



Mediastinal tumors of peripheral nerve origin (so-called neurogenic tumors)

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Abstract: The mediastinum can be the site of origin of a variety of benign and malignant tumors of peripheral nerve sheath origin. Although schwannoma is one of the most common tumors found in the posterior mediastinum, peripheral nerve sheath tumors are reported in all compartments of the mediastinum. The majority of peripheral nerve sheath tumors in the mediastinum as in other anatomic sites occur sporadically, and a subset of them, most notably neurofibromas, and to a lesser extent, schwannomas and malignant peripheral nerve sheath tumors, occur in patients with syndromes such as neurofibromatosis 1 (NF1). In this review, the characteristics of mediastinal nerve sheath tumors along with the histologic differential diagnosis are summarized. Primary emphasis is placed upon the use of morphologic criteria for establishing a definitive diagnosis with reference to photomicrographs to illustrate the classic and sometimes unusual features of this varied group of tumors. The judicious application of ancillary testing, most frequently immunohistochemistry, for separating peripheral nerve sheath tumors from each other and from their morphologic mimics is reviewed. Included in the review are the clinicopathologic features, clinical management and prognostic implications of benign and malignant mediastinal peripheral nerve sheath tumors.

Keywords: Mediastinal nerve sheath tumor; thoracic nerve sheath tumor; schwannoma; malignant peripheral nerve sheath tumor

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Introduction

The mediastinum can be the site of origin of a variety of benign and malignant tumors of peripheral nerve origin that have been usually reported as “mediastinal neurogenic tumors” (MNT) (1-4). Anatomically, the mediastinum can be compartmentalized into anterior, middle, and posterior regions (5-12), which can be useful in prioritizing differential diagnostic entities when evaluating mass lesions with the assistance of radiologic correlation. The vast majority of MNT’s arise in the posterior mediastinum, typically arising from the spinal nerve roots, although they may develop from any intrathoracic nerve (1), such as the

vagus nerve, or recurrent laryngeal nerve in the superior mediastinum. The majority of MNT’s occur in adult patients, but pediatric cases are described (3,4,13). *Table 1* summarizes the various peripheral nerve origin tumors that have been described in the mediastinum.

Benign tumors of peripheral nerve origin

Schwannoma

Schwannoma is the most frequent tumor of peripheral nerve origin in the mediastinum (14-24) and the majority occur in the posterior mediastinum (25,26). Schwannomas

Table 1 Mediastinal tumors of peripheral nerve origin

Benign
Schwannoma and variants:
Giant schwannoma
Ancient schwannoma
Melanocytic schwannoma
Neurofibroma
Neurofibromatosis 1
Neuromuscular choristoma (neuromuscular hamartoma)
Benign triton tumor
Granular cell tumor
Perineurioma
Extracranial meningioma
Malignant
Malignant peripheral nerve sheath tumor
Low grade MPNST/atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP)
High grade MPNST
Malignant triton tumor
Extraspinal ependymoma
MPNST, malignant peripheral nerve sheath tumor.

develop as sporadic tumors in children or adults but are more frequent in adult patients in their 3rd–6th decades of life. There is no gender preference. To our knowledge, there have been no mediastinal schwannomas described in patients with schwannomatosis or neurofibromatosis. Patients can be asymptomatic or present with chest pain or symptoms secondary to the extrinsic compression of airways or the esophagus by a large mediastinal tumor (5,14,27). Rarely schwannoma patients present with Horner's syndrome, pleural effusion, mediastinal hemorrhage or inappropriate secretion of antidiuretic hormone syndrome (IADH syndrome) (16,28–31). Vijendra *et al.* described an unusual schwannoma of the vagal nerve extending from the mediastinum into the base of the skull (32).

Schwannomas present grossly as well-encapsulated nerve sheath tumors. On cross section they exhibit a yellow-white appearance that is often associated with hemorrhage and/or cystic change (*Figure 1A,B*). They vary in size from a few centimeters in diameter to “giant” lesions measuring 20 cm in largest dimension (32–34).

Microscopically, schwannomas exhibit a distinct fibrous capsule that arises from epineurium and usually exhibit focal residual nerve fibers. They are composed of two alternating components: cellular spindle cell areas (Antoni A areas) and loose myxoid areas (Antoni B areas) (*Figure 2*). The

