



Primary mediastinal synovial sarcomas

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Abstract: Synovial sarcoma is a malignant mesenchymal neoplasm that accounts for approximately 10% of all soft tissue sarcomas. These tumors most commonly occur in the extremities of young adults but are not restricted to this site and can arise in virtually any organ system. Synovial sarcomas originating in the mediastinum are exceptionally rare and are often mistaken for other, more common neoplasms in this location, especially since there are no specific imaging characteristics or clinical manifestations. Contrary to synovial sarcomas of the extremities, mediastinal tumors more commonly affect male patients. Histologically, these tumors can be divided into monophasic, biphasic and poorly differentiated variants, further complicating the diagnostic process. Recent advances in immunohistochemical and molecular techniques have provided useful tools to confirm the diagnosis and distinguish these tumors from other mediastinal neoplasms. The treatment of mediastinal synovial sarcomas often requires multimodal therapy, including surgery, chemotherapy and radiation. Despite this, the prognosis for synovial sarcomas in this location appears to be worse than for their analogues in the soft tissue, likely related to the often large size of the lesions and close proximity to critical anatomic structures making complete surgical resection difficult to achieve. This review summarizes the clinicopathological, immunohistochemical and molecular characteristics of these rare neoplasms.

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Introduction

Synovial sarcoma derives its name from the initial assumption that the tumor originated from synovial cells, after a frequent association with joints, tendons and bursal structures was noted in early reports (1,2). Recognition of cases not associated with such structures and identification of variable epithelial differentiation in these tumors has subsequently led investigators to believe that synovial sarcomas are likely derived from pluripotent mesenchymal cells capable of divergent differentiation (3,4). Synovial sarcomas most commonly arise from the deep soft tissues of the extremities, accounting for 5–10% of all soft tissue sarcomas (5,6).

These tumors primarily affect a younger patient population, including adolescents and young adults (7,8). Apart from the soft tissues, synovial sarcomas have been recognized in most anatomic sites, including the thoracic cavity. Most of the thoracic cases occur in the pleuropulmonary system while the mediastinum is an exceptionally rare site (9-13). In largest series to date, reporting 21 cases, the incidence of mediastinal synovial sarcomas was estimated at 11.2% of all thoracic synovial sarcomas (11). Histologically, synovial sarcomas can display a spectrum of growth patterns, including monophasic, biphasic and poorly differentiated types, adding diagnostic difficulty to their recognition, especially in sites not commonly associated with these

neoplasms. The discovery that 95% of synovial sarcomas are characterized by a specific translocation $t(X;18)(p11;q11)$ that can be detected by fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) is a powerful tool in the differential diagnosis with other, more common neoplasms in the mediastinum and molecular confirmation remains the gold standard in the diagnosis of these tumors. This review provides a summary of the current knowledge concerning these unusual tumors and compares their clinicopathologic characteristics to those of their soft tissue analogues.

Table 1 Common presenting symptoms of primary mediastinal synovial sarcomas

Chest pain
Shoulder pain
Shortness of breath
Cough
Pericardial effusion
Pleural effusion
Fatigue
Weakness
Weight loss
Fever
SVC obstruction
SVC, superior vena cava.

Clinical features

Synovial sarcomas of the mediastinum can occur in any age group (range, 3–83 years) but are most commonly detected in the 4th decade of life. Contrary to their soft tissue analogues which show no gender bias, mediastinal primaries are more common among male patients (9–13). Although the spectrum of presenting symptoms is wide (*Table 1*), most patients complain of chest or shoulder pain, shortness of breath, cough and pericardial effusion. Notably, each patient's clinical history and physical examination should include assessment of prior history or concurrent soft tissue tumor in order to exclude a metastatic process.

