



The role of molecular pathology in mediastinal sarcomas

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Abstract: Mediastinal sarcomas represent rare neoplasms of mesenchymal origin. Most published data on mediastinal sarcomas is primarily derived from small series and case reports. Although rare, primary mediastinal sarcomas have a clinically aggressive course with worse 10-year survival rates than other types of mediastinal tumors, highlighting the importance of adequate diagnosis of these lesions. The diagnosis of mediastinal sarcomas is complicated by the varied histologic subtypes of tumors that can occur and which can sometimes display overlapping clinical, morphological, imaging, and immunohistochemical features. Cytogenetic analysis and more recently, molecular techniques, have provided new methods by which these tumors can be differentiated. Sarcomas occurring within the mediastinum are an extremely heterogenous group of tumors, although the specific incidence of the different subtypes of mediastinal sarcomas varies among studies, there is a subset of lesions that appear to occur more commonly across most published studies. These tumors include synovial sarcoma, liposarcoma, malignant peripheral nerve sheath tumor (MPNST), small round blue cell sarcomas (including Ewing sarcoma) and leiomyosarcoma (LMS). Other rare sarcoma subtypes may also less commonly occur within the mediastinum. Many of these sarcomas have specific, recurrent genetic abnormalities that can be identified through cytogenetic and molecular testing allowing for accurate diagnosis. This review aims to cover the role of molecular pathology, specifically with regards to diagnosis, as well as discuss the salient molecular genetic features of the various types of sarcoma that occur within the mediastinum. In addition, the various types of cytogenetic and molecular diagnostic tests available for the diagnosis of different types of sarcomas will be reviewed.

Keywords: Mediastinum; sarcoma; molecular genetics; next generation sequencing (NGS); thoracic

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Introduction

Primary mediastinal sarcomas represent an extremely rare and heterogenous group of mesenchymal neoplasms comprising <10% of primary mediastinal tumors and 1–2% of all soft tissue sarcomas (1-4). Despite their rare occurrence, primary mediastinal sarcomas tend to have an aggressive clinical course with a poor overall survival, usually worse than that of other types of mediastinal tumors (4-6). The mediastinal compartment is unique in that it houses multiple different tissue types allowing for great heterogeneity of both benign and malignant mesenchymal tumor types (7,8). It is difficult to determine the exact incidence of sarcoma subtypes arising within

the mediastinum given their rarity and because multiple studies have reported different incidences for the different tumor types (4-7,9,10). Although predicated upon the accuracy of the initial diagnosis and proper reporting, evaluation of the National Cancer Database and the Surveillance, Epidemiology, and End Results Program (SEER) database highlights a group of tumors that appear to occur most commonly as primary mediastinal sarcomas (5,9). These tumors include synovial sarcoma, liposarcoma, malignant peripheral nerve sheath tumor (MPNST), small round blue cell sarcomas (including Ewing sarcoma) and leiomyosarcoma (LMS) (4-7,9). A single study lists angiosarcoma with the common mediastinal sarcomas,

Table 1 Common and uncommon mediastinal sarcomas

More common mediastinal sarcomas
Synovial sarcoma
Well-differentiated liposarcoma
Dedifferentiated liposarcoma
Malignant peripheral nerve sheath tumor
Ewing sarcoma
Leiomyosarcoma
SMARCA4-deficient thoracic sarcoma
Solitary fibrous tumor [^]
Less common mediastinal sarcomas
Rhabdomyosarcoma
Clear cell sarcoma
Low-grade fibromyxoid sarcoma
Myxoid liposarcoma
Alveolar soft part sarcoma
Epithelioid hemangioendothelioma
Epithelioid sarcoma
Extraskeletal myxoid chondrosarcoma
Mesenchymal chondrosarcoma
Extrarenal rhabdoid tumor
Malignant pcoma
Follicular dendritic cell sarcoma
Angiosarcoma*
Chondrosarcoma
Osteosarcoma
Chordoma
Various undifferentiated sarcomas

[^], solitary fibrous tumor is generally not included under the category of “sarcoma” but is included here due to its frequent occurrence and potential for aggressive/malignant behavior. *, the majority of angiosarcomas of the mediastinum have been reported in studies in which cardiac tumors were included, primary mediastinal angiosarcoma not associated with cardiac tissue is exceedingly rare.

however it is unclear whether these represented primary cardiac angiosarcomas or true primary mediastinal angiosarcomas (5). A wide variety of other sarcoma types

have also been reported to occur in the mediastinum (*Table 1*) (6,8,9,11-24). Another soft tissue mesenchymal neoplasm that occurs with some frequency within the mediastinum is solitary fibrous tumor (SFT). Although generally regarded as having indolent or low-grade behavior, these tumors may behave in an aggressive manner and have a small, but definitive, malignant potential and are therefore included in this discussion (25,26). In addition, a recently described entity that can occur within the mediastinum, pleura, or chest wall; *SMARCA4*-deficient undifferentiated tumor/sarcoma will be briefly discussed (27).

The differential diagnosis of mediastinal sarcomas may be difficult due to their rare nature and often overlapping clinical and histologic features. Generally, the workup and diagnosis of primary mediastinal sarcomas is similar to that of their extramediastinal soft tissue counterparts. Traditionally the diagnosis has been based on a combination of clinical, radiological, histologic and immunohistochemical features, however, various cytogenetic and molecular tests have proved to be valuable ancillary modalities to help differentiate soft tissue sarcomas (28-31). Within the past decade the emergence of massively parallel sequencing technologies such as next generation sequencing (NGS) have allowed for more comprehensive evaluation of soft tissue sarcomas and the discovery of new genetic driver events underlying these lesions (32-37). Although the management of sarcomas is still evolving, access to new information about the underlying molecular genetic events driving these lesions will soon become a routine part of clinical practice as personalized medicine continues to advance. This review aims to focus on molecular diagnostics and their contribution to the differential diagnosis of mediastinal sarcomas with a focus on the most common tumor subtypes.

