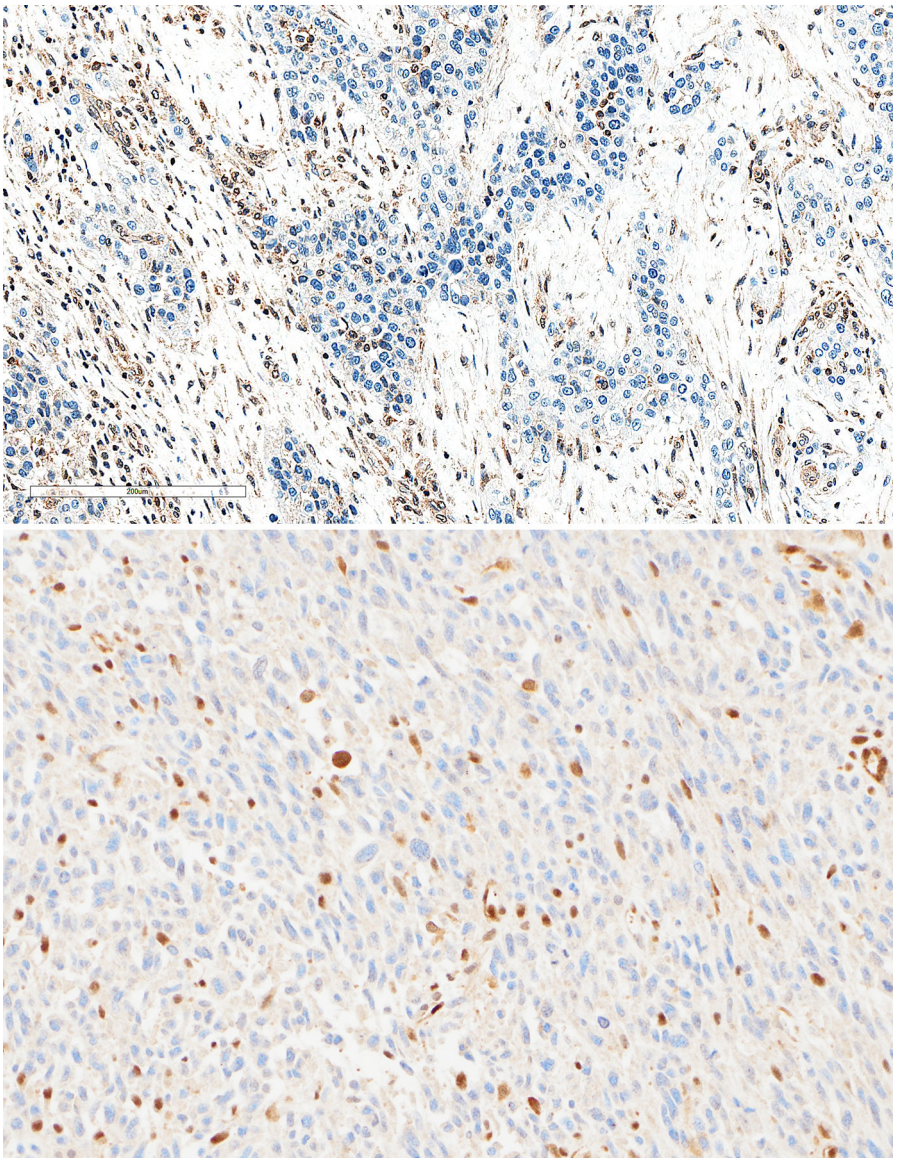

Figure 10.

MTAP immunohistochemical staining. Nuclear loss in epithelioid mesothelioma (above), and nuclear loss in sarcomatoid mesothelioma (below).