Radiological features

Mediastinal synovial sarcomas can arise in any mediastinal compartment, most commonly the anterior mediastinum, followed by the posterior mediastinum and middle and superior compartments (10,11,13). The radiological appearance of mediastinal synovial sarcomas is non-specific, often precluding separation from other mediastinal neoplasms. On chest radiographs, the tumors appear as well circumscribed neoplasms with sharply marginated borders or as ill-defined infiltrative lesions. Computed tomography (CT) scanning will reveal large tumor masses with homogeneous or heterogeneous enhancement that show high uptake on positron emission tomography (PET) (*Figure 1A,B*). At magnetic resonance imaging (MRI), the tumors typically demonstrate heterogeneous signal intensity

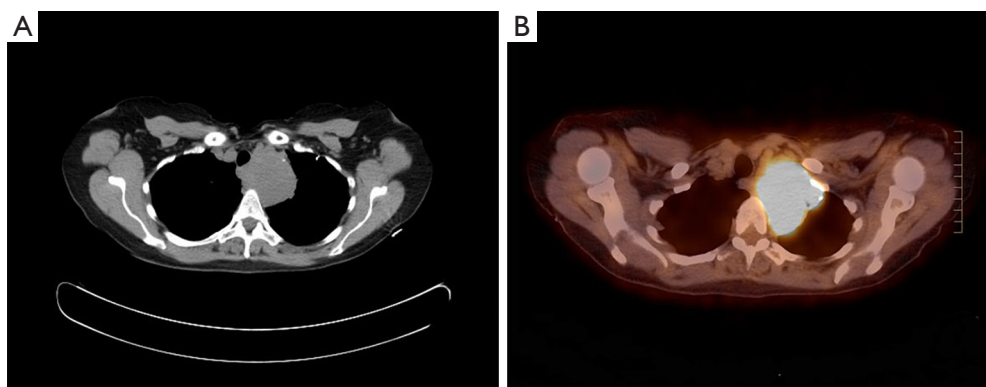


Figure 1 Imaging features of a primary synovial sarcoma of the mediastinum. (A) On a CT scan of the chest, the tumor is apparent in the left superior mediastinum; (B) high uptake is seen on PET scan. CT, computed tomography; PET, positron emission tomography.

on T1- and T2-weighted images and may contain fluid-fluid levels due to hemorrhage or necrosis within cystic tumor components. Cyst formation, areas of calcification, necrosis and hemorrhage are common findings (10,12,14).



Figure 2 Gross features of a primary mediastinal synovial sarcoma. The tumor is multinodular, relatively circumscribed and lined by a thin fibrous membrane.

Pathological features

Grossly, synovial sarcomas arising in the mediastinum are large tumors with reported sizes ranging from 5 to 23 cm and an average size around 12 cm (9-11). The tumors may be well circumscribed and surrounded by a thin fibrous capsule or poorly delineated masses that infiltrate surrounding anatomic structures (*Figure 2*). The cut surface is gray-white to tan and can have a soft or firm consistency. Areas of calcification, cystic degeneration, gelatinous change, hemorrhage or necrosis can often be identified in varying proportions (9,10). Histologically, the tumors can be divided into three different subtypes: monophasic, biphasic and poorly differentiated synovial sarcoma. Monophasic tumors are characterized by a monotonous, highly cellular spindle cell proliferation growing in sheets, fascicles or storiform patterns (*Figure 3A,B*). In some areas, a palisading nuclear pattern reminiscent of Verocay bodies or a tigroid appearance can be observed