General molecular features and use of molecular diagnostics in mediastinal sarcomas

Bone and soft tissue tumors of the mediastinum can generally be characterized into two broad categories: those with complex karyotypes that lack recurrent genomic alterations and those with relatively simple karyotypes that harbor specific, recurrent genomic alterations. Tumors with a high degree of genomic instability, such as LMS, osteosarcoma and undifferentiated pleomorphic sarcoma, generally do not lend themselves to molecular diagnostic testing due to their

Table 2 Translocations and other genetic alterations in the most common mediastinal sarcomas

Tumor type	Genetic alteration	Recurrent fusion or abnormality
Synovial sarcoma	t(X;18)(p11;q11), t(X;20)(p11;q13)	SS18-SSX1, SS18-SSX2, SS18-SSX4, SS18L1-SSX1
Well-differentiated and dedifferentiated liposarcoma	Supernumerary ring and giant chromosome markers with amplification of 12q13-15, including <i>MDM2</i> and <i>CDK4</i>	Cell cycle dysregulation, overexpression of <i>MDM2</i> and <i>CDK4</i>
Leiomyosarcoma	Generally complex karyotypes with numerous gains and losses. No consistent recurrent aberrations at the chromosomal level	None
Ewing sarcoma/PNET	t(11;22)(q24;q12), t(21;22)(q22;q12), t(7;22)(q22;q12), t(17;22)(q21;q12), t(2;22)(q36;q12)	<i>EWSR1-FLI1</i> , <i>EWSR1-ERG</i> , <i>EWSR1-ETV1</i> , <i>EWSR1-ETV4</i> , <i>EWSR1-FEV</i>
Solitary fibrous tumor*	Intrachromosomal inversion of 12q13 region	<i>NAB2-STAT6</i>
SMARCA4-deficient thoracic sarcoma	Point mutations leading to loss of <i>SMARCA4</i>	Dysregulation of SWI/SNF (BAF) complex
Malignant peripheral nerve sheath tumor	Various somatic alterations in <i>CDKN2A</i> , <i>NF1</i> , <i>EED</i> , <i>SUZ12</i> , <i>SMARCB1</i> (epithelioid variant)	Dysregulation of polycomb repressive complex 2 (PRC2)

* , solitary fibrous tumor is generally not regarded as a “true sarcoma”, however, it is included here due to its potential for malignant and/or aggressive behavior and relatively common occurrence within the mediastinum. PNET, peripheral neuroectodermal tumor.

lack of specific or recurrent genetic aberrations, although investigations may still be carried out to rule out other sarcoma subtypes in the differential diagnosis or provide the maximal amount of information on the patient’s tumor to the clinician (such as identifying a potential alteration that would qualify a patient for an experimental trial). However, a large subgroup of bone and soft tissue tumors which occur within the mediastinum are characterized by consistent and recurrent genetic abnormalities similar to their extra-mediastinal counterparts. For this group of tumors, the high rate of specific, recurrent genetic abnormalities allows molecular testing to offer important diagnostic and prognostic information, help guide clinical management and treatment, and allows for recruitment of patients in ongoing clinical trials (37).

Genetic features of mediastinal sarcomas

Recurrent genetic abnormalities in soft tissue tumors in general most commonly fall into one of four categories: translocations, activating oncogenic mutations, inactivating oncogenic mutations, and copy number alterations such as gains, deletions, and amplifications (38). The commonest mediastinal sarcomas are almost exclusively comprised of tumors defined by translocations, inactivating oncogenic mutations, and amplification events of specific chromosomal regions (Table 2).

Translocations

Approximately 30% of bone and soft tissue tumors are characterized by recurrent chromosomal translocations (38-40). Translocations are rearrangements of genetic material that lead to novel juxtapositions of particular genes based on where chromosomal breaks have occurred. These gene rearrangements result in the formation of fusion oncogenes which are often involved in the pathogenesis and proliferation of the neoplastic cells, although it is worth noting that not all rearrangements lead to functional fusion proteins depending on the genes translocated as well the orientation of the genes themselves. One of the best characterized gene fusions in soft tissue sarcoma is the *EWSR1* translocation in Ewing sarcoma. The most common rearrangement involves the long of arm of chromosome 11 with the long arm of chromosome 12, t(11;22)(q24q12), leading to a *FLI1-EWSR1* fusion gene (41). At the molecular level fusions in many tumors may occur through a diverse combination of genetic material with various different transcripts existing for one fusion gene (see Ewing sarcoma section). It is worth noting that recurrent translocations usually occur in the background of simple karyotypes and that some genes involved in translocations have a diverse array of partner genes. In addition, certain genes are known to be involved in numerous translocations across multiple tumor types, for example, other than

Ewing sarcoma the *EWSR1* gene can also be identified in the translocations of round cell liposarcoma, extraskelatal myxoid chondrosarcoma, atypical Ewing sarcomas, and clear cell sarcoma amongst others (42).