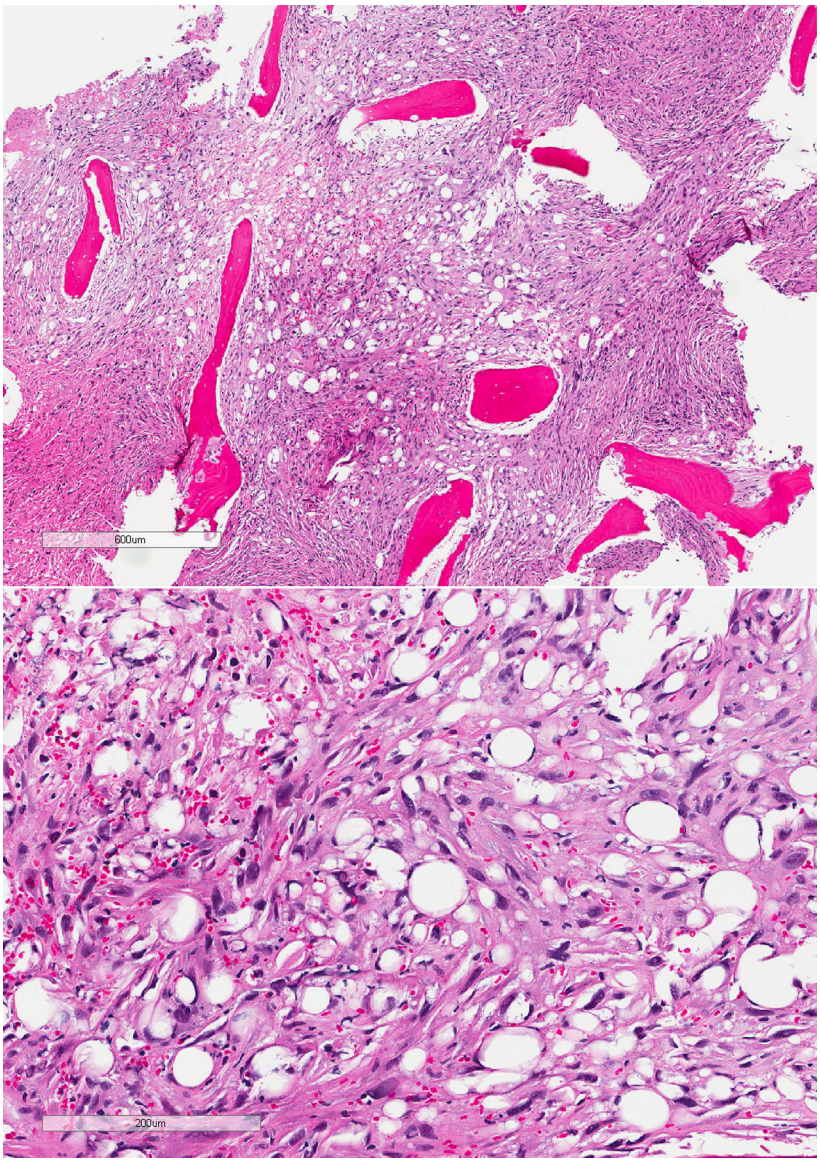

Figure 11.

Sarcomatoid mesothelioma metastatic to bone. Sarcomatoid malignant neoplasm on H&E (above). Pancytokeratin immunohistochemical stain (below). Because the patient's primary tumor was in the files, further testing was not performed.

Table 1.

Sarcomatoid meso v. fibrosing pleuritis

	Sarcomatoid mesothelioma	**Fibrosing pleuritis**
Gross features	• Parietal pleura based • Irregular nodules	• Visceral pleural base • Relatively uniform thickness
Histologic features	• Haphazard growth • Growth into fat or fascia, not parallel to surface	• Uniform fibrosis • Spindled mesothelial cells relatively uniform • Entrapment of “fake fat” common
Immunohistochemical features	Diffuse pancytokeratin positivity Usually negative for mesothelial markers	• Patchy pancytokeratin positivity, with areas without keratin-positive spindled cells common • Often positive for mesothelial markers in spindled areas
Molecular features	CDKN2A loss (homo-or heterozygous) (~90%)	CDKN2A preserved

Table 2.

Differential diagnosis of sarcomatoid mesothelioma from fibrous pleuritis, using BAP-1 and MTAP IHC, and CDKN2A FISH - Adapted from Kinoshita et al, 2018 (20)

Test	Sarcomatoid MPM, % (30 cases)	Reactive spindled mesothelial proliferation in fibrous pleuritis % (17 cases)	Sensitivity	Specificity
MTAP IHC loss	80	0	80	100
BAP1 IHC loss	36.7	0	36.7	100
CDKN2A FISH homozygous deletion	93.3	0	93.3	100
BAP1 IHC loss ***OR*** MTAP IHC loss	90	0	90	100
BAP IHC loss *OR* CCDKN2A homozygous deletion	100	0	100	100

IHC = immunohistochemical

MPM = malignant mesothelioma of the pleura