

The pathology of mesenchymal tumors of the mediastinum

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Abstract: Soft tissue tumors of the mediastinum (MST) are rare, but can pose considerable diagnostic and differential diagnostic problems due to morphological overlap with non-mesenchymal tumors. Many MST occur in quite typical mediastinal compartments, in typical age groups or with a specific gender predilection, or show important clinical clues. Consideration of clinical, epidemiological and anatomic background information is therefore essential to reach a correct diagnosis. With very few exceptions, the morphology and molecular features of MST are identical to their respective counterparts elsewhere in the body, although their prognosis may be different due to, e.g., late diagnosis, anatomic restrictions and the possible extent of surgical interventions. In the era of personalized medicine, many MST require both an extended panel of immunohistochemical antibodies and molecular tests for their diagnosis. In this brief review, we will outline a practical pathohistological approach to MST that tries to incorporate morphological and clinical features that aid in the diagnosis.

Keywords: Mediastinum; sarcoma; pathology; thymus; molecular

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Introduction and diagnostic approach to mediastinal neoplasms

Mesenchymal soft tissue tumors (MST) account for only 2% of all tumours in the mediastinum. With very few exceptions, their morphological and molecular features are identical to their respective counterparts elsewhere in the body, although the prognosis of MST seems to be more guarded due to therapeutic restrictions related to the complicated anatomy. Since the available literature on the epidemiological and molecular features and clinical presentation of MST have been extensively reviewed (1,2), we will focus here on the practical approach to the diagnosis of the most frequent MST and on the interpretation of growth patterns rather than on clinical or molecular issues. It cannot be overemphasized that consideration of clinical, epidemiological and anatomic background

information is essential to reach a correct diagnosis. Many MST (as well as non-mesenchymal lesions that come into the differential diagnosis) occur in quite distinct anatomic locations (see *Table 1*), in typical age groups or with gender predilection, or have clinical clues (such as Myasthenia gravis or Neurofibromatosis type 1). However, in the era of personalized medicine, many of the entities discussed here require both an extended panel of immunohistochemical antibodies and molecular tests for their diagnosis (*Table 2*).

Neoplasms with a lipomatous component

Lipomatous tumors are frequent in the mediastinum and account for up to 10% of mediastinal masses. Especially in young adults with a mass lesion in the anterior mediastinum, thymolipoma is a major consideration. Presence of autoimmune phenomena (usually myasthenia

Table 1 Summary of preferred mediastinal localization and other helpful features of mediastinal soft tissue neoplasms

Entity	Mediastinal compartment*		Age (& gender)	Clues & comments
	Anterior	Posterior		
Mesenchymal soft tissue tumors				
Lipomatous tumors				
Thymolipoma	+		Young adults	10% myasthenia gravis
Myelolipoma		+	Adults	
Liposarcoma	+	+	Adults	<i>Mdm2</i> gene amplifications ¹ , <i>FUS-DDIT3</i> gene fusions ²
Spindle cell tumors				
Solitary fibrous tumor	+		Adults	<i>NAB2-STAT6</i> gene fusions
Inflammatory myofibroblastic tumor	+	+		<i>ALK</i> , <i>ROS</i> , <i>PDGFRB</i> , <i>NTRK3</i> gene fusions
Follicular dendritic cell sarcoma	+	+	Adults	Association with Castleman disease. Rare cases with myasthenia gravis or pemphigus
Rhabdomyosarcoma	+		Children and young adults	In older patients usually a component of other tumors
Desmoid fibromatosis		+	Young adults	<i>CTNNB1</i> gene mutations
Neurofibroma and Schwannoma		+	Adults	
Melanotic schwannian tumors		+		Variable association with Carney syndrome
Malignant peripheral nerve sheath tumor		+	Adults	Association with Neurofibromatosis type 1
Synovial sarcoma	+	+	Young adults	<i>SYT-SSX</i> gene fusions
Epithelioid tumors				
Epithelioid hemangioendothelioma	+		Adults, M>F	<i>WWTR1-CAMTA1</i> gene fusion
(Epithelioid) Angiosarcoma	+		Adults, M>F	Occasional occurrence as “somatic type malignancy” in a mediastinal germ cell tumor
Small blue round cell tumors				
Ewing sarcoma	+	+	Children and young adults	<i>EWSR1</i> gene translocations; cases in post. mediastinum sometimes with nerve compression syndrome
(Ganglio)neuroblastoma	+	+	Children	<i>MYCN</i> gene amplification in two thirds of cases. Cases in anterior mediastinum were adult patients
Non-mesenchymal mediastinal tumors				
Thymoma and thymic carcinoma	+		Elderly, M = F	Myasthenia gravis (30–50% of thymomas)
T lymphoblastic lymphoma/leukemia	+		Young adults (M>F)	
Primary mediastinal large B cell lymphoma and Hodgkin disease	+		Young adults, F>M (2:1)	Dense fibrosclerosis may sometimes obscure underlying disease
Metastatic malignant melanoma	+	+	Adults	
Malignant mesothelioma	+	+	Elderly males	Pleural involvement, asbestos exposure, homozygous <i>p16</i> deletion
Small cell carcinoma of the thymus	+		Adults	Paraneoplastic symptoms (e.g., Cushing, Lambert-Eaton syndrome)