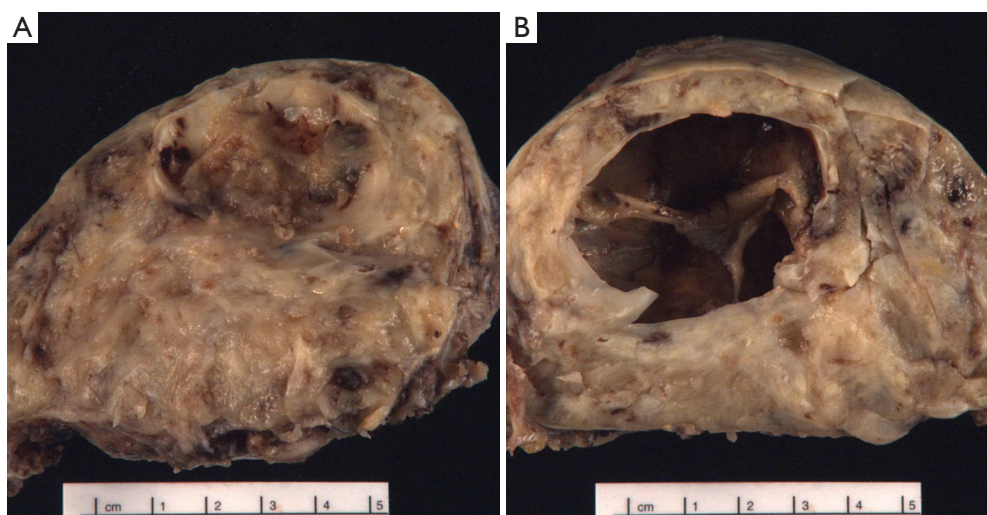


Figure 1 (A) Solid change in encapsulated schwannoma. (B) Grossly cystic change in a large schwannoma showing peripheral solid elements and capsule.

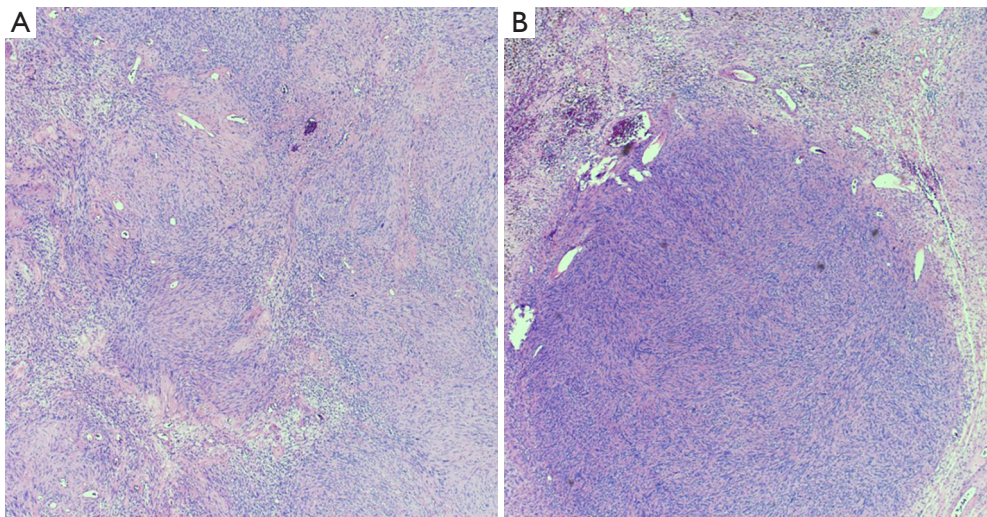


Figure 2 (A) Schwannoma demonstrating Antoni A and B areas with some hyalinized vessels (40×, H&E). (B) A cellular nodule within schwannoma composed primarily of Antoni A areas (40×, H&E).

Antoni A areas of schwannomas are composed of spindle cells showing elongated nuclei with inconspicuous nucleoli, amphophilic cytoplasm and indistinct cellular borders. The spindle cells are arranged in short fascicles or whorls and characteristically exhibit nuclear palisading and variable number of Verocay bodies. The latter are composed of two compact rows of well-aligned spindle-shaped nuclei separated by fibrillary cell processes. The Antoni B areas of schwannomas are composed of loose myxoid tissue that often exhibits xanthomatous change, areas of hyalinization and/or cystic change. The hyalinized stroma often exhibits characteristic ectatic, irregularly shaped vessels that can become focally thrombosed. Mitoses are infrequent in schwannomas. Rarely, schwannomas exhibit the presence of focal, benign glands. The spindle cells of schwannomas exhibit, particularly in Antoni A areas, diffuse and often strong cytoplasmic immunoreactivity for S100 protein and nuclear immunoreactivity for SOX-10, a marker of neural crest differentiation. Schwannomas can also exhibit cytoplasmic immunoreactivity for CD57 and glial fibrillary acidic protein (GFAP).

Schwannomas can exhibit extensive areas of degeneration with marked nuclear atypia, hemosiderosis, cystic change, hyalinization, hemorrhage and/or calcification, particularly in patients with longstanding tumors (so-called ancient change) (Figure 3) (17,19,35,36). Schwannomas with ancient change exhibit atypical cells with large hyperchromatic and frequently multilobed nuclei with occasional eosinophilic

inclusions (Figure 4). Schwannomas showing ancient change can pose a diagnostic challenge in distinguishing them from other tumors, most importantly those which show more aggressive or malignant biologic behavior, such as malignant peripheral nerve sheath tumors (MPNST) or pleomorphic hyalinizing angiectatic tumor. However, they lack mitotic activity and the presence of highly cellular areas and they maintain the thick-walled hyalinized vessels and foam cells. In addition, this variant of schwannoma maintains its strong diffuse S100 positivity by immunohistochemistry, which helps distinguish it from the above histologic mimics.

A rare variant of schwannoma can also exhibit areas of pigmentation with melanocytic cells, and rare cases of melanotic schwannoma have been described in the mediastinum (37) (Figures 5,6). To our knowledge other schwannoma variants such as cellular schwannoma and epithelioid schwannoma have not been described as mediastinal lesions.

