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Neurogenic tumours of the posterior mediastinum and differential diagnosis considerations

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The mediastinal compartment harbours vital organs and structures, including the heart, great vessels, major airways, and thymus. These structures are embedded in and associated with soft-tissue elements consisting of adipose and fibro-collagenous tissue in which soft-tissue tumours may develop. A detailed inventory of soft-tissue tumours that may be encountered in the mediastinum based on the WHO 2013 classification was published in 2015. In addition, several comprehensive reviews on mediastinal soft-tissue pathology are available, including reviews focusing specifically on a single tumour type. This review will focus on primary neurogenic and spindle cell tumours of the somatic soft tissue of the posterior mediastinum and provide a discussion of the pertinent differential diagnoses.

Introduction

Soft-tissue tumours (STTs) in the mediastinum comprise almost the complete spectrum of entities encountered elsewhere in the body, with a few organ-specific exceptions, but with markedly different frequency. Some STTs are more specific for the mediastinum, such as the myxoid pleomorphic liposarcoma. This review will focus primarily on STTs located in the posterior mediastinum. A detailed inventory of soft-tissue tumours that may be encountered in the mediastinum based on the WHO 2013 classification was published in 2015.[1,2,3] In addition, several comprehensive reviews on mediastinal soft-tissue pathology are available, including reviews focusing specifically on a single tumour type.[4,5,6,7,8] The spectrum of STTs in the posterior mediastinum is skewed towards those with neurogenic/ganglionic differentiation, given the topological location of elements of the autonomic nervous system and spinal nerve structures in the posterior aspect of the mediastinum. This is particularly the case for the paediatric population, where the vast majority of mesenchymal tumours are of neural crest origin.[9] Peripheral nerve sheath tumours may also arise in other compartments of the mediastinum, given the presence of larger nerve trunks, such as the vagus nerve.

The neurogenic STTs in the posterior mediastinum thus may originate from neuroblastic cells, elements of the sympathetic nervous system (paraganglionic), or from nerve sheath elements (Schwann cells, perineurial cells).[1] The spectrum of neurogenic tumours is summarized in Table 1. The specific entities are further discussed in detail.

Neuroblastic tumours

The neuroblastic tumours are essentially tumours of childhood with rare cases diagnosed in adults. These tumours show a spectrum of differentiation, more or less recapitulating the formation of ganglionic structures in which neuronal and Schwannian cells

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Table 1. Neurogenic tumours in the posterior mediastinum (adapted from den Bakker *et al.*)[2]

Derivation	Type	Behaviour	Age of onset
Neural tumours of the mediastinum			
Nerve sheath/Schwannian	Schwannoma	Benign	Adult
	Cellular schwannoma	Benign	Adult
	Malignant melanotic psammomatous schwannoma	Malignant	Adult
	Nerve sheath myxoma	Benign	ND
	Hybrid schwannoma – perineurioma	Benign	ND
	Neurofibroma	Benign	Adult
	Plexiform neurofibroma	Benign	Adult
	MPNST	Malignant	Adult
	Malignant Triton tumour	Malignant	Adult
	Granular cell tumour	Benign	Adult
	Malignant granular cell tumour	Malignant	Adult
Ganglionic/autonomous nervous system			
Sympathetic ganglia, neuronal/neuroblastic	Ganglioneuroma	Benign	Adult/young adult
	Neuroblastoma	Malignant	Paediatric
	Ganglioneuroblastoma	Malignant	Paediatric
Paraganglioma	Paraganglioma	Benign/malignant	Adult

MPNST, malignant peripheral nerve sheath tumour; ND, not determined.

participate. The tumour constituents, neuroblastic/neuronal-ganglion and Schwannian cells, vary in proportion and maturation, the composition of which underlies the current classification set out by the International Neuroblastoma Pathology Committee.[10,11] The clinical, molecular, and diagnostic features are well established. A brief discussion of the various entities is provided below; specific details can be found in several comprehensive reviews.[12] Neuroblastoma, ganglioneuroblastoma, intermixed type, and ganglioneuroma are considered tumours showing a spectrum with increasing Schwannian component, while ganglioneuroblastoma, nodular type (composite) is composed of multiple components originating from multiple developing clonal precursor elements.

NEUROBLASTOMA

Neuroblastoma is a tumour of primitive neuroblastic cells which, depending on the level of differentiation, ranges from a small blue round cell tumour (undifferentiated) to a proliferation of more mature ganglionic cells (differentiating type) in a neuropil background (stroma consisting of neurofibrillary matrix composed of unmyelinated axons and dendrites), with an intermediate poorly differentiated type with some ganglionic maturation and the presence of Homer–Wright pseudorosettes.[12] Neuroblastoma is typically a paediatric tumour; the vast majority are diagnosed in young children,[12] primarily occurring in the adrenal gland and abdominal autonomous nervous system, but ~20% of cases are located in the posterior mediastinum. Rarely, primary thymic cases (i.e. located in the anterior mediastinum) may occur.[13,14] The tumours may reach a large size and vary from circumscribed to infiltrative lesions. The histological criteria for diagnosing neuroblastoma are well established.[11] Briefly, undifferentiated neuroblastoma is composed of small cells with slightly coarse chromatin arranged in sheets with a degree of nesting (Figure 1A,B). Ganglionic differentiation by definition is not seen and neurofibrillary stroma is absent. Rarely, anaplastic cells may be present, which may be associated with *MYCN* amplification.[12] In the poorly differentiated subtype, neurofibrillary stroma is present and there may be minor maturation towards

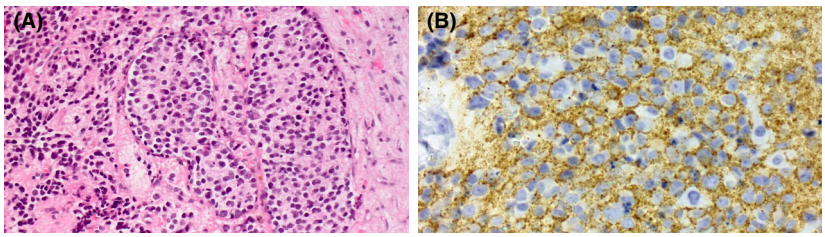

Figure 1. (A,B) Neuroblastoma. Posterior/superior mediastinal tumour in a 1-year-old infant showing the typical appearance of neuroblastoma composed of immature neuroblastic cells with a high nuclear–cytoplasmic ratio and slightly coarse chromatin and indistinct nucleoli (A, haematoxylin and eosin [HE] stain). Immunohistochemistry showing diffuse synaptophysin staining (B).