*Definition of mediastinal compartments according to Carter *et al.* (3). Anterior (“prevascular”) mediastinum: sternum to anterior pericardium and parietal mediastinal pleura (contains thymus, fat, lymph nodes, left brachiocephalic vein). Visceral mediastinum: posterior boundaries of anterior mediastinum to a vertical line connecting each thoracic vertebral body at 1 cm posterior to its anterior margin (contains trachea, large vessels, heart, lymph nodes, etc.). Posterior (“paravertebral”) mediastinum: posterior boundaries of visceral compartment to a vertical line against the posterior margin of the chest wall at the lateral margin of the transverse processes of the thoracic spine (contains paravertebral soft tissues). ¹, well differentiated and dedifferentiated liposarcomas; ², myxoid and round cell liposarcomas.

Table 2 List of useful antibodies and molecular tests that help in the diagnosis of soft tissue sarcomas

Immunohistochemistry
Keratin
EMA
S100
Actin
Desmin
Caldesmon
Myogenin
WT1, Calretinin
Melan A, HMB45, SOX10
INI1
CD31
CD34
ERG
DOG1
CD99
Beta-Catenin
STAT6
MUC4
TLE1
TFE3
HHV8, EBV
Estrogen-/Progesterone receptor
Mdm2, CDK4
P53, PTEN

Table 2 (continued)

gravis, but also autoimmune thyroiditis and others) is rare, but an important clue to the diagnosis. The diagnosis requires demonstration of thymic tissue in an adipose mass lesion, but the relative proportion of both components can be quite variable and absence of thymic tissue in a biopsy does not rule out this possibility. In elderly patients, thymic involution may be a differential diagnosis, but this condition does not form a mediastinal mass. Thymolipoma can go undetected for a long time and may be quite large (up to 30 cm), raising concerns of malignancy. Careful macroscopic grossing and histological sampling of all areas

Table 2 (continued)

Molecular tests
<i>c-KIT</i> (mutations)
<i>PDGFRA</i> (mutations)
<i>mdm2</i> (amplification)
<i>EWS1</i> (translocation)
<i>CIC-DUX</i> (translocation)
<i>SYT-SSX</i> (translocation)
<i>FUS</i> (translocation)
<i>DDIT3</i> (CHOP) (translocation)
<i>cMYC</i> (amplification)
<i>PDGFB</i> (translocation)
<i>FOXA1, PAX3/7</i> (translocation)
<i>JAZF1</i> (translocation)
<i>USP6</i> (translocation)
<i>NR4A3</i> (translocation)
<i>WWTR1</i> (translocation)
<i>CTNN1B</i> (mutation)
<i>BRAF/RAS</i> (mutation, translocation)
<i>TFE3</i> (translocation)
<i>ALK1</i> (translocation)
<i>ROS1</i> (translocation)
<i>NTRK3</i> (translocation)

Please note that most molecular tests can be performed using different techniques (e.g., PCR, FISH, CISH, amplicon- or hybrid capture-based “next generation” sequencing, etc.).

that differ in color or consistency is essential in such cases. In tumors of the posterior mediastinum, myelolipoma with a hematopoietic component may be a consideration (4).