Schwannomas are benign tumors that are cured by surgical resection (14,38). Depending on the tumor location, the tumors can be resected with thoracotomy, sternotomy, supraclavicular excision, posterior approach with laminectomy, video-assisted thoracoscopic surgery or other techniques (14). Preoperative embolization of giant thymomas has also been used to facilitate tumor resection (21). To our knowledge, there have been no reports of mediastinal schwannomas undergoing malignant transformation after successful resection.

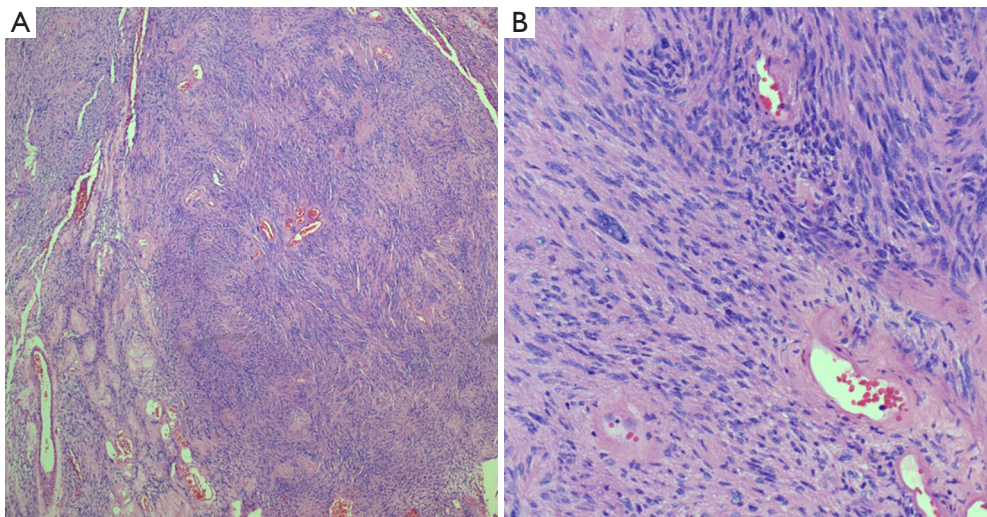


Figure 3 (A) Ancient schwannoma showing hyalinized vessels and Verocay bodies (H&E, 40×). (B) Ancient schwannoma showing degenerative atypia and nuclear inclusions (200×, H&E).

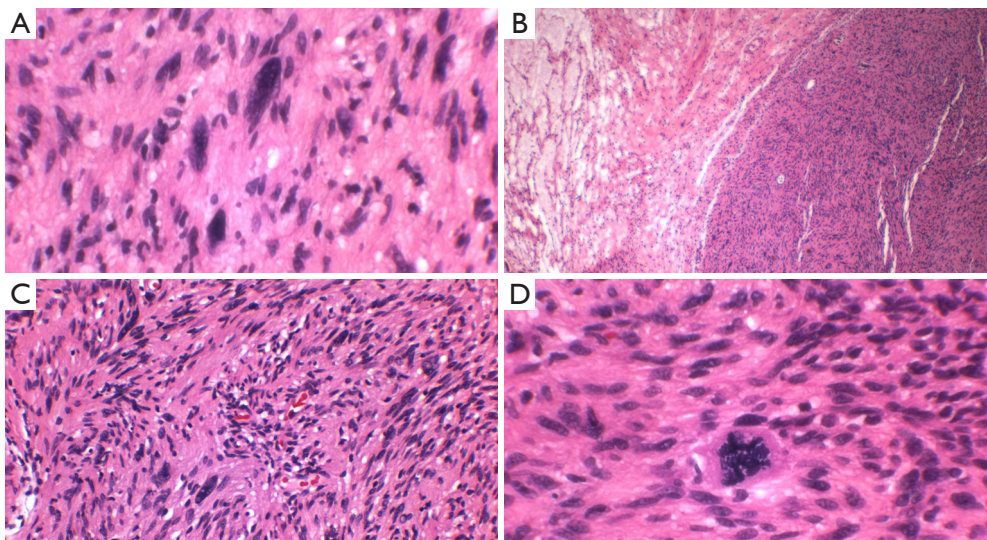


Figure 4 (A) Nuclear enlargement and hyperchromatic chromatin within ancient schwannoma (400×, H&E). (B). Cellular nodule within a schwannoma with adjacent loose myxoid stroma (20×, H&E). (C). Cellular areas of schwannoma with atypical cells seen at high power in (A) (100×, H&E). (D) Atypical mitotic figure within schwannoma with degenerative atypia (400×, H&E).

Ganglioneuroma

Ganglioneuromas are neoplasms arising from the dorsal root ganglion of the spinal cord and can grow almost anywhere along the paravertebral sympathetic ganglia and in the adrenal medulla. They can arise *de novo* and result from the maturation of ganglioneuroblastoma or neuroblastoma. They are rare benign fully differentiated

tumors composed of spindled Schwannian or fibroblastic cells, ganglion cells, and nerve fibers without immature elements, atypia, significant mitoses, or intermediate cells. Most cases have been described in the posterior mediastinum of children (39,40). Lee *et al.* described a patient with a posterior mediastinal ganglioneuroma in a patient with neurofibromatosis (41). The histopathologic features are dependent upon the admixture of elements