Inactivating oncogenic mutations

Single nucleotide variants as well as small insertions and deletions are responsible for a variety of inactivation events in many different tumor types. In the mediastinum, a small group of sarcomas are characterized primarily by inactivating oncogenic events including extrarenal rhabdoid tumor, epithelioid sarcoma, epithelioid MPNST and the recently described *SMARCA4*-deficient undifferentiated thoracic tumor/sarcoma (1,4,17,20,27). Loss of gene function may occur through a combination of events including deletions, inactivating point mutations, copy neutral loss of heterozygosity and epigenetic events such as DNA methylation and histone modification (43-46). The diverse modes of gene inactivation present in these tumor types may require multiple testing modalities to accurately identify, although NGS with large mutation/fusion panels that also provide copy number information allow for evaluation of many of these changes in a single test (37,45,47).

Amplification events

Copy number alterations and amplification events occur less commonly in mediastinal sarcomas and usually apply to sarcomas which fall into the complex karyotype category of tumors (undifferentiated high-grade sarcomas, LMS and osteosarcoma). Well-differentiated and dedifferentiated liposarcoma are also characterized by a recurrent amplification event (48-51). Tumors in the high complexity category tend to have multiple different chromosomal events leading to copy number alterations in combination with other types of molecular abnormalities such as mutations—the majority of these tend to be non-recurrent events between different tumor subtypes as well as within the same tumor types making molecular evaluation of the lesions less useful in routine clinical practice. However, amplification events of a specific region of 12q13-15 tend to be the sole abnormality in well-differentiated liposarcoma and dedifferentiated liposarcoma (although dedifferentiated may have additional genetic alterations such as mutations) (50,52). Copy number alterations in soft tissue neoplasms are particularly amenable to rapid diagnostic

testing by fluorescence *in situ* hybridization (FISH) when probes are available, but may also be identified by array-based techniques or sequencing assays.

Advantages and disadvantages of different cytogenetic/molecular tests

As mentioned before, FISH, array-based assays including array comparative genomic hybridization (aCGH)/single nucleotide polymorphism (SNP) arrays, polymerase chain reaction (PCR) based assays and early-generation sequencing technologies such as Sanger sequencing and pyrosequencing have all traditionally constituted the backbone of molecular diagnostics in bone and soft tissue tumors (29,30,32). More recently the introduction of massively parallel targeted sequencing assays, including NGS, has opened new avenues for testing of soft tissue tumors by allowing a single tumor to be tested for multiple different genetic abnormalities with one assay (35-37). All of these technologies have certain advantages and disadvantages (*Table 3*) and the type of testing offered by different laboratories varies widely making it important for pathologists to understand the advantages and limitations of particular assays to identify the proper type of test for a identifying a particular genetic alteration. For example, FISH and PCR may be used to identify specific genetic abnormalities in a case where a particular diagnosis is suspected at a low price with a rapid turnaround time. While array, karyotype and sequencing may be better options for difficult tumors where the diagnosis is unknown and the pathologist desires the maximum amount of genetic information to help inform the differential diagnosis. Particular attention should also be paid to the type of sample required for the different assays with the caveat that many molecular assays such as FISH, array, PCR, and NGS may not work properly or completely fail when attempted on decalcified specimens due to the degradation of nucleic acids (53,54).

Common mediastinal sarcomas

While primary mediastinal sarcomas are extremely rare tumors in general, there is a group of sarcomas that appear to occur more commonly across multiple published series as compared to other sarcoma subtypes (1,3,5,6,8,9). These mediastinal sarcomas for the most part have some specific, recurrent genetic abnormalities that allow for molecular testing to play a significant role in the diagnosis of these

Table 3 Advantages, disadvantages and use of different cytogenetic and molecular testing modalities

Test	Advantages	Disadvantages	Sensitivity	Best used for
Karyotype	Available in most academic centers; reasonable turnaround time (5–10 days); provides information about all chromosomes present within a cell; easily identifies complex karyotype sarcomas; relatively cheap	Requires fresh tissue; technically demanding assay to set up and perform; dependent on culture and growth of malignant cells; low resolution: ~10 Mb; complex, small or cryptic rearrangements may be missed; provides no information on mutations	5–10%	Identifying large chromosomal rearrangements as well as large gains and losses of genomic material
FISH	Available in most academic centers; can be performed on FFPE samples; rapid turnaround time (3–5 days); alternative FISH modalities, such as multicolor FISH, may provide additional information on specific rearrangements; probes for numerous genes available	Generally, only used to target specific chromosomal alterations; can be technically difficult to interpret signals; relatively low resolution: 200 kb; misses CN-LOH; provides no information on mutations	1–10%	Confirmation/identification of genetic alterations when a specific diagnosis is suspected, particularly rearrangements, deletions and amplifications
Array	aCGH and SNP array available in most cytogenetic laboratories; SNP array can identify CN-LOH; can identify specific areas of gains and losses; relatively fast turnaround time (5–10 days)	Relatively low resolution: 10–100 kb; Cannot detect balanced rearrangements; provides no information on mutations; fresh tissue is preferable, analysis of degraded (such as FFPE) samples is difficult	15–20%	Identifying gains and losses of genomic material, identifying CN-LOH, and identifying unbalanced rearrangements
PCR	Relatively easy assay to set up and perform; equipment widely available; fast turnaround time (3–7 days); works well on FFPE samples; highly sensitive; high resolution: down to 1 nucleotide	Most assays interrogate only specific suspected alterations (although assays such as RACE circumvent this); primers must be designed to cover specific areas of interest; RT-PCR assays require RNA which can be difficult to work with and degrade easily	Most assays <1%	Confirmation/identification of rearrangements or mutations when a specific diagnosis is suspected
Sequencing	Older generation sequencing technologies (Sanger, Pyrosequencing) slowly being replaced by NGS; NGS can interrogate tumors for multiple different genetic abnormalities depending on the panel used; high throughput; generates millions of sequencing “reads”; can easily be performed on FFPE samples; high resolution: down to 1 nucleotide	Longest turnaround time (1–4 weeks depending on laboratory workflow); Analysis (NGS) requires complex bioinformatics pipelines to be available; Analysis requires specially trained personnel to interpret sequencing data; NGS equipment and reagents currently very expensive; NGS Primarily only available at larger academic centers and reference laboratories	Sanger ~20%; Pyroseq ~1%; NGS <5%	Analyzing a tumor for various genetic abnormalities including mutations, rearrangements, and copy number alterations