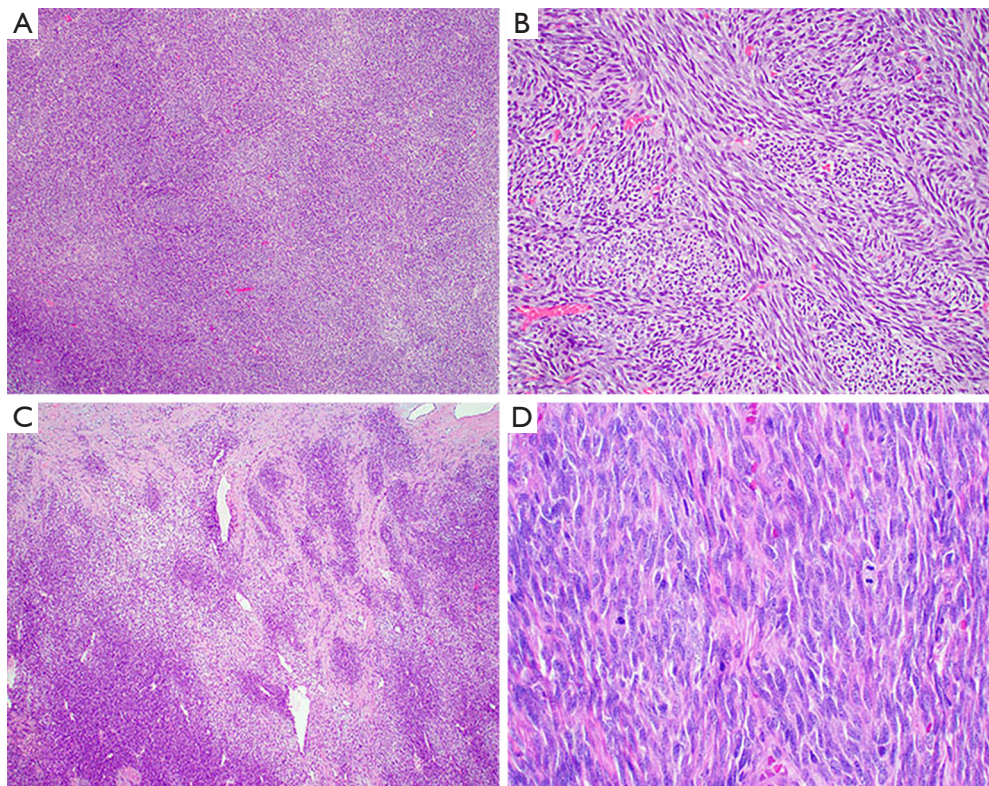


Figure 3 Histopathological features of monophasic synovial sarcoma. (A) Low power view shows a neoplasm composed of sheets of monomorphic spindle cells (H&E, $\times 4$); (B) in some cases, the tumor cells are arranged in fascicles (H&E, $\times 10$); (C) alternating hypo and hypercellular areas are a common finding in these tumors (H&E, $\times 4$); (D) the mitotic activity is typically increased (H&E, $\times 20$).