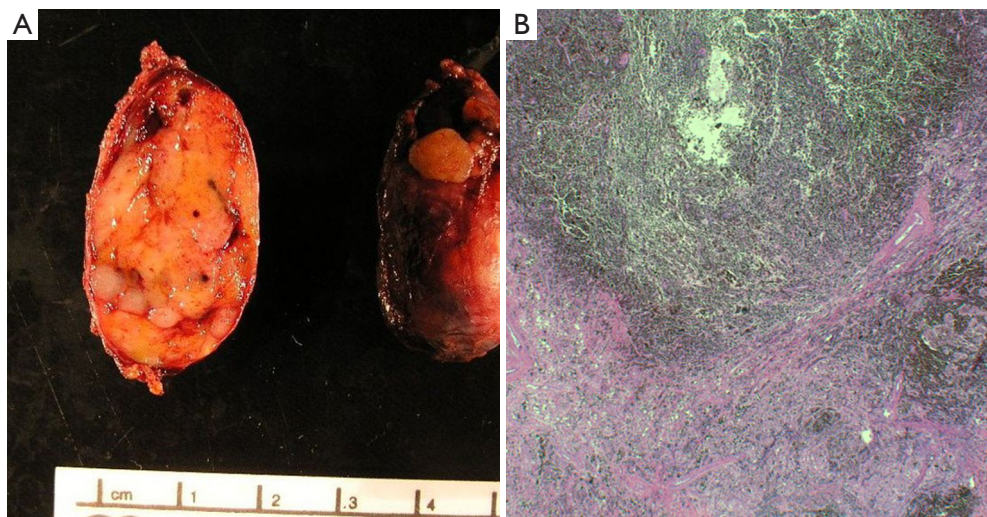


Figure 5 (A) Gross appearance of cut surface of melanotic schwannoma. (B) Low power view of heavily melanotic pigment deposition in a melanotic schwannoma (40x, H&E).

described above and the immunophenotype is similar to that seen in schwannomas, admixed with scattered ganglion cells. Ganglioneuromas are cured by surgical resection, and to our knowledge there have been no reports of mediastinal lesions progressing to a malignancy (13,39).

Neurofibroma and neurofibromatosis 1 (NF1)

Neurofibromas are benign tumors of peripheral nerve origin that can present as localized, diffuse or plexiform lesions (26). Localized neurofibromas usually develop as sporadic tumors in patients that do not have NF1. Diffuse neurofibromas are an uncommon but distinctive variant of neurofibroma, usually occurring in young adults. It is unclear how often diffuse neurofibromas are associated with neurofibromatosis, though many experts suggest that about 10% of patients with diffuse neurofibromas have NF1, and some reviews suggest that up to 60% of neurofibroma patients exhibit diffuse neurofibromas. Diffuse neurofibromas appear as plaque-like lesions in the head and neck area of children (26). To our knowledge, they have not been reported in the mediastinum. In contrast, plexiform neurofibromas are essentially pathognomonic of NF1. Most mediastinal neurofibromas have been plexiform neurofibromas arising in NF1 patients (42-45). Neurofibromas usually occur in patients in their 3rd and 5th decade of life, without gender predominance. Neurofibromas associated with NF1 are usually diagnosed in children or young adults.

Localized, solitary neurofibromas usually appear as superficial, subcutaneous tumors and only rare examples have been reported in the mediastinum of patients without NF1 (44,46). Al-Hajjaj *et al.* reported a rare patient with Ehler-Danlos syndrome that presented with a mediastinal neurofibroma and bronchiectasis (47). Localized neurofibromas appear grossly as localized, fusiform lesions that expand the nerve of origin (Figure 7 A,B,C). Microscopically, they are composed of interlacing bundles of spindle cells showing hyperchromatic, wavy nuclei and amphophilic cytoplasm, admixed with ropey, wire like strands of collagen, dense collagen bundles, and variable amounts of intercellular myxoid stroma. Variable amounts of mast cells can also be seen. The spindle cells exhibit a distinctive Schwannian morphologic and immunohistochemical phenotype, with S100 protein and SOX-10 immunoreactivity. However, the proportion of cells and intensity of such immunoreactivity is decreased compared to what is characteristic of schwannomas. Neurofibromas are benign lesions that can be cured with surgical resection, anatomic constraints permitting; however, diffuse and plexiform neurofibromas may inextricably surround vital structures, limiting complete excision.

Most mediastinal neurofibromas are plexiform neurofibromas and several patients with mediastinal either single or bilateral lesions arising from the vagus nerve have been described (42-45). These tumors are pathognomonic of NF1 and develop in early childhood as widely distributed growths within the subcutaneous tissue of extremities and/