FISH, fluorescence in situ hybridization; aCGH, array comparative genomic hybridization; SNP, single nucleotide polymorphism; RT-PCR, reverse transcriptase-polymerase chain reaction; PCR, polymerase chain reaction; NGS, next generation sequencing; Pyroseq, pyrosequencing; RACE, rapid amplification of cDNA ends; Mb, mega base pair; Kb, kilo base pair; bp, base pair; CN-LOH, copy neutral loss of heterozygosity; FFPE, formalin fixed paraffin embedded.

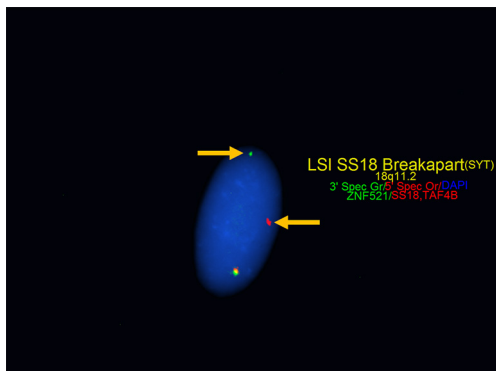


Figure 1 FISH performed on paraffin embedded tissue for *SS18* (18q11.2) shows one green/red/yellow signal (intact probe, no rearrangement) as well as separated green and red signals (arrows) representing the 3' and 5' ends of the *SS18* break apart probe. Break apart FISH probes are a common strategy for detecting rearrangements in which a dual color FISH probe is applied across a gene of interest and if a translocation is present that disrupts the gene the probe physically “breaks apart” as seen here.

tumors. It is important to note that many of the lesions in this category present with a characteristic clinical picture, as well as distinct morphological and immunohistochemical profiles that potentially allows for diagnosis without molecular diagnostics. However, molecular testing can help confirm a suspected diagnosis and is also useful for high grade lesions where the morphology or immunohistochemistry (IHC) profile may be non-specific. As mentioned previously, the mediastinum encompasses multiple different tissues types and depending on one's definition of the mediastinal compartment the diagnosis of a primary mediastinal sarcoma may change. For example, true primary mediastinal angiosarcoma unassociated with the heart is exceedingly rare (55), despite being included in the analysis of some studies (5). What follows is a brief review of the molecular aspects of the most common mediastinal sarcomas.

Synovial sarcoma

Synovial sarcoma has been traditionally grouped with tumors of uncertain histogenesis. Recent molecular expression studies suggest a myogenic origin, although this is inconsistent with the characteristic IHC profile that shows epithelial marker expression and lack of expression of myogenic markers (56). Synovial sarcoma is defined by a fusion oncoprotein; *SS18*-*SSX*, resulting

from a characteristic reciprocal $t(X;18)(p11.2;q11.2)$. This translocation fuses *SS18* with one of three *SSX* genes clustered on chromosome X (Xp11.2); either *SSX1*, *SSX2*, or rarely *SSX4* (57). An alternative, much less common, $t(X;20)(p11;q13)$ has also been described which leads to an *SS18L1*-*SSX1* fusion oncoprotein (58). The fusion oncoprotein results in dysregulation of *SS18*, a member of the chromatin remodeling SWI/SNF (BAF) complex (56). Studies correlating specific *SS18*-*SSX* fusion transcripts with histologic subtype or impact on prognosis have had conflicting results and primary mediastinal synovial sarcomas have not been well represented (59-61). Diagnosis of the fusion protein may be quickly performed with reasonably high sensitivity by FISH and PCR (Figure 1) (59,60). Testing of synovial sarcoma with NGS fusion panels allows for identification of the specific partner genes which cannot be identified through FISH and may be missed by PCR depending on the primer sets or type of PCR assay used (57,62). Studies that have examined primary mediastinal synovial sarcomas have identified that they share the same genetic alterations as their soft tissue counterparts (63,64).

Liposarcoma

Liposarcoma is a tumor of adipocytic origin characterized by supernumerary ring and marker chromosomes (Figure 2A). The supernumerary chromosomes are most often composed of genomic material from the q13-15 region on chromosome 12 (65,66). The q13-15 region contains several genes, including the genes *MDM2* and *CDK4* (67). Although many other genetic alterations including numerous somatic mutations, other gene amplification events, and gene deletions have been described in well- and dedifferentiated liposarcoma, amplification of *MDM2* and *CDK4* (particularly *MDM2*) has been accepted as the diagnostic criteria for well-differentiated liposarcoma and de-differentiated liposarcoma (68-70). *MDM2* amplification leads to overexpression of *MDM2*, promoting tumorigenesis by dysregulation of the p53 pathway (Figure 2B) (71). Amplification of *CDK4* leads to overexpression of *CDK4* that can then bind to cyclin D at increased levels, leading to interference with the E2F-RB interaction that acts as a cell cycle progression check from the G1 to S phase transition (72). Few series exist examining mediastinal liposarcomas; however, the predominant tumor subtypes across all series appear to be well- and dedifferentiated liposarcoma, the majority of which