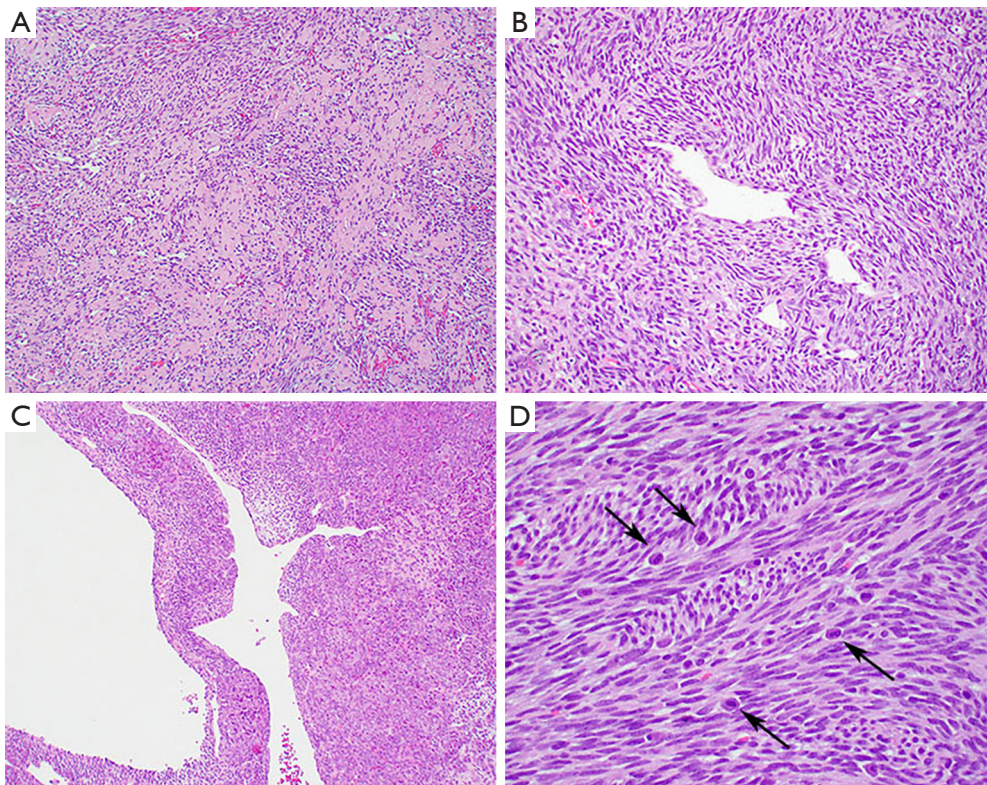


Figure 4 Frequent stromal changes associated with mediastinal synovial sarcomas. (A) Prominent stromal hyalinization in a mediastinal synovial sarcoma (H&E, $\times 4$); (B) hemangiopericytoma-like blood vessels are a characteristic finding in these tumors (H&E, $\times 10$); (C) cystic changes are another very common feature in synovial sarcoma (H&E, $\times 4$); (D) stromal mast cells (arrows) are frequently seen in these neoplasms (H&E, $\times 40$).

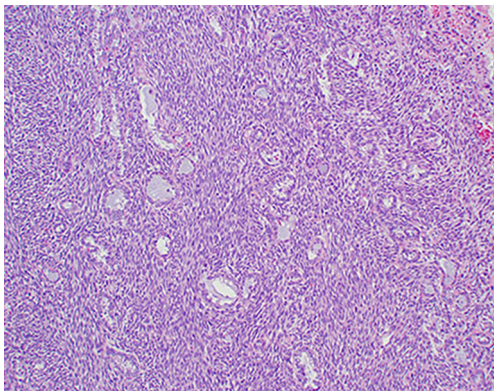


Figure 5 Biphasic synovial sarcomas contain epithelioid elements, here in the form of glandular spaces (H&E, $\times 4$).

and alternating hypo and hypercellular fascicles are also very common (Figure 3C). Individual tumor cells have fusiform nuclei with indistinct nucleoli and a scant rim of

eosinophilic cytoplasm. Cytologic atypia is not a feature of these tumors but the mitotic activity is typically increased, ranging from 2 to more than 20 mitoses per 10 high power fields (HPF) (Figure 3D). Frequent stromal changes include myxoid change or hyalinization (Figure 4A), a hemangiopericytic (staghorn) vascular pattern (Figure 4B), foci of calcification, cystic change (Figure 4C), and areas of necrosis or hemorrhage. Another characteristic finding is the presence of scattered mast cells among the tumor cells (9-13) (Figure 4D). The biphasic variant contains an additional epithelioid component that can comprise 20–80% of the tumor volume (9). These epithelioid elements consist of nests, clefts, papillary formations and glandular structures and are composed of round, cuboidal or columnar cells with round to oval nuclei, inconspicuous nucleoli and abundant eosinophilic cytoplasm (Figure 5). In cases with glandular structures, the lumina may be filled with homogeneous eosinophilic material (9-13). Poorly differentiated tumors can manifest as proliferations of

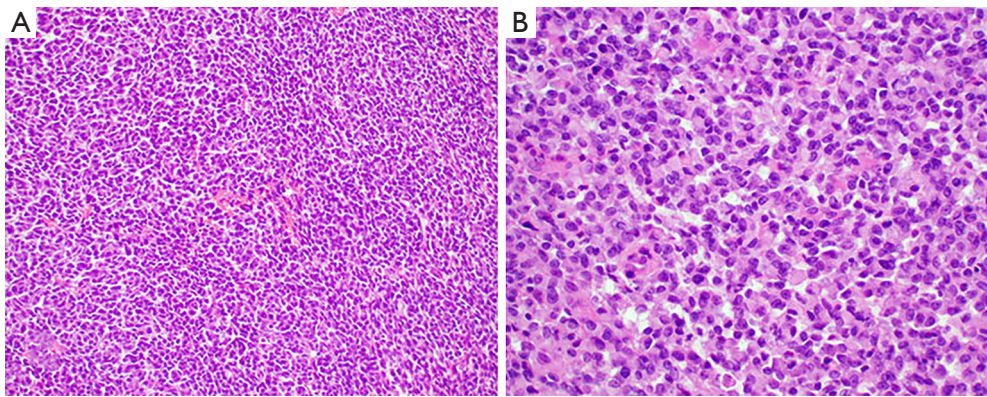


Figure 6 Histopathological features of mediastinal synovial sarcoma, poorly differentiated variant. (A) These tumors can be composed of sheets of small round cells (H&E, ×10); (B) in some areas, the tumor cells can show prominent rhabdoid changes, characterized by eosinophilic cytoplasmic inclusions (H&E, ×20).