ganglionic cells (<5%). More extensive ganglionic differentiation, in which large cells have eccentrically placed vesicular nuclei with distinctive large nucleoli placed within abundant eosinophilic cytoplasm, is present, set within a background of neurofibrillary stroma. As expected, the immunohistochemical profile of neuroblastoma is a consequence of its neural crest origin, with expression of CD56, synaptophysin, chromogranin, neuron-specific enolase (NSE), and PGP9.5. More specific markers include NB84, tyrosine hydroxylase, and PHOX2B, with the latter reported as being the most sensitive and specific marker.[15] The molecular features of neuroblastoma have to a large extent been elucidated.[12] Most important aberrations include *MYCN* amplification in up to 25% of patients and implying aggressive disease, *ALK* mutation or amplification and mutations in genes involved in telomere length regulation, *ATRX* and *TERT*.

GANGLIONEUROBLASTOMA

Ganglioneuroblastoma is primarily defined by the presence of a distinct component (>50%) of Schwannian stroma, containing Schwann cells and fibroblasts. There may be ganglionic cell differentiation, but this is not required for the diagnosis. In addition, there may be neurofibrillary stroma (neuropil) and immature neuroblastic cells in variable stages of differentiation. Two subtypes of ganglioneuroblastoma are recognized that are thought to have a different pathogenesis. The *intermixed type* has Schwannian stroma with scattered nests of neuroblastic cells. The *nodular type* contains segregated nodules of neuroblastoma (without Schwannian stroma) combined with ganglioneuroblastoma elements and ganglioneuroma tissue. The latter subtype is believed to arise from several individual clones that differentiate along different lines.

GANGLIONEUROMA

Immature neuroblastic cells are not present in ganglioneuroma. Mature ganglion cells, which sometimes display brown melanin pigment in their cytoplasm, are seen within a background of fibrillary or Schwannian stroma (mature subtype) (Figure 2A,B). While neuroblastoma and ganglioneuroblastoma are typically tumours of young children, ganglioneuroma is seen in adolescents and young adults. In the review by Zhuang *et al.* of 71 published cases, the median age was 11 years, with an average age of 21 years (range: 2–62 years), and a female predominance (ratio: 1.7).[16] Given the histological continuum of maturing neuroblastic tissue in neuroblastoma and ganglioneuroblastoma, it has been suggested, but not

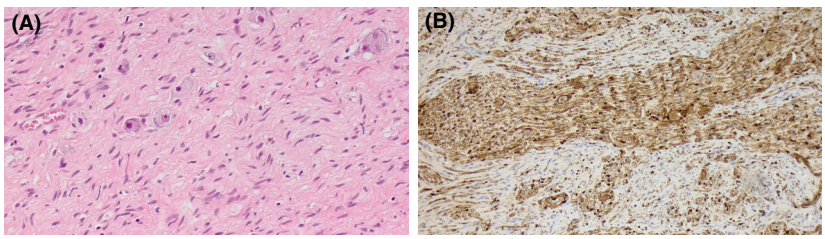

Figure 2. (A,B) Ganglioneuroma. Resected large tumour from the posterior mediastinum of a 22-year-old female with large ganglionic cells with copious cytoplasm and large nuclei with a single large nucleolus in a background of Schwann cells (A, HE stain), which show diffuse S100 positivity (B).

universally accepted, that ganglioneuroma is in fact a fully matured neuroblastoma.[17] Because of the mixed composition of ganglioneuroblastoma and partial histological overlap with ganglioneuroma, distinguishing these entities in a biopsy may be very difficult if not impossible.[18,19] This is particularly the case for ganglioneuroblastoma nodular type, in which biopsy sampling of a component may yield fully mature ganglioneuromatous tissue. Establishing a diagnosis in these cases will generally require integration of histology, imaging, and laboratory investigations.[18] The outcome of neuroblastic tumours is highly correlated with histology. Ganglioneuroma and ganglioneuroblastoma, intermixed type, generally behave in a benign fashion and often do not produce any symptoms. It has been suggested that asymptomatic patients with favourable parameters may not require surgery and could be followed up closely.[20] The prognosis of immature neuroblastic tumours (neuroblastoma and ganglioneuroblastoma, nodular type) is highly variable. It is noted that the prognosis of mediastinal neuroblastic tumours is more favourable than of those in other locations.[12] The risk of progressive disease of primitive neuroblastic tumours depends on multiple factors, including age, stage, tumour histology, *MYCN* amplification, and tumour cell ploidy, which are incorporated in the classification systems of the International Neuroblastoma Risk Group and Children's Oncology Groups, and which have been combined in the Revised Neuroblastoma Risk Classification System.[21–23]

As the histology and clinical setting of neuroblastic tumours is distinct, the histological differential diagnosis is limited and will predominantly pose problems in tumours that are poorly differentiated or arise in an unusual setting, such as in adults. Moreover, as patients with these rare tumours will almost always be evaluated in specialized paediatric centres with expertise in diagnosing and treating neuroblastic tumours, establishing the correct diagnosis will therefore seldom be problematic.

Conventional neuroblastoma is a small blue round cell tumour (SBRCT). The differential diagnosis in the posterior mediastinum therefore may include Ewing sarcoma/peripheral neuroectodermal tumour (ES/PNET), rhabdomyosarcoma, lymphoblastic lymphoma, poorly differentiated synovial sarcoma (SyS), and non-Hodgkin lymphoma, and may be particularly challenging in undifferentiated neuroblastomas lacking neurofibrillary stroma or rosette formation. ES/PNET may arise in the mediastinum, including the posterior mediastinum.[2,24,25] Distinguishing ES/PNET from neuroblastoma is generally accomplished by immunohistochemistry (Table 2). ES/PNET stains for CD99 and NKX2.2 (Figure 3A,B), but both markers may rarely be positive in neuroblastoma.[26,27] Recently, GATA-3 was shown the be a promising marker for distinguishing neuroblastoma and ES/PNET, although care should be taken to exclude other SBRCTs, as T-cell lymphoblastic lymphoma similar to neuroblastoma was shown to stain for GATA-3 and otherwise shows an overlapping immunoprofile, with ES/PNET sharing expression of CD99.[28,29] A highly specific marker for neuroblastoma is PHOX2B, which in large series failed to stain in other SBRCTs, including ES/PNET.[15,30] Molecular identification of *EWSR1* gene aberrations may be useful in difficult cases, confirming the diagnosis of ES/PNET. Rhabdomyosarcoma can be distinguished from neuroblastoma by desmin and myogenin immunoreactivity (Figure 4A,B).[31]