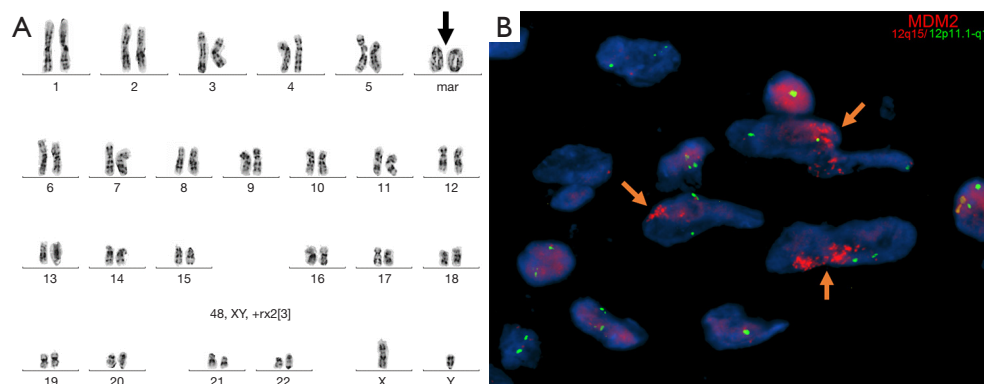


Figure 2 MDM2 amplification in dedifferentiated liposarcoma. (A) Karyotype from a dedifferentiated liposarcoma shows a 48,XY,+rx2 karyotype (identified in 3 out of 20 cells) with two supernumerary marker ringed chromosomes (arrow). These ringed chromosomes may contain material from the 12q13-15 region including *MDM2* and *CDK4*. Note the remaining chromosomes appear normal (Image courtesy of Dr. Christine Bryke, Boston, MA, USA). (B) Interphase FISH using a probe for *MDM2* on FFPE tissue shows multiple cells (arrows) with increased *MDM2* copy number consistent with amplification, magnification: 100 \times .

showed the characteristic amplifications or IHC expression (73-76). Amplification of *MDM2* and *CDK4* has been shown to correlate extremely well with IHC for *MDM2* and *CDK4*, allowing IHC to serve as an excellent screening tool, however confirmation of the diagnosis by molecular techniques is always recommended (77). Generally, this is best accomplished with FISH using probes specific to *MDM2* that are widely available, although copy number alterations may be assessed by array as well as certain NGS-based assays that provide copy number information (70). Of note, other subtypes of liposarcoma, such as myxoid and pleomorphic, may less commonly occur in the mediastinum (75).

LMS

LMS represents a mesenchymal tumor of smooth muscle origin characterized by complex cytogenetic and molecular aberrations (78,79). Cytogenetically LMS displays complex karyotypic changes that can include numerous gains, losses, rearrangements as well as chromothripsis (chromosomal shattering) in up to 35% of cases (79). Targeted exome sequencing studies have identified that the most frequent cytogenetic changes involve losses of material containing important tumor suppressor genes including *PTEN* (10q), *RB1* (13q), *CDH1* (16q), and *TP53* (17p) (78). Mutations in *TP53*, *RB1*, and *ATRAX* have been identified as the most common mutations to occur in LMS, although additional mutations in genes related to multiple signaling pathways, cell cycle regulation, DNA damage repair, muscle cell

proliferation and epigenetic regulation are enriched as well (79). Primary mediastinal LMS have only been reported in small series or case reports, although they comprised a significant percentage of mediastinal sarcomas (~10%) in a large study which reviewed the National Cancer Database for cases of mediastinal sarcomas (5,80-82). Few, if any, primary mediastinal LMS's have been examined by molecular techniques, although they likely share similar genetics to their soft tissue counterparts at extramediastinal sites. LMS is a clinicopathologic diagnosis and can often be made in the context of appropriate histomorphology and IHC supporting smooth muscle differentiation, making molecular genetic testing for the purposes of diagnosis less useful compared to sarcomas with specific, recurrent genetic abnormalities. However, clinically relevant molecular subtypes of LMS have been described and as new targeted therapies emerge molecular testing may play a larger role in guiding management and informing prognosis (83).

MPNST

MPNST is a tumor of neural origin which can occur in the mediastinum and which arises most commonly in patients with neurofibromas and neurofibromatosis type 1 (NF1) (5,9). The tumors occur most often within the posterior mediastinum in association with nerves located within that compartment, although rare cases have been described in the anterior mediastinum (84-87). These lesions may arise from malignant transformation of benign neural