Although the salient morphological features of well-differentiated liposarcoma (variable size of adipocytes, enlarged hyperchromatic nuclei, fibrous septa with a subtle inflammatory component) are absent in (thymo)lipoma, regressive changes can sometimes mimic these features. Moreover, spindle cell lipoma, a distinctive CD34+ lipoma variant with highly variable lipomatous differentiation, characterized by „ropey collagen“ (*Figure 1A*) and slender

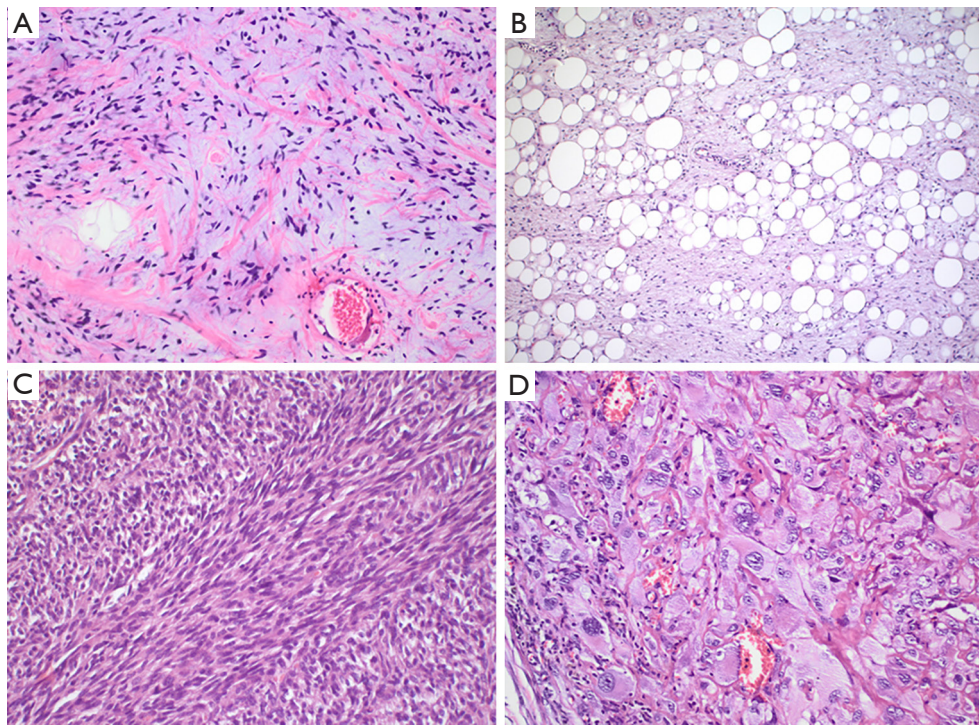


Figure 1 Lipomatous tumors. (A) Spindle cell lipoma with typical slender spindle cell morphology and “ropey collagen”. (B) Well-differentiated liposarcoma with partial loss of adipocytic differentiation. Slight nuclear polymorphism and single multinucleated tumor cells are evident even at this low magnification. (C) Dedifferentiated liposarcoma with striking „fibrosarcoma-like“ fascicular growth. (D) Dedifferentiated liposarcoma with pleomorphism and Epithelioid morphology resembling e.g. melanoma. Both examples shown in c+d had high level gene amplifications of *mdm2* on FISH analysis. (HE staining of paraffin embedded sections; A, C, D: original magnification $\times 200$, B: original magnification $\times 100$).

nuclei embedded in a sometimes myxoid stroma, can be quite cellular and may raise concern for malignancy (5,6). In these cases, immunohistochemistry for *mdm2* and CDK4 or FISH probes for the detection of *mdm2* gene high level amplifications on Chr. 12q13-21 are required. Well differentiated liposarcoma can show a sclerosing or inflammatory pattern with focal loss of lipocytic differentiation (Figure 1B), but cytological atypia is mild and mitotic counts are low. These variants must be distinguished from dedifferentiated liposarcoma (see below), which is characterized by a poorly differentiated sarcomatous morphology (Figure 1C,D).

Ancillary studies are also usually required for the diagnosis of the two other liposarcoma types that may occur in the mediastinum, myxoid- and pleomorphic liposarcoma. Myxoid liposarcoma is characterized by a prominent myxoid stroma with relatively few spindle cells that may form a pseudo-alveolar pattern, and delicate capillaries with very characteristic branching. Importantly, the round cell variant

of myxoid liposarcoma, a progression pattern of these tumors, has not been reported in the mediastinum. There is no specific immune phenotype and FISH analysis for the demonstration of *DDIT3* rearrangements is required. Finally, pleomorphic liposarcoma, a high grade sarcoma with complex genetics and without *mdm2* or *DDIT3* abnormalities that usually occurs in older adults, has also been rarely described in the mediastinum (7). Pleomorphic liposarcoma is characterized by giant pleomorphic fat cells and may otherwise show overlapping features with dedifferentiated liposarcoma.