Table 2. Typical immunohistochemical profile of neuroblastoma and differential diagnoses in the posterior mediastinum

	PHOX2B	CD99	GATA3	NKX2.2	TdT	Desmin	Myogenin	SSX	TLE1	Molecular aberration
NBL	+	–	+	–	–	–	–	–	ND	MYCN amplification (25%); ALK mutation/amplification (10–25%)
ES/PNET	–	+	–	+	–	–/+	–	–	–/+*	*EWSR1* rearrangement
EmRMS AlRMS	–	+/–	–	–	–	+	–	–	–	*PAX3-FOXO1*, PAX7-FOXO1 rearrangement
PD-SyS	–	+	–	–	–	–	–	+	+	t(X;18) *SS18/SSX1/2/4* rearrangement
LBL	–	+	+	–	+	–		–	–	

AlRMS, Alveolar rhabdomyosarcoma; EmRMS, Embryonal rhabdomyosarcoma; ES/PNET, Ewing sarcoma/peripheral neuroectodermal tumour; LBL, Lymphoblastic lymphoma); NBL, Neuroblastoma; ND, No data; PD-SyS, Poorly differentiated synovial sarcoma.
*Antibody dependent.

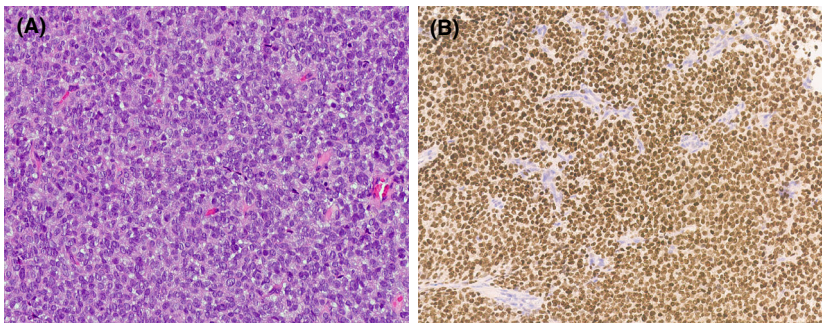

Figure 3. (A,B) PNET. A highly cellular SBRCT (A, HE stain) with NKX2.2 staining (B) diagnosed as PNET/Ewing sarcoma.

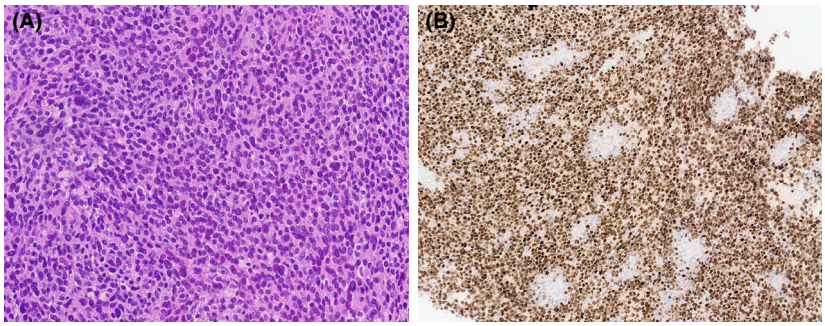

Figure 4. (A,B) Rhabdomyosarcoma. Small blue round cell tumour in the posterior mediastinum (A, HE stain) devoid of morphological clues of differentiation. Strong myogenin staining confirms rhabdomyosarcoma (B).

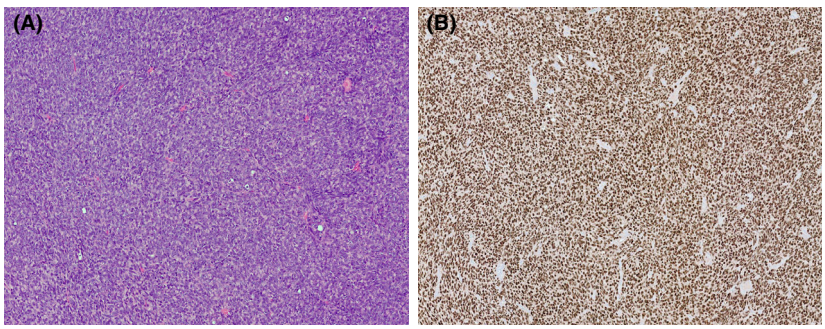

Figure 5. (A,B) Poorly differentiated synovial sarcoma. While conventional SyS is a cellular spindle cell tumour, PD-SyS presents as an SBRCT (A, HE stain). The specific SSX-SS18 translocation can reliably be identified by immunohistochemistry (B, SS18 stain).

However, primary rhabdomyosarcoma of the posterior mediastinum is exceptionally rare, with only a single case reported.[32] Lymphoblastic lymphoma is readily distinguished from neuroblastoma and other SBRCTs by an appropriate immunohistochemistry panel, although care must be taken with CD99, which is positive in ES/PNET and GATA-3, which will mark both neuroblastoma and T-cell lymphoblastic lymphoma.[28] Poorly differentiated SyS, which appears to be more common in the mediastinum than elsewhere in the body,[4] will not stain for the highly specific markers for neuroblastoma, such as PHOX2B. Conversely, recently highly specific immunohistochemical markers associated with the specific t(X;18) *SSX-SS18* molecular translocation in SyS were reported, which may be a useful adjunct tool to distinguish SyS and neuroblastoma (Figure 5A,B).[33–36] Theoretically, desmoplastic small blue round cell tumour (DSRCT) would also enter the differential diagnostic spectrum of neuroblastoma. However, only a single case has been reported in the anterior mediastinum, while to date DSRCT has not been reported in the posterior mediastinum.[37]

Unusual histologic variants of neuroblastoma include large cell/anaplastic neuroblastoma. These tumours with pleomorphic large nuclei and mitotic activity may be difficult to recognize as neuroblastoma. Identification of *MYCN* abnormalities is common in this subset.[33,38] To date, large-cell/anaplastic neuroblastoma has not been reported in the mediastinum.