Table 2 Histological subtypes of primary mediastinal synovial sarcomas

Monophasic (48%)	Biphasic (<5%)	Poorly differentiated (~50%)
Monotonous spindle cells	Monotonous spindle cells	Small round blue cells
Sheets, fascicles, storiform patterns	Nests, clefts, papillae, glandular structures composed of epithelioid cells	Rhabdoid cells
Hypo and hypercellular areas	Minimal cytologic atypia	Epithelioid cells
Minimal cytologic atypia		High grade spindle cells
Increased mitotic activity		
Stromal mast cells		
Cyst formation		
Hemangiopericytoma-like blood vessels		
Calcification		
Myxoid change		
Hyaline change		
Necrosis		
Hemorrhage		

small round blue cells, large epithelioid/rhabdoid cells or high-grade spindle cells (11,15-18) (Figure 6A,B). Areas composed of poorly differentiated cells may be seen in the other subtypes or may occasionally constitute the entire tumor. In contrast to their soft tissue counterparts, mediastinal synovial sarcomas are more likely of monophasic (48%) and poorly differentiated types (~50%) as opposed to the biphasic type (<5%) (11,13) (Table 2).

Immunohistochemical and molecular features

The diagnosis of synovial sarcoma is generally straightforward in the right clinical setting and typical tumor location. When arising in unusual sites, the tumors may be more difficult to diagnose and ancillary methods become indispensable. Until recently, the immunophenotype of synovial sarcoma was non-specific. Common markers that are expressed by these tumors,

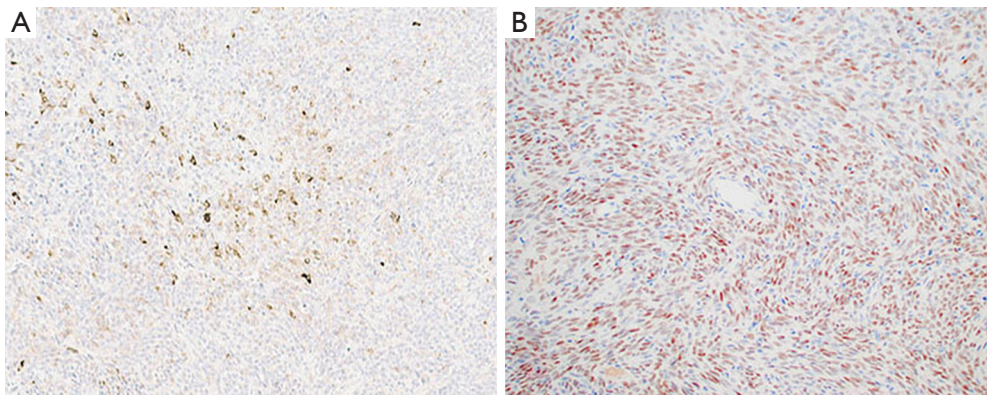


Figure 7 Immunohistochemistry of mediastinal synovial sarcoma. (A) Expression of EMA in a monophasic synovial sarcoma ($\times 4$). The pattern of staining is typically weak and focal; (B) TLE1 is the most specific and sensitive marker for synovial sarcoma and usually shows strong and diffuse nuclear reactivity ($\times 10$). EMA, epithelial membrane antigen; TLE1, transducer-like enhancer of split 1.