Neoplasms with spindle cell morphology

A majority of biopsies and resections specimens taken from the mediastinum will have a spindle cell morphology (Figure 2). The diagnosis should start with a review of the patient's age and clinical presentation, as well as consideration of the anatomic location of the tumor.

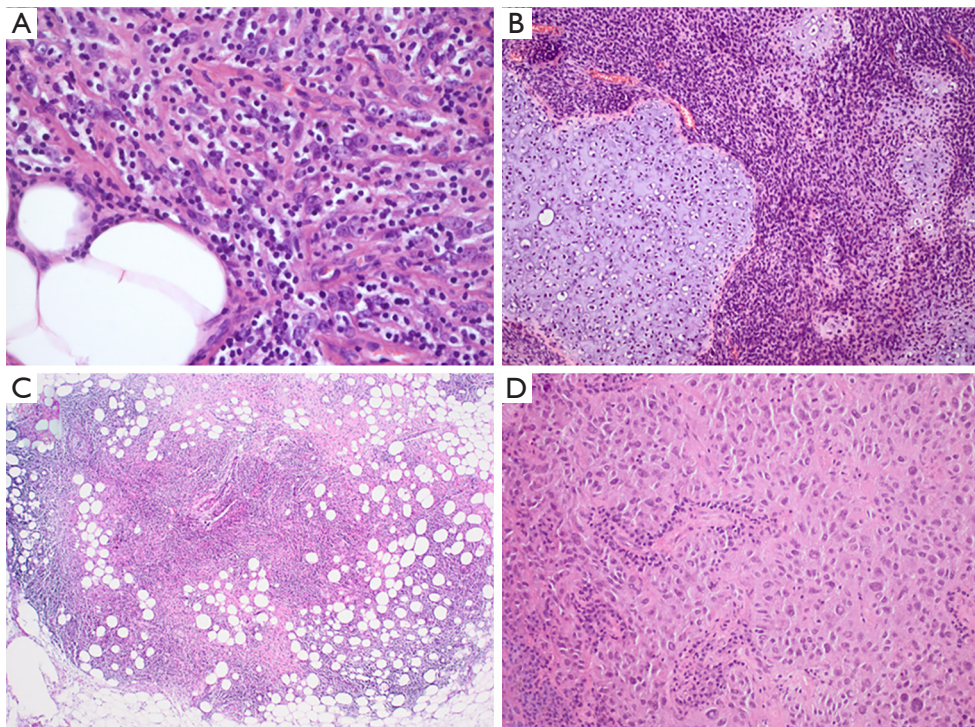


Figure 2 Selected examples of malignant tumours with a spindle cell morphology. (A) Follicular dendritic cell tumor/sarcoma of the mediastinum. Characteristic spindle cells with low grade morphology and a prominent admixed lymphocytic component. (B) Malignant peripheral nerve sheath tumor with heterologous chondroid differentiation in the posterior mediastinum of an elderly male patient. (C) Low power view of Hodgkin lymphoma with an unusual infiltration of perithymic fat, thus mimicking a lipomatous or histiocytic lesion. The case had high numbers of eosinophils, but only few mummified Hodgkin cells. (D) Metastatic malignant melanoma with a striking resemblance to type B3 thymoma and formation of perivascular spaces. Note that the nuclear polymorphism is somewhat higher than would normally be expected in a B3 thymoma. (HE staining of paraffin embedded sections; A, D: original magnification $\times 200$; B, C: original magnification $\times 100$).