The differential diagnosis of neuroblastic tumours with maturation, such as ganglioneuroblastoma, exemplified by the presence of neurofibrillary or Schwannian stroma, is more extensive and may contain SSTs with a spindle cell morphology, in particular tumours of nerve sheath derivation. In this context, schwannoma and neurofibroma have to be considered. The histology of mediastinal schwannoma is similar to other locations. Schwannoma does not contain ganglionic cells, nor does it contain immature neuroblastic cells, setting it apart from ganglioneuroma, intermixed and nodular types, respectively. In cases of ganglioneuroblastomas (intermixed type) devoid of ganglionic cells, diffuse and strong staining with S100 favours a diagnosis of schwannoma. Recognition of the cytological features and matrix composition of neurofibroma readily distinguishes this tumour from ganglioneuroblastoma devoid of ganglion cells.

PARAGANGLIOMA

Paraganglioma may occur in the posterior mediastinum and is thought to arise from the sympathetic nervous system. These tumours appear slightly more common in males and occur over a wide age range. Paraganglioma in the posterior mediastinum is more frequently functional than those in other compartments of the mediastinum, with secretion of catecholamines, or rarely other substances, which will often, but not invariably, cause systemic symptoms.[39–42] These tumours may grow to reach a large size, which may result in nonfunctional symptoms owing to their space-occupying properties.[43]

Paraganglioma is associated with inherited cancer syndromes in 25–50% of cases. Several germline genetic aberrations are known to underlie the development of paragangliomas; this should be borne in mind when paraganglioma is diagnosed in younger individuals (<45 years of age) or when multiple tumours are present.[44] Germline mutations in succinate dehydrogenase (SDH) genes (in particular SDHD and SDHB) may underlie the development of paraganglioma. Paraganglioma may further occur in von Hippel–Lindau syndrome, neurofibromatosis (NF) type 1, multiple endocrine neoplasia (MEN) 2 syndrome, Carney's triad, and in patients with recently described germline mutations of *DNMT3A* and *DLST*.[44–46] The histology of paraganglioma in the posterior mediastinum is no different from that in other locations (Figure 6A–C). A nested growth pattern of epithelioid cells with vesicular nuclei and copious eosinophilic to basophilic slightly granular cytoplasm, with a delicate fibrovascular stroma is prototypical, forming the commonly quoted "Zellballen". Mitotic activity is generally very low and necrosis is not present in untreated cases. Immunohistochemistry will typically show a neuroendocrine profile, with positive staining for chromogranin A, synaptophysin, CD56, and INSM1.[47] Additional useful markers include GATA-3 and S100, the latter of which will highlight the slender sustentacular cells. The underlying genetic tumour defect, either germline or somatic, may also be identified by immunohistochemistry by showing loss of expression of target genes.[48,49] Negative stains include cytokeratins, which may be included in a panel to rule out other neuroendocrine tumours. The clinical behaviour of paraganglioma is notoriously difficult to predict. Most paragangliomas will behave in a benign fashion, but metastasis occurs in 20% of patients.[44] Scoring systems based on histology, biochemical, and genetic features provide some indication of the risk of progressive disease, but are less than optimal. The differential diagnosis of paraganglioma arising in the posterior mediastinum is limited and will in most cases by resolved by appropriate use of immunohistochemistry. In contrast to paraganglioma, low-grade neuroendocrine tumours (carcinoid tumours) stain for cytokeratin, do not contain S100 positive sustentacular cells, and do not stain for GATA-3.[29] Neuroblastic tumours do not have the typical nested growth pattern of paraganglioma, do not contain sustentacular cells, and will have a characteristic neurofibrillary or Schwannian stroma. In equivocal cases, specific immunohistochemical markers may be applied; however, PHOX2B has also been reported to be positive in paraganglioma.[28,50] Alveolar rhabdomyosarcoma may show a nested growth pattern but lacks sustentacular cells and will stain for desmin and myogenin. Moreover, alveolar rhabdomyosarcoma has not been reported in the posterior mediastinum.[2]

Nerve sheath tumours

Collectively, nerve sheath tumours (NST) arise from constituent cells of the nerve sheath, including perineurial cells, fibroblasts, and Schwann cells that support the nerve fibres. Nerve sheath tumours thus may have a mixed composition as in neurofibroma,

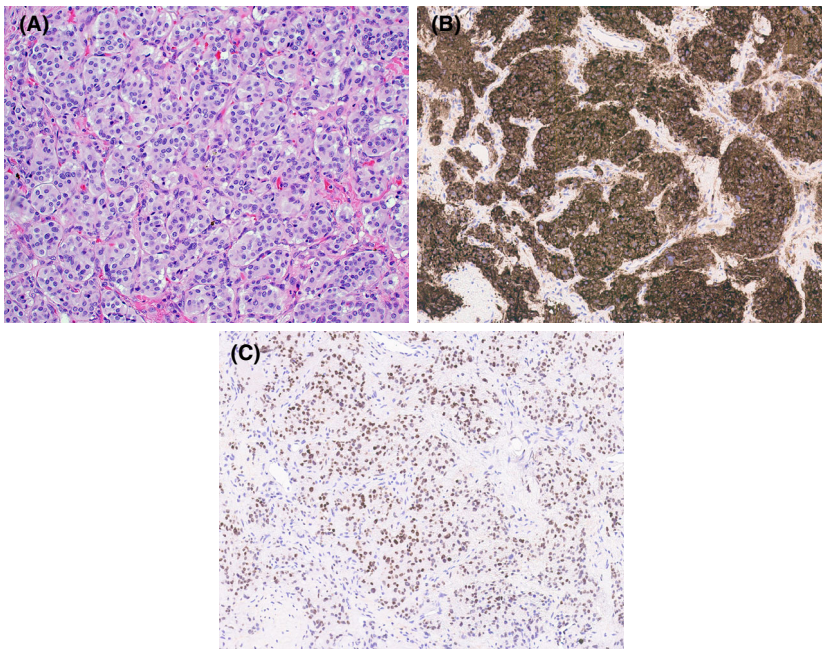

Figure 6. (A–C) Paraganglioma. The nested architecture resulting in the "Zellballen" pattern is seen in the HE stain (A). Confirmation of the diagnosis is achieved by staining for synaptophysin (B) and/or GATA-3 (C).

