Review Article

Histopathological features of giant mediastinal tumors—a literature review

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Background and Objective: Mediastinal lesions are uncommon. However, because of the vital structures in the mediastinum, large lesions specifically can lead to life-threatening situations. Treatment and management vary considerably with the disease. Therefore, the correct histopathologic diagnosis is important. Here we review lesions that have the potential to present as a giant lesion in the mediastinum. While we focus on the review of histopathologic, immunohistochemical (IHC), and molecular features of these lesions, clinical symptoms and characteristics and prognosis will also be discussed.

Methods: "Giant" was arbitrarily defined as a size of at least 10 cm in greatest dimension. The 2021 World Health Organization (WHO) classification of mediastinal tumors was searched for tumors reported to be larger than 10 cm. Tumors that can present as giant mediastinal lesions based on our own experience were also included. PubMed search was then performed for these lesions.

Key Content and Findings: A great variety of mediastinal lesions can present as giant mass. Those include for instance tumors of blood and lymph vessels, tumors of neurogenic origin, mesenchymal neoplasms, thymic epithelial tumors (TETs), and non-neoplastic cysts. Lesions range from benign to malignant. This review focuses on the most common lesions.

Conclusions: Many benign and malignant lesions can become a large mass in the mediastinum. Their correct diagnosis is important for the treatment and management of the patient.

Keywords: Mediastinum; giant mass; thymoma; germ cell tumor (GCT); cyst

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Introduction

The mediastinum can harbor a broad range of neoplasms including thymic epithelial tumors (TET), lymphoproliferative diseases, germ cell tumors (GCTs), mesenchymal tumors, and metastases among others. In addition, benign lesions such as cysts can also occur in that location. The prevalence of solitary lesions in adults varies by the mediastinal compartment (1). In the prevascular mediastinum, the most common solitary lesions in adults are thymomas followed by benign cysts, lymphomas, thymic carcinomas, GCTs, metastases, and others (2). In the visceral mediastinum, benign cysts are followed by metastases, benign thyroid lesions, lymphomas, and small cell carcinomas while in the paravertebral mediastinum, neurogenic tumors represent by far the most common solitary lesions; occasionally benign cysts are identified in the paravertebral compartment (2). The mediastinum encompasses a number of vital organs such as the heart, aorta, superior vena cava (SVC), brachiocephalic vein, esophagus, large airways, and nerves. Giant tumors can

Table 1 Distribution of giant mediastinal tumors according to mediastinal compartments (3)

Prevascular compartment	Visceral compartment	Paravertebral compartment
Thymoma, thymic carcinoma	Cysts	Peripheral nerve sheath tumor
Germ cell tumor	Lymphoma	Neuroblastic tumor
Lymphangioma	Hemangioma	Lymphangioma
Angiosarcoma	Liposarcoma	Paraganglioma
Synovial sarcoma	Desmoid fibromatosis	Synovial sarcoma
Thymolipoma		Cysts
Thymoliposarcoma		Lymphoma
Lipofibroadenoma		Hemangioma
NUT-carcinoma		Liposarcoma
SMARCA4-deficient undifferentiated tumor		Desmoid fibromatosis
Cysts		
Lymphoma		
Hemangioma		
Liposarcoma		
Desmoid fibromatosis		

NUT, nuclear protein in testis.

impinge on these structures resulting in their compression or obstruction leading to symptoms such as dyspnea, cough, wheezing, chest pain, and SVC syndrome. Giant mediastinal tumors (in this review defined as tumors that are 10 cm and larger) pose, of course, a substantial clinical problem not only because of the symptoms they may cause but also for therapy planning and management of the patient. The correct diagnosis is crucial as some tumors such as TET benefit from surgical treatment if completely resectable while others such as many of the malignant GCTs or lymphomas are treated with chemotherapy and/or radiation.

There are various, partially overlapping, schemes of dividing the mediastinum in compartments, sometimes causing confusion. To standardize their classification and to ease the communication between radiologists, surgeons, pathologists, pulmonologists, medical oncologists, and radiation oncologists, the International Thymic Malignancy Interest Group (ITMIG) developed a multidetector computed tomography (CT)-based definition of mediastinal compartments (3). This clinically-oriented scheme includes three compartments: prevascular, visceral, and paravertebral (*Table 1*). Importantly, in this model, compartment borders follow true anatomical planes.

In this review, we describe, from the pathologist's point of view, lesions in the mediastinum that most commonly can present as a giant mass. A paragraph of the review will be dedicated to difficulties inherent to small biopsies, where one of the main problems can be the sample's representativeness. However, it is not feasible to cover all possible giant lesions. Furthermore, benign giant lesions such as cysts can also occur in that location. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-23/rc).