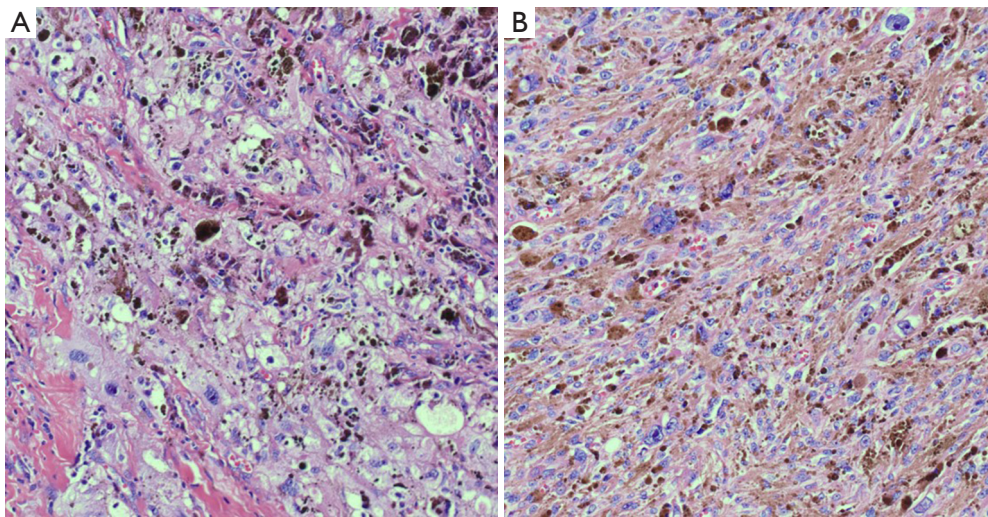


Figure 6 (A) Melanotic schwannoma showing atypical cells with heavy melanotic pigment and foam cells (200x, H&E). (B) Slightly fasciculated appearance of melanotic schwannoma with large intranuclear inclusions and heavy melanin pigment (200x, H&E).

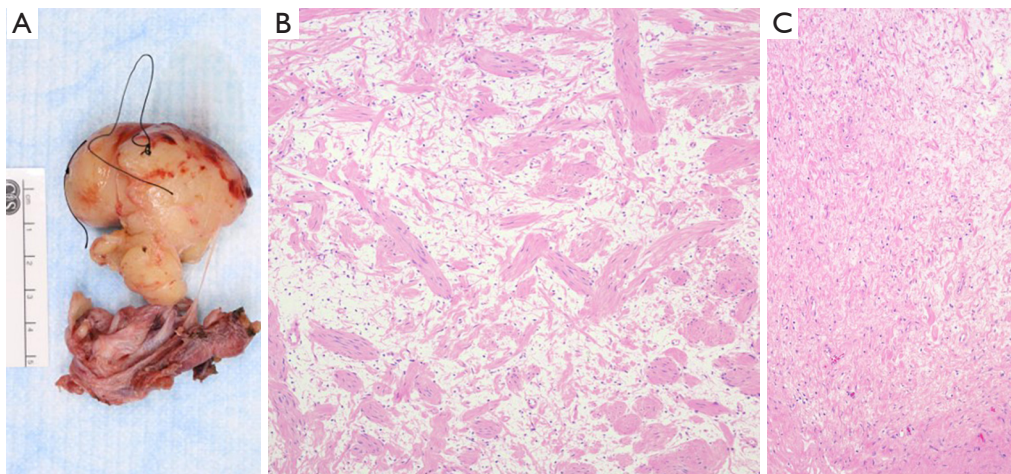


Figure 7 (A) Gross appearance of somewhat dumbbell shaped neurofibroma. (B,C) Low power views of myxoid and spindled Schwannian cells with associated collagen bundles (40x, H&E).

or deep sites (26). The mediastinal tumors appear as large lesions that present as multiple areas of ill-circumscribed enlargement that deform the nerve of origin into a pattern described as a “bag of worms”. The diagnosis of plexiform neurofibroma is usually made on clinical grounds and correlation with the history of NF1, clinical presentation and radiologic features is essential for making the diagnosis. Microscopically, the lesions show expanded and tortuous nerve branches showing separation of small nerve fibers by endoneurial matrix material with a myxoid appearance (Figure 8). Because plexiform neurofibromas can become

cellular and show atypical changes and undergo malignant transformation to MPNST (estimated to be 2% to 29% of cases (48). The histopathologic distinction between atypia and truly malignant transformation in a neurofibroma is notoriously difficult, due to the continuum of histopathologic changes between benign and malignant tumors. Miettinen *et al.* has proposed to classify these lesions as either atypical neurofibromatous neoplasm of uncertain biologic potential (ANNUBP) or low grade MPNST (49). ANNUBP are diagnosed in the presence of at least two of the following features: high cellularity, cytologic atypia, loss of

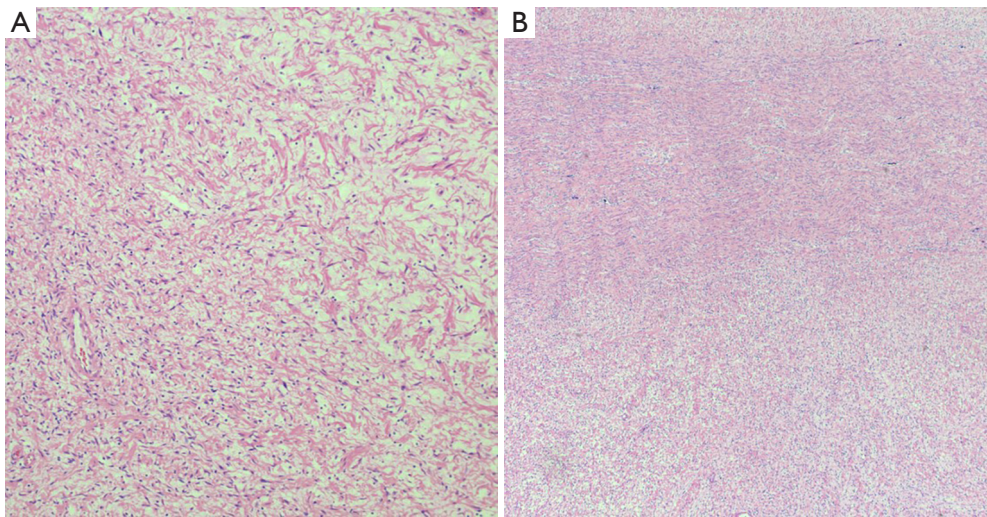


Figure 8 (A) Myxoid areas of plexiform neurofibroma with conventional appearing histology and Schwannian cells intimately associated with curved collagen bundles (40x, H&E). (B) Lower power view of plexiform neurofibroma (20x, H&E).