In a resection specimen, it is of crucial importance to carefully analyze adjacent tissues (blood vessels, bone, mediastinal fat and thymus etc.), since they can also offer valuable clues (for example, atypical fat cells may hint to a dedifferentiated liposarcoma). Next, the morphology and degree of cytologic atypia in the neoplastic cells and any inflammatory bystander cells should be determined. Careful characterization of the inflammatory infiltrate is important and may require immunohistochemistry: demonstration, e.g., of immature T-cells (preferably through TdT staining) in a spindle cell neoplasm more or less narrows the differential diagnosis down to thymoma and follicular dendritic cell (FDC) tumor/sarcoma (Figure 2A). Presence of a mixed infiltrate with eosinophils may hint to an inflammatory myofibroblastic tumor (IMFT). Of note, a sparse inflammatory infiltrate is also a consistent

feature of well-differentiated liposarcoma (e.g., sclerotic or inflammatory variant), which is among the most frequent soft tissue sarcomas in virtually any organ and which should always be in the differential diagnosis. Although not the subject of this review, it should be noted that hematological neoplasms of the mediastinum can be either very sclerotic (primary mediastinal large B cell lymphoma) and/or may contain eosinophils (Hodgkin lymphoma, Langerhans cell histiocytosis), and should be considered in the differential diagnosis (Figure 2C).

In a highly cellular tumor with compact spindle cells and mild to moderate atypia in the anterior mediastinum, the differential diagnosis should include type A or AB thymoma and synovial sarcoma. Synovial sarcoma tends to occur in young adults (median 35 years), while especially type A thymoma is usually a tumor of the elderly. Based

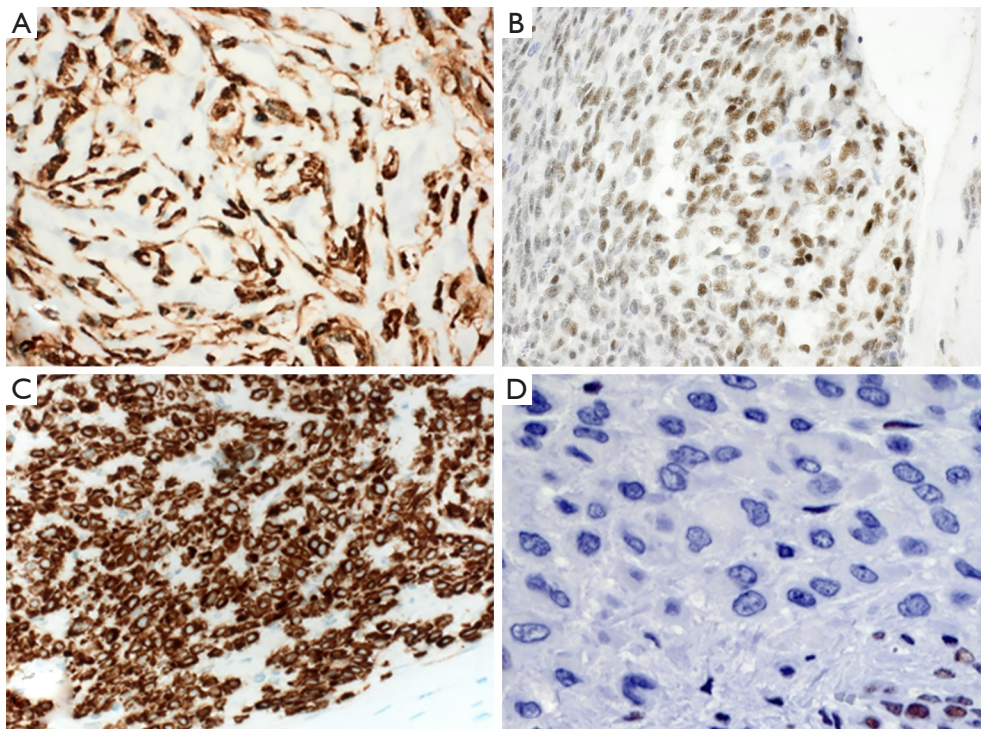


Figure 3 Examples of more recently available immunohistochemical antibodies that aid in the diagnosis of MST. (A) STAT6 (nuclear staining is a strong argument in favour of solitary fibrous tumor). (B) TLE1 (nuclear staining favours synovial sarcoma). (C) MUC4 (positive staining points to sclerosing epithelioid fibrosarcoma or low grade fibromyxoid sarcoma). (D) INI1 (loss of expression points to epithelioid sarcoma, but is also observed in many tumors with epithelioid morphology, including some MPNST). (Immunoperoxidase on paraffin embedded sections; A-C: original magnification, $\times 200$; D: original magnification, $\times 400$).