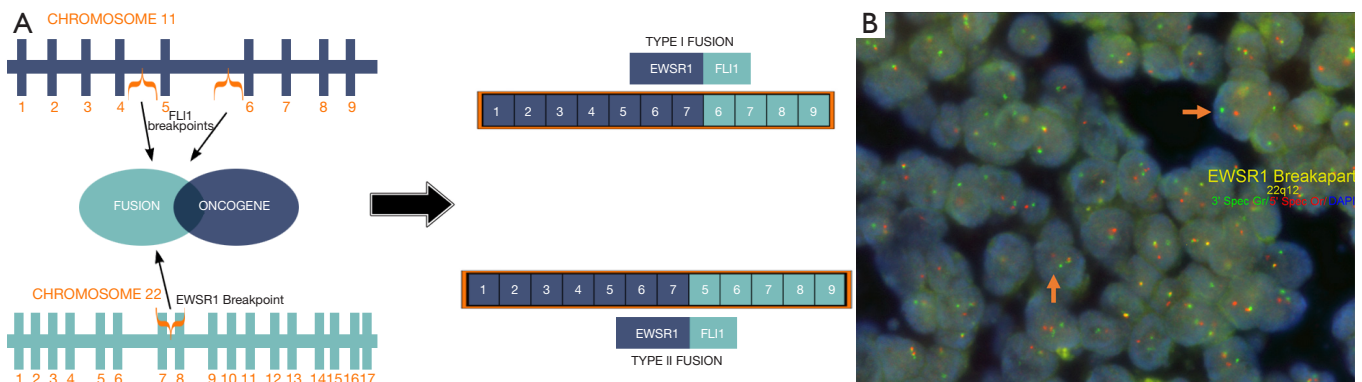


Figure 3 *EWSR1-FLI1* rearrangement in Ewing sarcoma. (A) Graphic depicting the formation of the *EWSR1-FLI1* fusion oncogene with the two most common *EWSR1-FLI1* transcripts. Type 1 transcripts occur between exon 7 of *EWSR1* and exon 6 of *FLI1*, while type 2 transcripts occur between exon 7 of *EWSR1* and exon 5 of *FLI1*. Other transcripts may less commonly occur (not pictured here). (B) Regardless of the transcript type or even the gene partner; FISH break apart probes are an effective strategy for identifying rearrangements involving *EWSR1*. FISH performed on FFPE tissue using an *EWSR1* (22q12) break apart probe shows multiple cells with separation of the 3' and 5' ends of the probe indicating a rearrangement is present (arrows), magnification: 60x.

tumors, but may also occur sporadically (88,89). MPNST is characterized predominantly by recurrent mutations in *NF1*, *TP53*, *CDKN2A*, *SUZ12*, and *EED* (88-91). In particular, recurrent loss of function mutations in *SUZ12* and *EED* lead to dysregulation of the polycomb repressive complex 2 (PRC2) with downstream dysregulation of the Ras pathway (92). MPNST's with PRC2 loss have been shown to have loss of trimethylation at lysine 27 of histone H3 (H3K27me3) which can be identified with a monoclonal antibody against H3K27me3 (88,93). The epithelioid variant has been shown to have loss of *SMARCB1* (94). The diagnosis of MPNST is currently accomplished primarily through clinicopathologic correlation and IHC, although the discovery of recurrent mutations in a high proportion of MPNST's may allow molecular testing to play a larger role in their diagnosis.

Ewing sarcoma/primitive neuroectodermal tumor (PNET)

Ewing sarcoma represents an undifferentiated primitive small round blue cell sarcoma of uncertain histogenesis (8). This sarcoma is characterized by a classic t(11;22) (q24;q12) creating an oncogenic fusion protein; *EWSR1-FLI1* (32,94). Less commonly, other *EWSR1-ETS* family rearrangements may occur (Table 2). The *EWSR1-FLI1* fusion may form from various different transcripts at the molecular level; 60% are designated as type 1 fusions that fuse exon 7 of *EWSR1* to exon 6 of *FLI1*, while 20% are

designated as type 2 fusions that fuse exon 7 of *EWSR1* to exon 5 of *FLI1* (Figure 3A) (41). Numerous additional variant fusions have been described including breakpoints in the regions of exons 3 through 8 on *FLI1*, however these are less common than type 1 or type 2 changes (32). In past years the specific transcript identified held clinical significance as the patients could potentially respond to treatment differently, however, updated treatment regimens appear to have eliminated these differences and the need for reporting the exact transcript (41). Given that *EWSR1* is a constant fusion partner in Ewing sarcoma, molecular testing can be rapidly and easily done using FISH break apart probes (Figure 3B) (95). As many of the *EWSR1* fusion partners have been delineated over the years, reverse transcriptase PCR may also be used to accurately and quickly identify rearrangements (96). Tumors occurring within the mediastinum have been shown to harbor the characteristic translocations and are thus amenable to molecular testing for confirming the diagnosis (8,97,98). Of note, in recent years molecular diagnostics have expanded the spectrum of small round blue cell sarcomas (sometimes referred to as Ewing's-like tumors) to include several new rearrangement partners for *EWSR1* as well as other small round blue cell sarcomas with novel translocations such as *CIC-* and *BCOR-* rearranged sarcomas (99,100). Small round blue cell sarcomas that are negative for the classic Ewing's translocation should be submitted for expanded molecular

genetic testing to identify other possible translocations.

SMARCA4-deficient undifferentiated thoracic tumor/sarcoma

SMARCA4-deficient thoracic sarcoma (also known as *SMARCA4*-deficient undifferentiated tumor or *SMARCA4*-deficient thoracic sarcomatoid tumor) is a recently described entity of uncertain histogenesis (27). Some authors have postulated that these lesions represent undifferentiated epithelial malignancies and that they are part of the disease spectrum of *SMARCA4*-deficient carcinoma, particularly since many of the tumors studied have been identified to harbor smoking related genomic signatures (101). The tumors thus far designated as sarcomas tend to have different clinicopathologic parameters than the carcinomas, including different age ranges, extrapulmonary locations, and a different pattern of metastasis suggesting they represent a distinct clinicopathologic entity (27,102,103). A small percentage of these lesions also occur in the absence of a smoking history making their exact histogenesis unclear (101). Whether these undifferentiated tumors represent epithelial malignancies, mesenchymal malignancies or both still requires some additional clarification. While it remains unclear whether these tumors definitively arise as primary mediastinal sarcomas, the tumors can commonly involve the mediastinal compartment and some show no evidence of pulmonary involvement raising the possibility that some may indeed occur as primary mediastinal tumors (27,101-103). Given that a large percentage of these lesions involve the mediastinum they are included here as pathologists should include them in the differential diagnosis of poorly differentiated sarcomas with rhabdoid morphology.