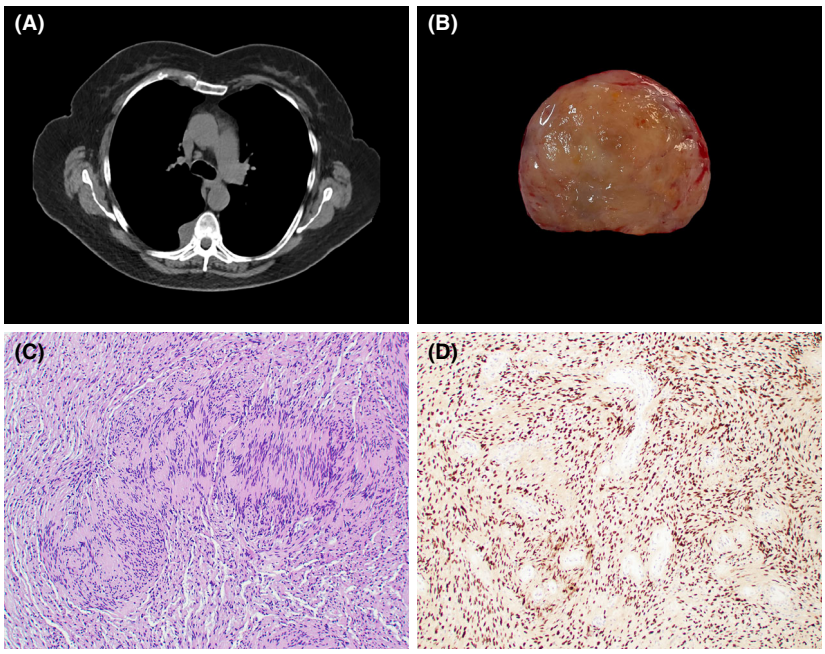

Figure 7. (A–D) Schwannoma. Computed tomography (CT) image (A) of a paravertebral mass in the posterior mediastinum. The resected specimen (B) shows a circumscribed gelatinous tumour. Typical palisading of elongated nuclei results in the characteristic Verocay bodies (C). Strong universal Sox10 staining is supportive of the schwannoma diagnosis (D).

or may be more singularly composed, such as in schwannoma and perineurioma.

Schwannoma is the most common mediastinal neural tumour and is particularly prevalent in the posterior mediastinum, owing to its origin from spinal nerve roots. The histology of mediastinal schwannoma is similar to that in other locations, presenting as an encapsulated tumour composed of spindle cells

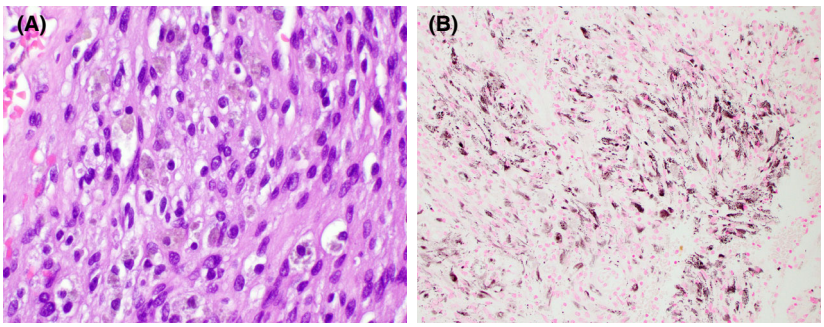

Figure 8. (A,B) Melanotic schwannoma. Cellular spindle cell proliferation with pale tan melanin pigmentation (A, HE stain), highlighted by the Masson-Fontana stain (B).

with typical variability in cellularity (Antoni A and B areas), tumour cell palisading (Verocay bodies), hyalinization of vessel walls, and sparse scattered inflammatory cells (Figure 7A–D). Degenerative ("ancient") changes may occur, manifested by stromal changes with oedema, fibrosis, cystic changes, and mild cytologic atypia. Extension through spinal root foramina may result in so-called dumbbell tumours. The tumours may reach a large size before producing symptoms.[43] Variants of schwannoma, in particular the *cellular variant*, which does not show the typical alternating hyper- and hypocellular areas and Verocay bodies, appears particularly prevalent in the posterior mediastinum.[51] *Melanotic schwannoma* (malignant melanotic nerve sheath tumour; psammomatous melanotic schwannoma) is an unusual variant of schwannoma characterized by melanin pigmentation, absence of encapsulation, Antoni A and B areas, and Verocay bodies (Figure 8A,B). Melanotic schwannoma may be associated with Carney complex; in these cases psammomatous calcifications may be present.[52] The melanotic pigmentation is mirrored by the immunohistochemical profile, as these tumours in addition to S100 and SOX10 positivity will stain with Melan-A and HMB45.[53] Melanotic schwannoma is frequently associated with spinal nerve roots and thus frequently occurs in the posterior mediastinum. In contrast to the conventional type, melanotic schwannoma may metastasize and is considered a malignant tumour. Other rare variants such as *neuroblastoma-like schwannoma* and *microcystic schwannoma* have not been reported in the mediastinum to date.

As may be expected, neurofibroma is, similar to schwannoma, particularly found in the posterior mediastinum. Because these are usually associated

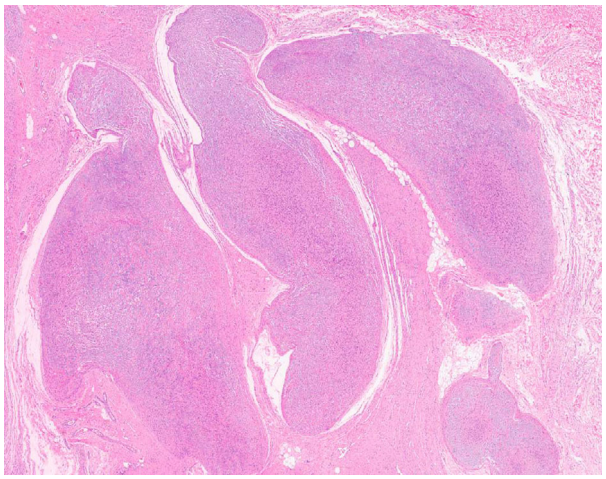

Figure 9. Mediastinal plexiform neurofibroma. Broad circumscribed bundles of short spindle cells embedded in loose connective tissue containing in part a similar cell proliferation of fibroblasts, Schwann cells, and perineurial cells.