on morphology alone, the distinction can be challenging if not impossible and requires immunohistochemistry and/or molecular tests (Figure 3). Both entities show expression of cytokeratins and even p63 (8), although strong diffuse expression of cytokeratins rather indicates a thymoma. Many thymomas with a spindle cell morphology (type A and AB) show focal ectopic expression of CD20, a feature not seen in synovial sarcoma. Many synovial sarcomas express CD56 and CD99 (9), and >90% express TLE1 (Figure 3B). Demonstration of a t(X;18) (*SYT-SSX*) rearrangement e.g. by FISH is currently the gold standard to render a definite diagnosis. Two other low grade spindle cell tumors with overlapping morphological features are solitary fibrous tumor (SFT) and IMFT (which can show sclerotic areas depleted of the characteristic inflammatory infiltrate). “Hemangiopericytoma-like” or “stag-horn” blood vessels are usually much more prominent in SFT, but can be found in both. A combination of CD34 and strong nuclear STAT6 expression is the hallmark of SFT (Figure 3A), although CD34 expression can be focal or absent. Smooth-muscle

actin is usually not expressed in SFT and positive staining should trigger exclusion of IMFT especially in a young patient or a child. Although immunohistochemistry for ALK1 is a good screening marker for IMFT with ALK rearrangements, negative staining does not rule out IMFT, since only about 50% of cases are characterized by ALK rearrangements. Most of the ALK-negative tumors harbour chromosomal translocations that lead to “actionable” *ROS1-WYHAE*, *PDGFRB-NAB2*, and *NTRK3-ETV6* gene fusions (10,11). Detection of these clinically relevant genetic alterations will usually require ancillary molecular studies such as FISH or NGS.

FDC sarcoma is an uncommon malignancy that may occur in the mediastinum or in mediastinal lymph nodes of adults and may be associated with paraneoplastic immune phenomena such as myasthenia gravis or pemphigus. Its morphology is variable, but quite characteristic with spindle cells in a fascicular or storiform growth pattern that may or may not show nuclear pleomorphism. A very characteristic and important finding is a mild to moderate lymphocytic

component that often clusters around blood vessels (*Figure 2A*). These lymphocytes may show an immature phenotype with expression of TdT. A subset of cases is associated with hyaline-vascular Castleman disease which may coexist in the same tumor. The spindle cells are positive for FDC markers such as CD21, CD23, and CD35, while CD68 and S100 are variable and usually weakly expressed. D2-40 is positive in many cases. In contrast to thymoma, keratin is negative in FDC sarcoma.

The main differential diagnoses of spindle cell tumors with high grade morphology include malignant SFT, monophasic synovial sarcoma, dedifferentiated liposarcoma, (thymic) carcinoma, mesothelioma, melanoma and malignant melanotic schwannian tumors, and (preferentially in tumors of the posterior mediastinum) malignant peripheral nerve sheath tumor (MPNST). Especially in younger male patients, a sarcoma (usually rhabdomyosarcoma or angiosarcoma) arising as a so-called “somatic type malignancy” in a germ cell tumor may be a consideration. These secondary tumors have no distinctive histological features, but may contain small SALL4+ and/or OCT3/4+ remnants of the germ cell tumor. Since men with Klinefelter syndrome are at increased risk to develop mediastinal germ cell tumors, this is an important clinical information that should be asked for by the pathologist.

As discussed above, immunohistochemical demonstration of nuclear STAT6 expression is currently considered the most specific marker for SFT (*Figure 3A*), and nuclear TLE1 expression is a good screening marker for synovial sarcoma (*Figure 3B*), but should be confirmed by molecular tests (such as SYT FISH). Dedifferentiated liposarcoma is probably the most frequent malignant mesenchymal spindle cell tumor of the mediastinum and should always be in the differential diagnosis. Initial misdiagnoses are frequent due to its highly protean morphology, which can resemble fibromatosis and fibrosarcoma (*Figure 1C*), MPNST, tumors with epithelioid morphology such as melanoma, and undifferentiated pleomorphic sarcoma (type “MFH”) (*Figure 1D*). The diagnosis is further complicated by the fact that some cases can contain areas of heterologous differentiation such as rhabdomyosarcoma. Since a number of other tumors including MPNST, inflammatory myofibroblastic tumors (IMFTs), and germ cell tumors can show immunohistochemical overexpression of *mdm2*, only demonstration of *mdm2* gene amplification by, e.g., by FISH can be considered specific for the diagnosis of dedifferentiated liposarcoma at this time. Malignant melanoma is another malignancy notorious