Table 3 Immunohistochemical and molecular features of primary mediastinal synovial sarcoma

Immunohistochemistry/ molecular features	Reactivity
CK	+/- (+ in epithelioid components)
EMA	+/- (+ in epithelioid components)
Bcl-2	+
CD99	+/-
S100	+/-
Synaptophysin	+/-
CD56	+/-
Calretinin	+/-
SMA	+/-
TLE1	+
SYT-SSX1	+ (66%)
SYT-SSX2	+ (33%)

CK, cytokeratin; EMA, epithelial membrane antigen; SMA, smooth muscle antigen; TLE1, transducer-like enhancer of split 1.

such as cytokeratins, epithelial membrane antigen (EMA) and bcl-2, are not specific to synovial sarcoma and are also expressed by a wide range of unrelated neoplasms (10,13,19-22). Likewise, antibodies that are commonly expressed by tumors in the differential diagnosis, including S100, synaptophysin or CD99 can also be reactive in synovial sarcoma. Epithelial differentiation in the form of cytokeratin or EMA reactivity is often

focal in monophasic and poorly differentiated synovial sarcomas. Strong and diffuse expression of these markers is generally limited to the epithelioid elements in biphasic synovial sarcoma (10,22) (Figure 7A). The discovery that transducer-like enhancer of split 1 (TLE1) is overexpressed in synovial sarcomas has led to identification of TLE1 expression also on a protein level (23,24). Since then, TLE1 has emerged as a relatively sensitive and specific immunohistochemical marker for these tumors, with sensitivity rates ranging from 82% to 100% in various studies (19-21,25,26) (Figure 7B). On the other hand, TLE1 protein may also be detected in other mesenchymal neoplasms, including tumors in the differential diagnosis of synovial sarcoma, such as malignant peripheral nerve sheath tumor (MPNST) and solitary fibrous tumor (SFT) (20,23,25,26). One important aspect in this context is that TLE1 staining in synovial sarcoma is usually strong and diffuse while in other mesenchymal neoplasms is often less intense and more focal (Table 3). Synovial sarcomas are translocation-associated tumors. More than 95% of these tumors are characterized by a t(X;18)(p11;q11) translocation, leading to fusion of *SS18* to one of the *SSX* genes. *SS18-SSX1* is the most common fusion gene and can be identified in 2/3 of the cases while *SS18-SSX2* can be found in the remainder (27-32) (Table 3). FISH or RT-PCR are common methods used to detect these rearrangements, enabling diagnostic confirmation in the majority of cases and representing the most specific and sensitive tool in the diagnosis of synovial sarcoma. Molecular analysis is of particular benefit in cases where diagnosis relies on small

Table 4 Differential diagnosis of primary mediastinal synovial sarcoma

Anterior mediastinum	Posterior mediastinum	Other mediastinal locations
Spindle cell thymoma	Schwannoma	SFT
Spindle cell thymic carcinoma	MPNST	Malignant mesothelioma
Thymic carcinosarcoma	SFT	PNET/Ewing sarcoma
SFT	Malignant mesothelioma	
Malignant mesothelioma		

SFT, solitary fibrous tumor; MPNST, malignant peripheral nerve sheath tumor; PNET, primitive neuroectodermal tumor.

biopsy material or for tumors in unusual locations.

Differential diagnosis

The differential diagnosis for synovial sarcomas originating in the mediastinum is quite wide given the morphologic variability of tumors and broad spectrum of neoplastic conditions that can arise in the mediastinal space (*Table 4*). Monophasic synovial sarcomas must be distinguished from other spindle cell neoplasms. In the mediastinum, close attention should be paid to the tumor location within the individual compartments. For tumors in the posterior mediastinum, peripheral nerve sheath tumors should be considered. Both schwannoma and MPNST are composed of spindle cell proliferations that may be difficult to distinguish from synovial sarcoma based on tumor morphology alone. Schwannomas, however, are benign spindle cell tumors that should lack any features of malignancy, such as mitotic activity or areas of necrosis. MPNST and synovial sarcoma may share several morphological and immunohistochemical characteristics, including a malignant spindle cell proliferation and focal reactivity for cytokeratins and S100 protein. In this context, staining for TLE1 should be applied and usually demonstrates strong and diffuse reactivity in synovial sarcomas and absent or only weak non-specific staining in MPNST. SFT is another spindle cell neoplasm that can show strikingly similar tumor morphology as synovial sarcoma and that can arise in virtually any mediastinal compartment. These tumors are characterized by alternating zones of hyper and hypocellularity in a background of a variably fibrous stromal background. In contrast to synovial sarcoma, SFT is most commonly benign and devoid of malignant features. Furthermore, SFT is known to be positive for CD34 and STAT6 and negative for cytokeratins and TLE1 by immunohistochemistry and additionally