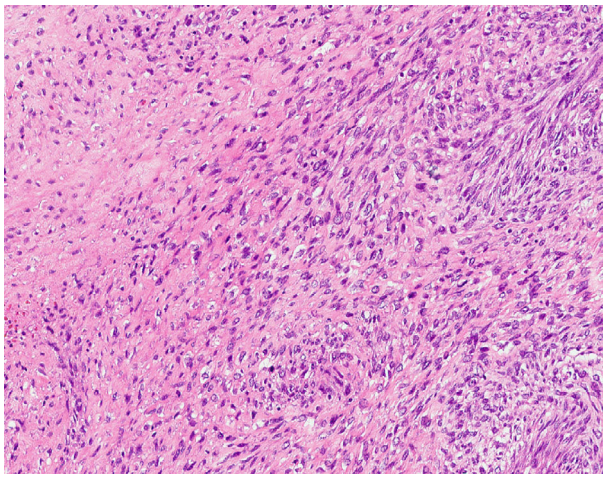

Figure 10. Malignant peripheral nerve sheath tumour. Cellular atypical spindle cell proliferation with few morphological diagnostic clues. Establishing a diagnosis will generally require ancillary tests.

Table 3. Typical immunohistochemical profile of MPNST differential diagnoses in the posterior mediastinum

	IHC										
Tumour	CK	S100	H3K27me3	Desmin	SSX	TLE1	Alk1	MDM-2	Beta-catenin	STAT6	Mol
MPNST	–	–/+	Loss (50–90%)	–/+*	–	–/+	–	–	–	–	*SUZ12/EED* mutation (inactivation)
SyS	+/–	–	Loss (0–60%)	–	+	+	–	–	–	–	t(X;18) *SS18/SSX1/2/4*
LMS	–/+	–	–	+	–	–	–	–	–	–	
IMT	–/+	–	–	–/+	–	–	+	–	–	–	*ALK* rearrangement
SFT	–	–	ND	–	–	–	–	–	–	+	*NAB2-STAT6*
dd-LiS	–	–	–	–/+†	–	–	–	+	–	–	*MDM-2* amplification
DF	–	–	–	–	–	–	–	–	+/– (70%)	–	*CTNNB1* mutation (85%)
Sarcomatoid mesothelioma	+/–	–	–	–	–	–	–	–	–	–	
Sarcomatoid carcinoma	+/–	–	–	–	–	–	–	–	–	–	

CK, Cytokeratin; dd-LiS, Dedifferentiated liposarcoma; DF, Desmoid fibromatosis; IMT, Inflammatory myofibroblastic tumour; LMS, Leiomyosarcoma; MPNST, Malignant peripheral nerve sheath tumour; ND, No data; SyS, Synovial sarcoma.
*Positive in cases with rhabdomyomatous features (Triton tumour).
†May be expressed in cases with smooth muscle features.

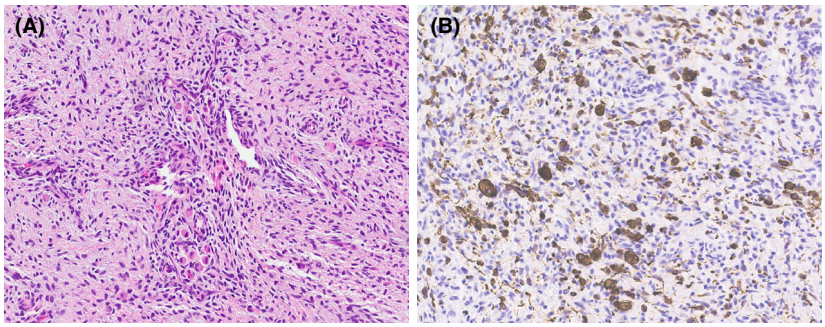

Figure 11. Malignant peripheral nerve sheath tumour with skeletal muscle differentiation. Spindle cell tumour with scattered rhabdoid cells with eccentrically placed nuclei and well-defined bright eosinophilic cytoplasm (A, HE stain). Skeletal muscle differentiation of the rhabdoid cells is further demonstrated by desmin staining (B).

with larger nerve trunks in the mediastinum they are often associated with NF1 and of plexiform type (Figure 9).[54–57] Atypia and worrisome histological changes may occur in neurofibroma; when these satisfy at least two of the following criteria: nuclear atypia, hypercellularity, variable loss of neurofibroma architecture, and appreciable mitotic activity (i.e. between 1–3 mitoses per high-power field), benign behaviour cannot be guaranteed, and the designation *atypical neurofibromatous neoplasm with uncertain biologic potential* (*ANNUBP*) should be used.[58] These tumours straddle the spectrum between atypical neurofibroma (those not meeting the criteria for ANNUBP) and low-grade malignant peripheral nerve sheath tumour (MPNST) (see below). Neurofibromas with these characteristics have been reported in the posterior mediastinum.[59]

Perineurioma in its pure form has not been reported in the posterior mediastinum; however, given its origin it is conceivable that these do exist in

this location but are underreported. Rare case reports with hybrid benign nerve sheath tumour with a perineurioma component have been reported.[60,61]

Frankly malignant nerve sheath tumours, MPNST, may arise in the posterior mediastinum, usually in the setting of NF1.[2] MPNST is typically a highly cellular fascicular spindle cell sarcoma with few diagnostic histological clues (Figure 10). Segregating MPNST from other spindle cell sarcomas will commonly require immunohistochemistry. Clinically, origin from a large nerve or occurrence in patients with NF1 are strong indicators for MPNST. In contrast to benign peripheral nerve sheath tumours, S100 and SOX10 will not, or only focally, stain MPNST. Loss of trimethylation of the lysine residue in position 27 of histone H3 (H3K27me3; an epigenetic change caused by mutations in the *SUZ12* or *EED* genes), which may be detected by immunohistochemistry, is a useful marker for MPNST but has relatively low sensitivity.[62–66] An appropriate immunohistochemical panel may serve to exclude other cellular spindle cell tumours (Table 3), which may arise in the posterior mediastinum, including SyS (*SSX-SS18* fusion or terminal SSX antibodies), leiomyosarcoma (LMS) (desmin, smooth muscle actin, caldesmon), solitary fibrous tumour (SFT) (STAT-6), and inflammatory myofibroblastic tumour (IMT) (ALK1).

An unusual variant of MPNST is characterized by epithelioid cytomorphology, rather than the conventional spindle cell type. In contrast to conventional MPNST, this variant shows diffuse S100 positivity.[67,68] To the best of our knowledge epithelioid MPNST has not been reported in the mediastinum.