for its highly variable histomorphology and lavish use of respective antibodies (such as S100, MelanA, and Sox10) is recommended. (Malignant) melanotic schwannoma is a distinctive neoplasm that usually arises in the spinal nerve roots and is thus located in the posterior mediastinum. Some cases (preferentially in young adults) are associated with Carney syndrome (myxomas of the heart and skin, epithelioid blue nevi, Cushing disease and acromegaly). The concept of melanotic schwannoma nicely illustrates the embryologic relationship between Schwann cells and melanocytes and is intermediate between a Schwann cell neoplasm and a melanoma with sometimes heavy pigmentation and expression of melanotic markers. Nuclear atypia, increased mitotic activity and absence of psammomatous calcifications are the main criteria used to differentiate benign melanotic schwannomas from malignant cases.

The diagnosis of malignant mesothelioma, especially of the sarcomatoid and desmoplastic variants, can be a major challenge and may sometimes be one of exclusion, since the overlap with other entities is huge and typical mesothelial markers are unreliable. Focal keratin expression, positivity for BAP1, detection of a homozygous *p16* deletion e.g. by FISH, and close correlation with the clinical presentation (pleural thickening on imaging studies, history of asbestos exposition) are important clues.

Sarcomatoid (thymic) carcinoma (a poorly differentiated (thymic) carcinoma with spindle cell morphology) and carcinosarcoma (a tumor with both a malignant epithelial and a spindle cell/sarcomatous component) are also mainly defined by their variable expression of keratins and EMA, and of markers that indicate a thymic origin such as CD5 and CD117. The carcinomatous component may consist of squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma. The sarcomatous component is usually spindle cell but may show heterologous differentiation (e.g., rhabdomyoblasts or osteoid). Many cases of sarcomatoid carcinomas contained a component of type A thymoma (12,13), which may be an important clue. Metaplastic thymoma is another biphasic tumor that lacks significant nuclear atypia in the spindle cell component and does not express CD5 and CD117.

MPNST typically arise in the posterior mediastinum of adult patients and have often contact to spinal nerve roots. About half of the cases are associated with neurofibromatosis type 1 (NF1). However, especially in small biopsies, a definitive diagnosis may not be possible due to lack of specific markers. The diagnosis is further complicated by

the fact that approximately 15% of cases show heterologous (e.g., epithelial/glandular, chondroid, rhabdomyoid, vascular, etc.) differentiation (*Figure 2B*). The typical growth pattern corresponds to what has formerly been called fibrosarcoma: slender spindle cells in a fascicular arrangement, often with alternation between cellular and less cellular areas, creating a vaguely nodular or “marbleized” appearance. Protrusion or “herniation” of tumor into blood vessels is a characteristic finding that may however not be present in all cases. Another typical although non-specific pattern is extensive tumor necrosis with preservation of perivascular areas. Well differentiated areas may resemble other nerve sheath tumors such as schwannomas or neurofibromas. Remnants of a neurofibroma in the vicinity of the tumor as well as intra- or perineural growth are strong diagnostic clues. It must be emphasized that most MPNST (with the exception of the epithelioid variant and the so-called perineurial variant) show only focal and/or weak expression of classical Schwann cell markers such as S100 and Sox10 (epithelioid MPNST) (14), as well as reduced numbers of CD34-positive fibroblasts (perineurial MPNST). Thus, in a biopsy, a diagnosis of MPNST should not be made in a spindle cell neoplasm with strong expression of S100 because of potential confusion with benign nerve sheath tumors such as cellular schwannoma. Features that are not helpful in the diagnosis of MPNST per se, but in the distinction between a benign and a malignant nerve sheath tumor include loss of p16 expression, strong nuclear p53 staining and complete loss of H3K27me expression (14). Contrary to spindle cell MPNST, the epithelioid variant is generally diffusely and strongly positive for S100 and Sox10 and in addition about two-thirds of epithelioid MPNSTs will show loss of INI1 (*Figure 3D*).