Molecularly these lesions are characterized by biallelic inactivation of the *SMARCA4* (SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4) gene that codes for Brahma-related gene 1 (BRG1); a member of the SWI/SNF complex (100,101). Inactivation occurs primarily through frameshift or nonsense mutations, although missense mutations, deletions, and splice site mutations have been identified as well (104). Mutations in *TP53*, *NF1*, *KRAS*, *STK11*, and *KEAP1* may also occur in addition to the mutations in *SMARCA4* (101,104). Cytogenetically the tumors can also show various copy number abnormalities, copy neutral loss of heterozygosity, and a generally complex genomic profile expected of a high-grade malignant neoplasm (104). Loss of *SMARCA4* leads to dysregulation of the SWI/SNF

(BAF) complex; a chromatin remodeling complex that is frequently mutated across many human cancers including synovial sarcoma, epithelioid MPNST, epithelioid sarcoma, and extrarenal rhabdoid tumor (*Figure 4A*) (105,106). Identification of the various mutations and complex genomic profiles of these tumors requires examination with advanced molecular techniques such as sequencing or a combination of various modalities (including array to identify copy neutral loss of heterozygosity), however the diagnosis can usually be made based on morphology combined with IHC showing loss of BRG1 expression (*Figure 4B,C*) (102,103).

SFT

SFT is a fibroblastic mesenchymal tumor that can occur with some frequency within the structures of the thorax including the mediastinum (107-109). The tumor is characterized by a pathognomic *NAB2-STAT6* fusion oncogene arising from a recurrent intrachromosomal rearrangement on chromosome 12q (109). Although most tumors follow an indolent clinical course, malignant variants or high-risk tumors have been reported, sometimes in association with additional genetic alterations such as *TP53* and *TERT* promoter mutations (110-112). The fusion may be identified through sequencing, FISH, or reverse transcriptase PCR (107,108), however due to the close proximity of the genes involved in the translocation it may be missed by FISH. The diagnosis is also usually facilitated by IHC for STAT6 which is expressed in nearly 100% of tumors (111).

Less common mediastinal sarcomas

A wide diversity of other less common sarcoma subtypes have been reported to occur in the mediastinum as primary mediastinal tumors (*Table 1*) (6,8,9,11-24,113-115). These include sarcomas such as non-Ewing small round blue cell sarcomas and undifferentiated pleomorphic sarcomas, vascular tumors such as angiosarcoma and epithelioid hemangioendothelioma, bone tumors such as osteosarcoma, chondrosarcomas, and chordoma as well as various other more esoteric tumors such as follicular dendritic cell sarcoma, malignant PEComa, clear cell sarcoma and alveolar soft part sarcoma. Strict clinicopathologic correlation is required to rule out metastatic lesions from other primary soft tissue sites in these cases. Many of these lesions harbor recurrent or specific genetic abnormalities that can be identified through various