So-called low-grade MPNST shows superficial morphological resemblance to neurofibroma but is more cellular, demonstrates cytological atypia, and has increased mitoses beyond the criteria for ANNUBP. In addition, these tumours have reduced S100/SOX10 expression, may show aberrant p53 staining, and loss of H3K27me3 staining.[58,65] Divergent differentiation may rarely be seen in MPNST, including rhabdomyosarcomatous (so-called *Triton tumour*) (Figure 11), chondroid and osseous differentiation.[69] Very rarely, true epithelioid differentiation with glandular morphology may be seen, raising the possibility of SyS.[2] However, to the best of our knowledge these features have not been described in posterior mediastinal MPNST.

Granular cell tumour (GrCT) is considered a neuroectodermal tumour and has been documented in the mediastinum, including the posterior mediastinum (Figure 12).[2] Although GrCT is generally benign, malignant cases in the posterior mediastinum are on record.[70,71]

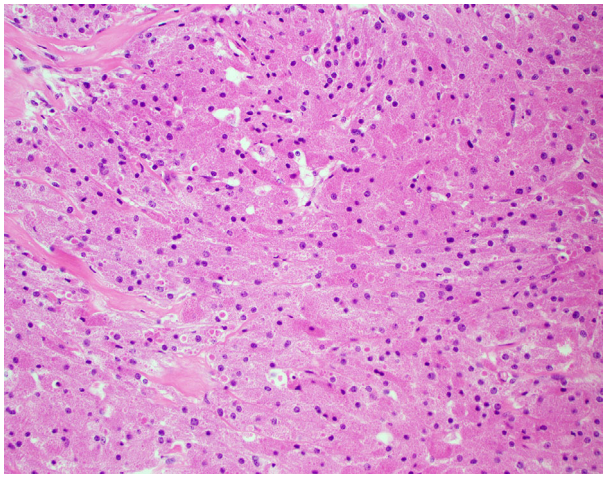

Figure 12. Granular cell tumour. Mediastinal tumour composed of sheets of cells with copious granular cytoplasm and centrally placed vesicular nuclei, often with a distinct single nucleolus.

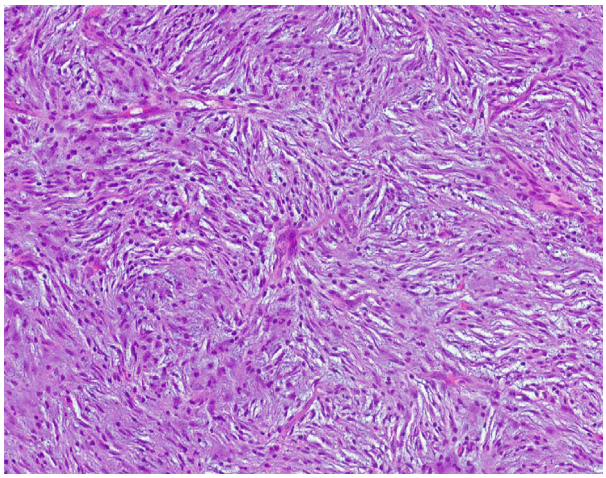

Figure 13. Inflammatory myofibroblastic tumour. Storiform cellular spindle cell tumour in the posterior mediastinum. Establishing a diagnosis will usually require immunohistochemistry.

The differential diagnosis of conventional MPNST in the posterior mediastinum will encompass other spindle cell neoplasms, in particular SyS, LMS, IMT, SFT, dedifferentiated liposarcoma (dd-LiS), and, for low-grade MPNST, desmoid fibromatosis, and pleomorphic sarcoma, not otherwise specified. Judicious use of an appropriate immunohistochemical panel will in most cases provide a diagnosis; in equivocal cases, molecular analysis may be of use (Table 3).

Although posterior mediastinal SyS is rare, its histology overlaps with MPNST.[4] Synovial sarcoma is typically a fascicular spindle cell sarcoma, which in its most characteristic form may have an epithelioid

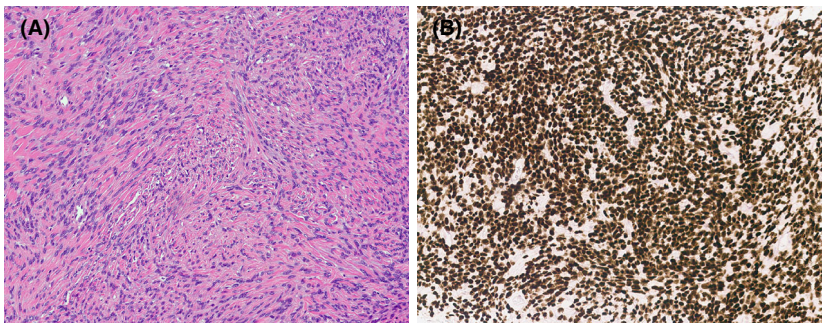

Figure 14. Solitary fibrous tumour. Fascicular-storiform moderately cellular tumour in a collagenous background, no atypia or necrosis (A, HE stain). The diagnosis is confirmed by STAT6 immunostaining (B).

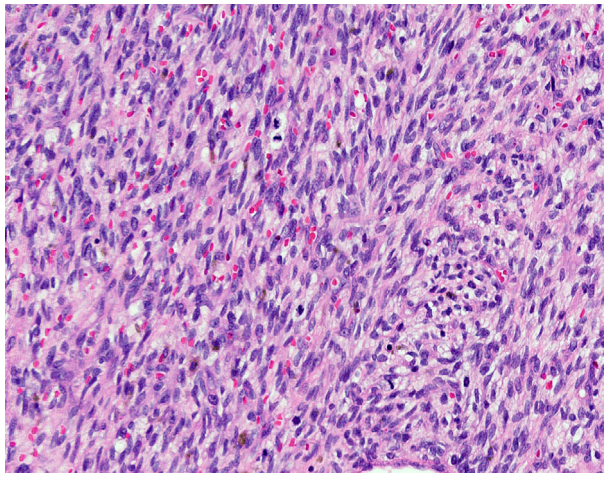

Figure 15. Dedifferentiated liposarcoma. A cellular spindle cell tumour from the posterior mediastinum. There are no histological clues in this example; the diagnosis was established by demonstrating MDM2 amplification.