neurofibroma architecture and/or 2–3 mitoses/10 high power field (HPF). Low grade MPNST's exhibit similar features to ANNUP but with a higher mitotic rate of 3–9 mitoses/10 HPF. Low grade MPNST's usually exhibit a number of genetic abnormalities, including p53, p16^{INK4A}, p14^{ARF}, and p27^{kip1} alterations and *EGFR* amplification (26). Compared to localized and diffuse neurofibromas, the plexiform subtypes have the highest risk of malignant transformation to malignant peripheral nerve sheath tumor (26). Mediastinal plexiform neurofibromas are difficult to treat surgically and patients that develop high grade MPNST have a poor prognosis (42,48).

Granular cell tumor

Several cases of benign and malignant granular cell tumors have been described in the mediastinum (50–57). The tumors develop as well-circumscribed lesions exhibiting a pale-yellow cut surface and are composed of round, polygonal or spindle cells characterized by the presence of abundant eosinophilic, granular cytoplasm. The cells exhibit multiple diastase resistant periodic acid-Schiff (D-PAS) granules and exhibit immunoreactivity for S100, consistent with neural origin and CD68 (Kp1) indicative of lysosomal granules. Granular cell tumors also exhibit nuclear immunoreactivity for TFE3 and Inhibin- α . The vast majority of granular cell tumors are benign, but histologically, they can exhibit a range of mild to moderate

nuclear atypia. Histologic criteria for malignancy in granular cell tumors includes the presence of spindle cells with vesicular nuclei and prominent nucleoli, necrosis, >2 mitoses/10 HPF, high nuclear/cytoplasmic ratio and cellular pleomorphism; however, in the absence of metastasis clinically malignant behavior remains uncertain because histology is not well correlated to biologic behavior in this set of tumors. Rarely histologically typical granular cell tumors may behave in a malignant fashion. Benign granular cell tumors are cured by surgical resection. Malignant granular cell tumors metastasize to lung, bone, liver and other organs over a number of years (26).

Perineurioma

A rare case of mediastinal perineurioma has been reported (58), in an endobronchial location. Perineuriomas are also subtyped, but in the mediastinum, they resemble the soft tissue perineurioma. Grossly, the cut surface of perineuriomas are white to gray, and they are well circumscribed but unencapsulated, with a firm texture. Histologically, soft tissue perineuriomas are composed of elongated neoplastic cells with wavy-shaped nuclei with eosinophilic cytoplasm and indistinct cell boundaries. Characteristically, the spindle cells have elongated nuclei and elongated and extremely thin, widely separated bipolar cytoplasmic processes. Architecturally, the cells may be seen in storiform, lamellar arrangements, or perivascular

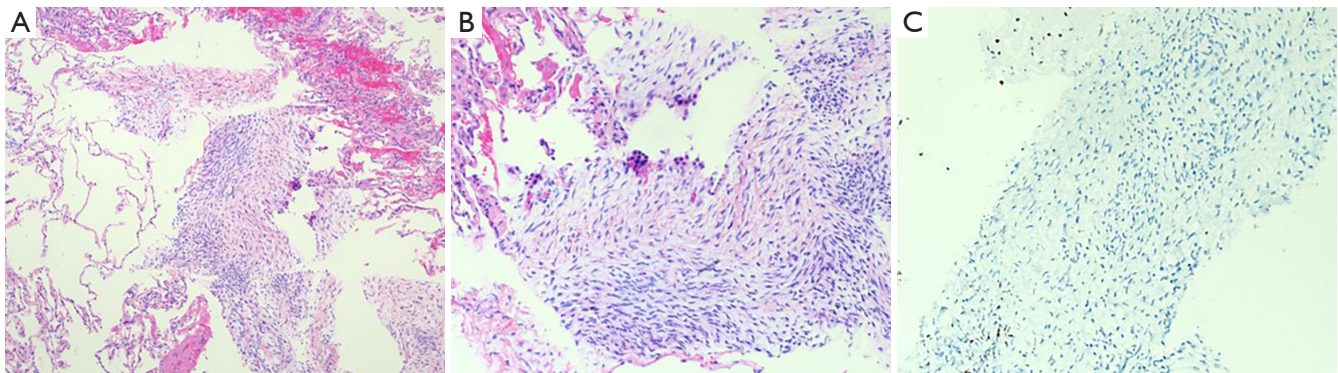


Figure 9 (A) Lung biopsy of MPNST from a 23-year-old patient with neurofibromatosis 1 showing fasciculated spindle cells with undulating nuclei (40x, H&E); (B) Nuclear hyperchromasia and variably cellular areas (100x, H&E). (C) Nuclear loss of trimethylation marker H3k27me3, characteristic of high grade MPNST (100x, immunohistochemical stain for H3k27me3). MPNST, malignant peripheral nerve sheath tumor.

whorling formations. The stroma can vary from a more collagenous to a more myxoid or hypocellular appearance and a collagenous-myxoid background. The differential diagnosis in the mediastinum includes solitary fibrous tumor, low grade fibromyxoid sarcoma and other low-grade spindle cell neoplasms. By immunohistochemistry, perineuriomas are positive for epithelial membrane antigen and Claudin-4, and unlike other benign peripheral nerve sheath tumors, lack expression of S100 and SOX10. In general, perineuriomas are clinically benign and treated by excision.