harbors a characteristic *NAB2-STAT6* gene fusion. For tumors arising in the anterior mediastinal compartment, thymic epithelial tumors with spindle cell morphology, i.e., spindle cell thymoma and spindle cell thymic carcinoma, need to be excluded. Spindle cell thymomas are low grade malignant neoplasms typically lacking mitotic activity while spindle cell thymic carcinomas show cytologic atypia and an increased mitotic rate. In cases of doubt, diffuse immunostaining with cytokeratin and p40 would favor a thymic spindle cell neoplasm while absent or focal keratin staining coupled with strong and diffuse reactivity for TLE1 would favor synovial sarcoma. Malignant mesothelioma may be confused with both monophasic and biphasic synovial sarcomas due to its similar morphological variability and growth patterns. In this context, sarcomatoid mesothelioma may closely mimic the monophasic type of synovial sarcoma whilst biphasic mesotheliomas and biphasic synovial sarcomas both contain spindle cell and epithelioid elements. However, mesotheliomas have a distinct disease distribution, typically affecting the pleural surfaces in a diffuse pattern, in contrast to synovial sarcoma which is usually a localized mass. Moreover, mesotheliomas are characterized by strong and diffuse staining for cytokeratin and other markers useful in the diagnosis of mesothelial lesions, for instance calretinin or WT-1. Reactivity for TLE1 is not a feature of these tumors. Another biphasic tumor that can occur in the anterior mediastinum is thymic carcinosarcoma. Unlike in synovial sarcoma, the glandular component in these tumors often shows overtly malignant features and contains poorly differentiated sarcomatoid elements that often lack the monotonous appearance of synovial sarcoma. Poorly differentiated synovial sarcoma may be difficult to distinguish from tumors in the primitive neuroectodermal tumor (PNET)/Ewing sarcoma group due to significant morphological and immunohistochemical overlap. In such cases, TLE1 should be applied and if positive would

favor a diagnosis of synovial sarcoma; identification of the characteristic *EWSR1* gene rearrangement in PNET/Ewing sarcoma by molecular methods offers another diagnostic tool in this context. Confirmatory molecular analysis for *SS18* gene rearrangement can establish or support the diagnosis of synovial sarcoma in all cases where tumor morphology and immunophenotype fail to provide unequivocal separation from its closest mimics (Table 4). Finally, a metastatic process to the mediastinum from an extrathoracic primary should always be excluded based on detailed clinical and radiological correlation.

Treatment and prognosis

The treatment of choice for patients with mediastinal synovial sarcoma is complete surgical resection which is the only factor associated with improved survival (33). Neoadjuvant chemotherapy and radiotherapy should be considered in patients with unresectable non-metastatic disease followed by surgical intervention. Chemotherapy, especially high dose ifosfamide with or without doxorubicin can be administered in unresectable patients. Adjuvant chemotherapy and radiotherapy should be considered as part of a multimodality approach in all patients (5). Despite these multimodal treatment options, the prognosis for patients with mediastinal synovial sarcomas remains poor, with a median overall survival of 36 months and a 5-year overall survival rate of 35.7%, compared to a 5-year overall survival rate of 50–80% for extremity primaries (10-12,33-35). This is likely due to presentation at advanced tumor stage, large tumor size, difficulty of complete surgical resection due to involvement of vital anatomic structures, and high incidence of the poorly differentiated subtype. The type of gene fusion (*SYT-SSX1* vs. *SYT-SSX2*) does not seem to have a significant effect on disease-specific survival among thoracic synovial sarcomas (13).

Comment

Synovial sarcomas originating in the mediastinum are rare neoplasms that may cause significant diagnostic difficulty due to the unusual tumor location. Although these tumors share many overlapping features with their soft tissue counterparts, they are characterized by slightly older age at presentation, bias towards the male gender, larger tumor size, advanced tumor stage and higher rate of the poorly differentiated subtype. These features contribute to the more aggressive clinical behavior and poor prognosis of

these tumors. Completeness of resection appears to be the single most critical factor for improved survival and should be aggressively pursued in all patients with potentially resectable disease.

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