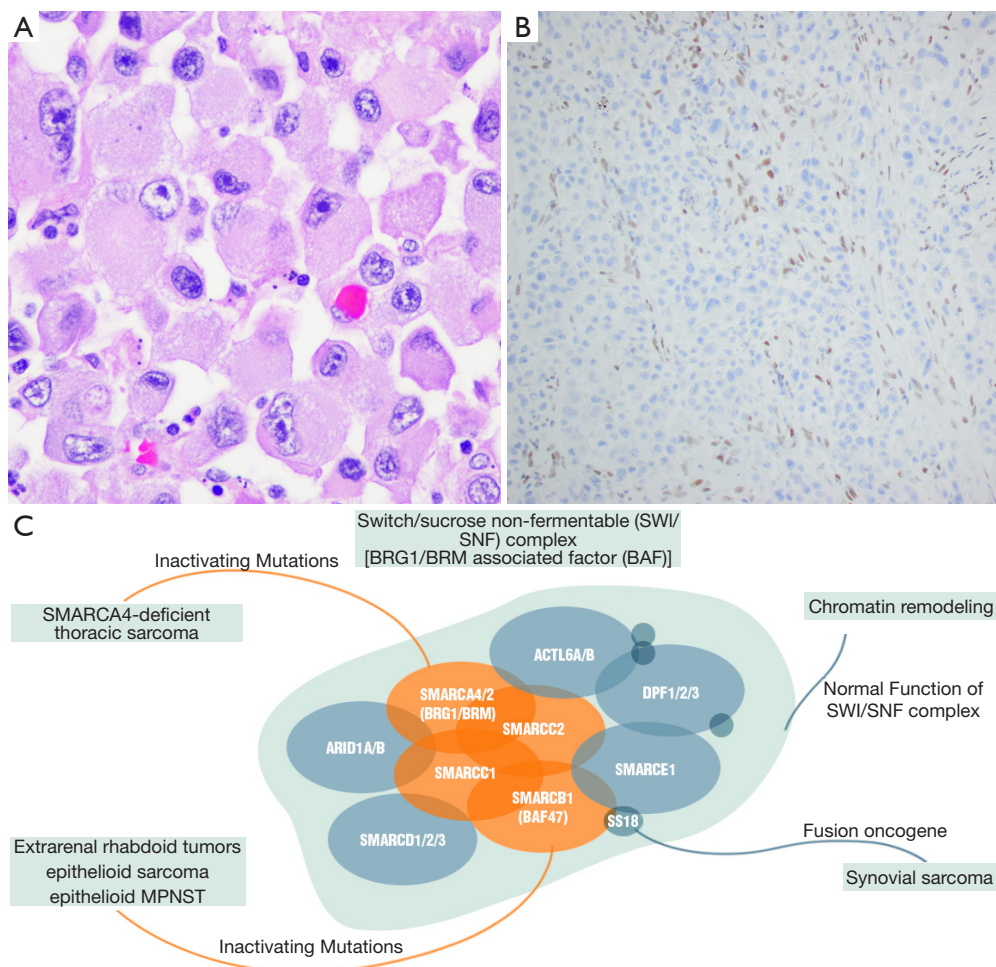


Figure 4 *SMARCA4*-deficient thoracic sarcoma. (A) Microscopic image (600 \times , hematoxylin and eosin) shows large epithelioid appearing cells with atypical nuclei, prominent nucleoli, and characteristic voluminous, sometimes eccentrically placed, eosinophilic cytoplasm consistent with “rhabdoid” morphology. (B) IHC for BRG1 shows complete loss of staining within the tumor cells indicating loss of function of the *SMARCA4* gene, magnification: 20 \times , BRG1 immunohistochemistry. (C) Graphic depicting the mammalian SWI/SNF (BAF) complex; as shown in the schematic, loss of function of *SMARCA4* through inactivating mutations is involved in the oncogenesis of *SMARCA4*-deficient thoracic sarcoma. Of note other sarcomas occurring within the mediastinum also contain alterations within this complex including synovial sarcoma, epithelioid sarcoma, epithelioid MPNST, and extrarenal rhabdoid tumors.

molecular or cytogenetic techniques (Table 4). One such example is a less common variant of liposarcoma; myxoid liposarcoma. Unlike well-differentiated and dedifferentiated liposarcomas, myxoid liposarcomas follow a different oncogenic mechanism characterized by a t(12;16)(q13;p11) that leads to the formation of the fusion oncogenes, *FUS-DDIT3* (95% of cases) or *EWSR1-DDIT3* (5% of cases) (75). Despite these recurrent genetic abnormalities, it is worth noting that many lesions in the less common category may be diagnosed on clinicopathologic grounds, however the use of ancillary molecular testing to confirm diagnoses and help

identify difficult lesions is always beneficial if available.

Conclusions

Mediastinal sarcomas represent a heterogeneous group of rare tumors. There is a small subset that appears to occur more frequently compared to some of the less common lesions. Many of these mediastinal sarcomas have specific, recurrent genetic abnormalities that can be identified through various molecular techniques to aid in diagnosis. These genetic abnormalities are often similar to their

Table 4 Translocations and other genetic alterations in less common mediastinal sarcomas

Tumor type	Genetic abnormality	Gene fusion or amplification product
Low-grade fibromyxoid sarcoma	t(7;16)(q32-33;p11), t(11;16)(p11;p11)	<i>FUS-CREB3L2</i> , <i>FUS-CREB3L1</i>
Myxoid/round cell Liposarcoma	t(12;16)(q13;p11), t(12;22)(q13;q12)	<i>FUS-DDIT3</i> , <i>EWSR1-DDIT3</i>
Alveolar soft part sarcoma	t(X;17)(p11;q25)	<i>ASPCR1-TFE3</i>
Translocation associated small round blue cell sarcomas	t(4;19)(q35;q13), t(10;19)(q26;q13), paracentric inv(X)(p11.4p11.22)	<i>CIC-DUX4</i> , <i>CIC-DUX4</i> , <i>BCOR-CCNB3</i>
Extrarenal rhabdoid tumor	Loss of <i>SMARCB1 (INI1)</i> secondary to biallelic loss of function mutations or heterozygous mutations in subunits of the SWI/SNF (BAF) complex	
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14), t(1;13)(p36;q14), t(2;2)(q35;p23), t(2;8)(q35;q13)	<i>PAX3-FOXO1</i> , <i>PAX7-FOXO1</i> , <i>PAX3-NCOA1</i> , <i>PAX3-NCOA2</i>
Embryonal rhabdomyosarcoma	Loss of heterozygosity on 11p15.5	
Epithelioid hemangioendothelioma	t(1;3)(p36;q25), t(X;11)(q22;p11)	<i>WWTR1-CAMTA1</i> , <i>YAP1-TFE3</i>
Epithelioid sarcoma	Loss of <i>SMARCB1 (INI1)</i> secondary to biallelic loss of function mutations or heterozygous mutations in subunits of the SWI/SNF (BAF) complex	
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12), t(9;17)(q22;q11), t(9;15)(q22;q21)	<i>EWSR1-NR4A3</i> , <i>TAF15-NR4A3</i> , <i>TCF12-NR4A3</i>
Chondrosarcoma	Somatic point mutations in <i>IDH1</i> and <i>IDH2</i>	
Mesenchymal chondrosarcoma	Del(8)(q13.3;q21.1), t(1;5)(q24;q32)	<i>HEY1-NCOA2</i> , <i>IRF2BP2-CDX1</i>
Osteosarcoma	Complex karyotypes with numerous structural changes reported and multiple types of mutations across many genes	
Follicular dendritic cell sarcoma	Often complex karyotypes, loss of function alterations in <i>NFKBIA</i> , <i>CYLD</i> , <i>CDKN2A</i> , <i>RB1</i> , <i>CD274</i> , <i>PDCD1LG2</i> and <i>BRAF</i> V600E mutations	Small subset with <i>MDM2</i> amplification
Undifferentiated pleomorphic sarcoma	Rare targetable fusions identified in some cases, complex karyotypes, mutations in <i>TP53</i> , <i>ATRX</i> , <i>RB1</i> , however no recurrent genetic abnormalities	

extramediastinal bone and soft counterparts.

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