Neoplasms with epithelioid morphology

Major differential diagnoses in this group include thymoma, lymphomas such as primary mediastinal large B cell lymphoma or anaplastic large cell lymphoma, melanoma, mesothelioma, epithelioid SFT, epithelioid MPNST, biphasic synovial sarcoma, and vascular tumors such as epithelioid hemangioendothelioma (EHE) and epithelioid angiosarcoma. Metastatic melanoma may have a striking epithelioid morphology and may sometimes resemble thymoma or thymic carcinoma. Since melanomas can express CD117 and even (focally) keratin (*Figure 2D*), this distinction is not always straightforward and requires inclusion of melanocytic markers such as MelanA and

SOX10.

Epithelioid hemangioendotheliomas (EHE) are rare tumors arising in the anterior mediastinum of adults with a slight male preponderance and may have contact to large blood vessels (superior vena cava or innominate vein). Due to their strikingly epithelioid morphology and expression of keratin in about one third of cases (15), an initial misdiagnosis as metastatic carcinoma is very frequent. An important clue is presence of a chondroid or sometimes myxoid stroma and “blistering” of tumor cells with intracytoplasmic and intranuclear inclusions. EHE show strong expression of vascular markers such as CD31 and ERG (which are preferred to CD34 due to its frequent loss in vascular tumors and its expression in many other entities), and harbour a diagnostic *WWTR1-CAMTA1* gene fusion [that can be detected by antibodies or by FISH (15)]. The distinction of EHE from epithelioid angiosarcoma on morphological grounds alone may be difficult if not impossible in small biopsies: features that favour angiosarcoma include high grade cytology, lack of myxoid/chondroid stroma, and slit like anastomosing blood vessels. *CAMTA1* abnormalities are absent in angiosarcomas and thus offer a reliable means to distinguish both entities (15). As pointed out above, in a male patient, angiosarcoma may occur as a “somatic type malignancy” in a person with Klinefelter syndrome and a mediastinal germ cell tumor.

Pleomorphic and small cell neoplasms

The differential diagnosis of pleomorphic neoplasms comprises many of the entities discussed above, including poorly differentiated or undifferentiated thymic carcinoma, mesothelioma, melanoma, or myeloid sarcoma (chloroma).

Cases of giant cell tumors of soft tissue and undifferentiated pleomorphic sarcomas (type “MFH”) have been described in the mediastinum. In some of these cases, a definite diagnosis may not be possible in a biopsy even after exhaustive immunohistochemical stainings.

The differential diagnosis of small cell tumors includes T-lymphoblastic lymphoma, small cell carcinoma, small blue round cell sarcomas (Ewing/PNET, *CIC-DUX* translocated sarcomas, small cell synovial sarcoma, rhabdomyosarcoma), and neuroblastoma. Lymphomas and small cell carcinomas can be readily sorted out by expression of lymphatic and epithelial/neuroendocrine markers, respectively. CD99 staining is of limited value in the differential diagnosis, since all of these tumors including rare cases of small cell carcinomas (16) express

CD99. Small cell carcinomas may be associated with paraneoplastic symptoms such as Cushing or Lambert Eaton syndrome (17).

Ewing sarcoma/PNET (“Askin tumor”) is very rare in the mediastinum and usually affects young adults. As in other anatomic locations, demonstration of a chromosomal translocation involving the *EWSR1* gene is required to confirm the diagnosis (18,19). The spectrum of small blue round cell sarcomas has recently been considerably extended beyond Ewing sarcoma/PNET by the definition of tumors with *CIC-DUX4* (20) and *BCOR-CCNB3* gene fusions (21). However, such cases have so far not been reported in the mediastinum. Rhabdomyosarcomas are exceedingly rare in the mediastinum and are usually seen as a heterologous component of other tumors. Neuroblastomas usually occur in the posterior mediastinum in children, but a few cases have been described also in the thymus of elderly patients. In addition to the well-known *MYCN* gene amplifications, mutations of *ALK*, *PHOX2B*, and *ATRX* have been described. In addition to neuron-specific enolase (NSE), expression of GATA3 has recently been described as a valuable diagnostic marker (22).

Summary

Mediastinal soft tissue sarcomas are rare, but pose a significant diagnostic challenge due to the exceedingly large variety of other tumors with overlapping morphological and immunohistochemical features (thymomas, lymphomas and leukemias, germ cell tumors, metastases, etc.) that occur in the mediastinum. Awareness of possible differential diagnoses, close attention to the patient’s age and clinical presentation as well as an increasingly large panel of immunohistochemical antibodies and molecular tests are required for correct interpretation.

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