Extracranial meningioma

Rare examples of extracranial meningiomas arising in the mediastinum or extending into the thorax from paraspinous or intracranial lesions have been described (59–64).

Malignant tumors of peripheral nerve origin

Malignant peripheral nerve sheath tumor

MPNST's are sarcomas that can be diagnosed in the presence of a tumor that either arises from a peripheral nerve or a pre-existent neurofibroma and/or display pathologic features of Schwannian differentiation. About 25–50% of MPNST develop in patients with NF1 (65). The sarcomas develop in 10–30% of patients with plexiform neurofibromas, usually after a 10–20 years latency period. Radiation exposure, including radiation therapy is also a predisposing factor to development of MPNST.

Anatomically, MPNST has been reported in all areas of

the mediastinum. Grossly, MPNST appear as large, fusiform tumors that arise from a major nerve and usually measure >5 cm in diameter (48,66,67). Histologically, MPNST has a variety of appearances; however, classically, they are composed of spindle cells with vague nuclear palisading recapitulating features characteristic of Schwann cells, with wavy, or comma-shaped nuclei and amphophilic cytoplasm (Figure 9). The tumor cells are arranged in fascicles that can vary in cellularity from hypocellular and myxoid areas to cellular areas resembling adult type fibrosarcomas or synovial sarcomas (Figures 10A,B, 11A,B). Proliferation of the malignant spindle cells into the perineurium or the subendothelial areas of vessels are characteristic of MPNST. Distinctive features of MPNST includes hyaline bands and nodules that resemble giant rosettes. The tumors can also exhibit heterologous elements with islands of mature cartilage or bone, mucin-secreting glands, and squamous epithelium, rhabdomyosarcomatous or angiosarcomatous elements (64). Histologically, MPNST range from low-grade lesions that can be difficult to distinguish from ANNUBP, as described above, to anaplastic tumors exhibiting a markedly pleomorphic clearly sarcomatous appearance. A small subset (5%) of MPNST's show epithelioid morphology (EMPNST), which raises a distinctive differential diagnosis separate from that of the classic or usual spindle cell MPNST. The differential diagnosis in EMPNST includes melanoma, carcinoma, myoepithelioma, extraskeletal myxoid chondrosarcoma and other sarcomas, including some small round cell sarcomas. Association of EMPNST with NF1 is not as strong as in ordinary MPNST. In addition, EMPNST is a pattern of malignant transformation in

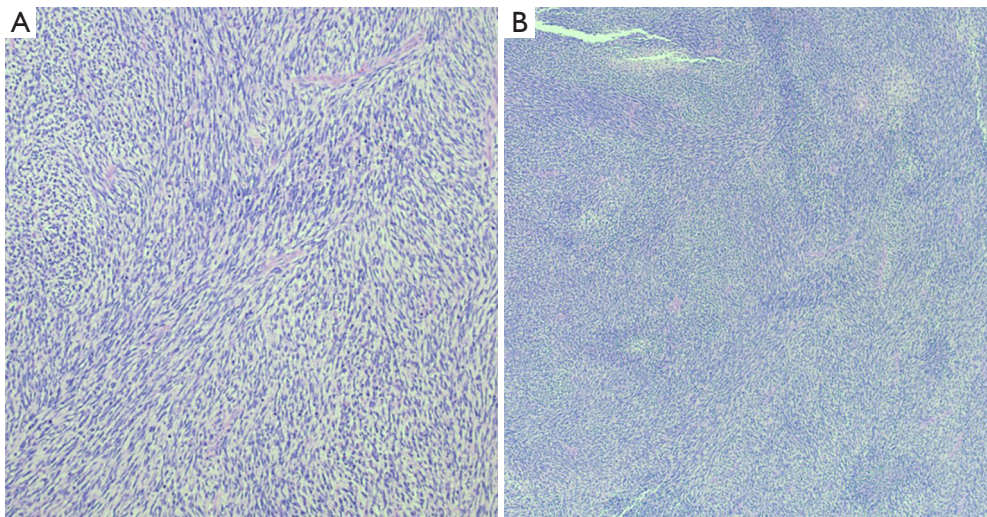


Figure 10 (A) High grade MPNST with herringbone pattern of fascicles of spindle cells with undulating nuclei, nuclear hyperchromasia, and easily found mitoses (100×, H&E). (B) MPNST showing intersecting fascicles and zones of hypercellularity (40×, H&E). MPNST, malignant peripheral nerve sheath tumor.