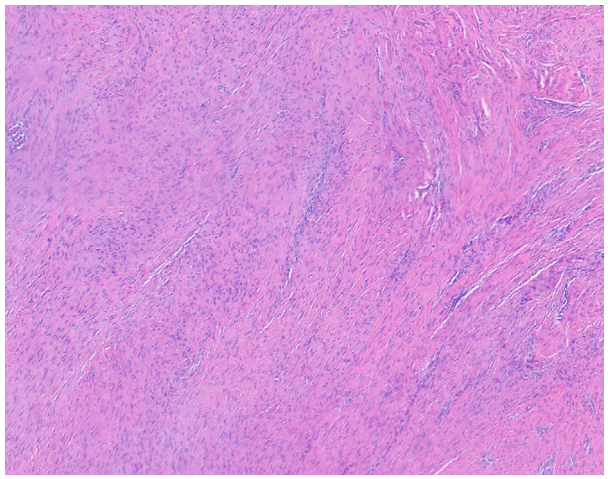

Figure 16. Desmoid fibromatosis. Moderately cellular bland spindle cell tumour composed of long sweeping fascicles of elongated cells. Delicate thin-walled blood vessels run parallel to the fascicles. Nuclear beta-catenin staining may support the diagnosis in up to 70% of cases.

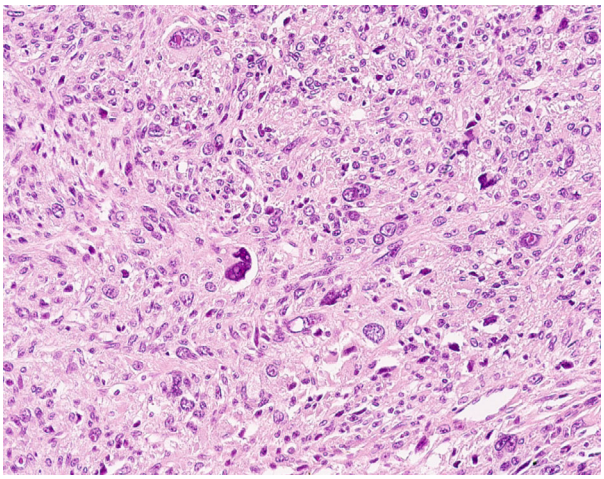

Figure 17. Undifferentiated pleomorphic sarcoma. A sarcomatous proliferation devoid of morphological clues to differentiation. Essentially a diagnosis of exclusion when immunohistochemical and molecular investigations fail to show a specific immunohistochemical or molecular profile.

component (biphasic SyS), occasionally with glandular structures. The epithelial nature is reflected by cytokeratin and/or epithelial membrane antigen (EMA) staining, although EMA will often stain the spindle cell component as well. However, as the histological spectrum of SyS is wide, poorly differentiated SyS may be difficult to recognize, and may present as an SBRCT. Relying on a limited immunohistochemical panel may lead to an erroneous diagnosis, as a considerable proportion of SyS are S100 positive.[5] As outlined previously, SyS is characterized by a specific genetic translocation, t(X;18) *SSX-SS18*, which can be reliably detected by immunohistochemistry. TLE1 staining is less useful in distinguishing MPNST and SyS, as this marker may be positive in MPNST.[4]

Leiomyosarcoma is mainly seen in the posterior mediastinum.[2] Similar to MPNST, this is a fascicular spindle cell sarcoma. Distinguishing LMS and MPNST is generally straightforward; well-differentiated cases

will have a distinctly fascicular architecture and are composed of elongated cells with fibrillary eosinophilic cytoplasm. LMS will in the majority of cases at least focally show desmin positivity. Solely relying on smooth muscle actin (SMA) for an LMS diagnosis is erroneous, as a significant proportion of SyS and other spindle cell sarcomas will stain for SMA.[72]

Inflammatory myofibroblastic tumour, which may occur in the posterior mediastinum (Figure 13),[73] may mimic MPNST and LMS and will have an overlapping immunoprofile. However, rearrangements of *ALK*, which may be identified by ALK immunohistochemistry, readily distinguishes IMT from MPNST and LMS.

Solitary fibrous tumour is one of the more common mesenchymal spindle cell neoplasms arising in the mediastinum, including in the posterior comportment.[2] In contrast to the early descriptions in which SFT is described as patternless, it generally shows a storiform/fascicular architecture. The cytology of SFT is typically bland, with elongated cells set in a collagenous stroma, and the nuclei frequently appear to lie attached to dense collagen fibres. Solitary fibrous tumour is almost always diffusely positive for CD34 and expresses the product of the *NAB2-STAT6* gene fusion, a highly specific marker for SFT, setting it apart from the differential diagnostic considerations (Figure 14).

Dedifferentiated liposarcoma may occur in the posterior mediastinum and may present as large spindle cell sarcomas. *MDM2* amplification detected by fluorescence in situ hybridization (FISH) or the resulting overexpression detected by immunohistochemistry serves to diagnose dd-LIS. An index of suspicion is required, as there may be no histological indication of lipomatous differentiation (Figure 15).

Low-grade MPNST may resemble desmoid fibromatosis, owing to the fascicular architecture and lack of atypia (Figure 16). Loss of staining of H3K27me3 favours low-grade MPNST, while nuclear staining of β-catenin resulting from *CTNNB1* gene mutation reported in up to 90% is diagnostic for desmoid fibromatosis.[74,75] However, loss of H3K27me3 is only seen in ~50% of MPNST, and although not totally specific, its loss has not been documented in desmoid fibromatosis.[66,76–78]

Undifferentiated pleomorphic sarcoma is a diagnosis of exclusion. These sarcomas fail to show a specific immunoprofile and will by definition not harbour specific genetic changes (Figure 17). However, in the authors' opinion, given the predilection of this subgroup of neoplasms for the posterior mediastinum and given the less-than-optimal sensitivity of MPNST markers, it is conceivable that a considerable proportion of the (so-called) undifferentiated pleomorphic sarcoma are in fact poorly differentiated MPNST.

Additional entities that may be considered when faced with a spindle cell neoplasm in the posterior mediastinum include sarcomatoid mesothelioma, sarcomatoid carcinoma, and incidentally described exceptionally rare spindle cell tumours.[5]

Conclusion

In conclusion, primary tumours in the posterior mediastinum are predominantly of neurogenic or neuroblastic derivation. The differential diagnosis of primitive neuroblastic tumours is essentially that of a small blue round cell tumour, while neuroblastic tumours with maturation need to be distinguished from nerve sheath tumours. Most spindle cell neoplasms in the posterior mediastinum are of mesenchymal derivation and many harbour specific genetic aberrations that may be identified by immunohistochemistry or molecular techniques. Judicious use of ancillary tests, along with close attention to the clinical circumstances, should be able to provide a confident diagnosis in most cases.

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Conflict of interest

The authors do not have any conflicts of interest to disclose.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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