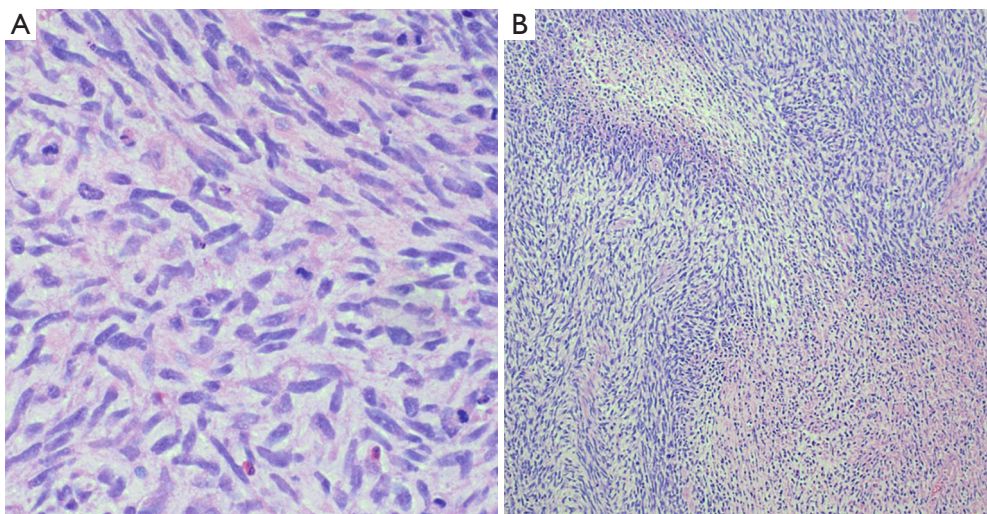


Figure 11 (A) High grade MPNST showing spindled Schwannian-like cells with mitotic figures and punctate single cell necrosis (400×, H&E). (B) Zones of geographic necrosis sharply juxtaposed with hypercellular fascicles of spindle cells (40×, H&E). MPNST, malignant peripheral nerve sheath tumor.

schwannomatosis.

Classically, MPNST exhibits limited S100 and SOX-10 immunoreactivity and diffuse strong expression in a tumor argues against MPNST. Loss of the trimethylation marker H3K27me3 is known to be deficient in high grade MPNST, but not in low grade MPNST. Some MPNST's show aberrant expression of desmin, myogenin and MyoD1 (*Figures 9C,12A,B*). Loss of neurofibromin expression

has been reported in the majority of MPNST associated with NF1 . In contrast EMPNST demonstrates strong diffuse SOX10 and S100 protein expression. Although it retains expression of H3K27me3, there is frequently loss of SMARCB1. In general, keratin expression is negative in MPNST and EMPNST. In general, MPNST are resistant to chemotherapy and radioresistant. They are highly malignant tumors that are treated with surgical excision (65,68).

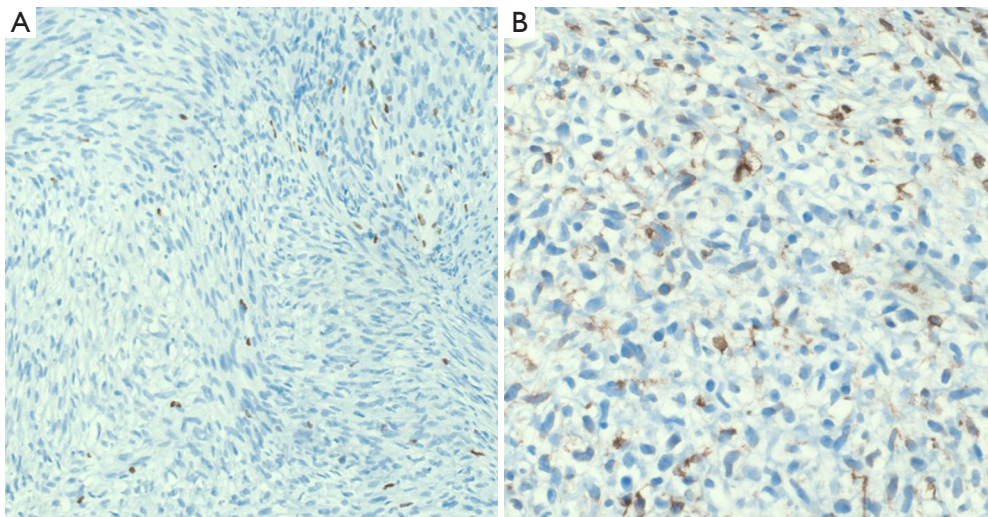


Figure 12 (A) Loss of H3k27me3 immunohistochemical expression in tumor cells of high grade MPNST (100x, PAP) and (B) scattered desmin positive cells (200x, PAP). MPNST, malignant peripheral nerve sheath tumor.

Malignant neuromuscular choristoma (malignant neuromuscular hamartoma (malignant triton tumor) (64)

Malignant neuromuscular choristomas, also reported as malignant neuromuscular hamartomas or malignant Triton tumors, are rare sarcomas that appear as well-circumscribed lesions composed of MPNST elements admixed with skeletal muscle fibers. A few cases have been described in the posterior mediastinum and the anterior mediastinum of adults in their 3rd to 5th decade of life (69-71). Patients have a poor prognosis after treatment with surgical resection and/or chemotherapy and tend to recur locally and/or develop lung metastases (68).

Extraspinal ependymoma

Rare examples of ependymomas involving the posterior mediastinum have been described (72-76). However, we have not seen any in our practice.

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