Methods

A "giant tumor" was arbitrarily defined as a tumor that measures at least 10 cm in greatest dimension. The 2021 World Health Organization (WHO) classification of mediastinal tumors was searched for tumors reported to be larger than 10 cm (4). Tumors that can present as giant mediastinal lesions based on our own experience were also included. PubMed search was then performed for these lesions (Table S1). Additional manuscripts were selected by reviewing reference lists of relevant publications. Publications, where the diagnosis was not straightforward,

Table 2 The search strategy summary

Item	Specification
Date of search	February 1st 2023
Databases and other sources searched	2021 WHO classification of mediastinal tumors was searched for tumors larger than 10 cm. Additionally, tumors larger than 10 cm based on the author's experience were included. PubMed was then searched for selected entities
Search terms used	See Table S1 for details
Timeframe	Date unrestricted to February 2023
Inclusion and exclusion criteria	Inclusion: (I) English and German language; (II) case reports, case series, retrospective cohort series, prospective studies; (III) focusing on subtopics of histology and diagnosis
	Exclusion: same tumors outside of mediastinum, questionable diagnosis
Selection process	L.B. selected literature, both authors chose those to be included
Any additional considerations, if applicable	References of selected manuscripts were reviewed for potential inclusion

WHO, World Health Organization.

were excluded. Additional information on the search strategy is presented in *Table 2*.

We did not include hematolymphoid neoplasms, even though they can present as giant tumors in the mediastinum. However, the large variety of hematolymphoid neoplasms would require a review on its own. Furthermore, for many of these neoplasms biopsies are performed but no resection. If a hematolymphoid neoplasm is in the differential diagnosis of any of the lesions we included, it will be discussed.

Histomorphologic classification of giant mediastinal neoplasms

The histomorphologic classification of giant mediastinal tumors is summarized in *Table 3*.

Tumors of blood and lymph vessels

Hemangioma

Hemangiomas are benign neoplasms that are classified as mesenchymal tumors of the thorax (4). These tumors are composed of vascular spaces or blood vessels. They can develop throughout the body, and their pathogenesis is unknown. In the mediastinum, they can occur in any compartment (2,5). Mediastinal hemangiomas are rather uncommon, accounting for less than 0.5% to 1% of mediastinal tumors (2,6,7). They are distributed across all age groups and are often asymptomatic. However, since they can be as large as 20 cm, they can cause symptoms due to expansion, including SVC syndrome, various neurological problems, dysphagia, and if ruptured, hemothorax (5). Usually, these lesions are well circumscribed, and only rarely infiltrate neighboring structures. The overall prognosis after surgical treatment is good, even for infiltrative tumors, since they do not progress (6).

Histologically, hemangiomas are characterized by vascular proliferation, including veins and capillaries (*Figure 1A,1B*). Even if they show invasive growth, it is mostly limited (8). In between vessels there is fibrous and smooth muscle tissue with inflammatory cells, and occasionally additional changes include myxoid degeneration, hyalinization, and ossification (5). The differential diagnosis includes lymphangioma and angiosarcoma. The distinction of hemangioma from its mimickers is largely based on morphologic characteristics (see below) as the expression patterns of immunohistochemical (IHC) stains can be overlapping.

Lymphangioma

Lymphangiomas are also benign although they can behave more aggressively due to their sometimes infiltrative and expansile growth. They can occur in any mediastinal compartment and encompass 0.3% to 4% of all mediastinal tumors (2,9,10). They are primarily regarded as developmental disorders, and therefore they are more common in children and young adults (11,12). *PIK3CA* mutations have been identified in lymphangiomas

Table 3 Histopathologic classification of giant mediastinal tumors (1)

Mesenchymal tumors	Tumors of the thymus	Germ cell tumors
Adipocytic tumors	Epithelial tumors	Teratoma
• Thymolipoma	• Thymoma	Mixed germ cell tumors
• Liposarcoma	• Thymic carcinoma	Seminoma
• Thymoliposarcoma	• NUT carcinoma	Embryonal carcinoma
Fibroblastic and myofibroblastic tumors	• Lipofibroadenoma*	Yolk sac tumor
• Desmoid fibromatosis		Choriocarcinoma
• Solitary fibrous tumor		
Vascular tumors		
• Hemangioma		
• Lymphangioma		
• Angiosarcoma		
Peripheral nerve sheath and neural tumors		
• Paraganglioma		
• Schwannoma		
• Malignant peripheral nerve sheath tumor		
• Ganglioneuroma		
• Ganglioneuroblastoma		
• Neuroblastoma		
Tumors of uncertain differentiation		
• Synovial sarcoma		
• SMARCA4-deficient undifferentiated tumors		

*, lipofibroadenomas are classified as thymic tumors in the 2021 WHO classification. NUT, nuclear protein in testis; WHO, World Health Organization.

which could be responsible for the aberrant development of lymphatic vessels (13,14). They are mostly cavernous and cystic and measure up to 20 cm in diameter (15). Surgery is the therapy of choice, although sometimes due to localization and infiltrative growth complete resection is impossible (16).

Lymphangiomas have some features that are overlapping with hemangiomas. Lymphangiomas are characterized by the accumulation and proliferation of lymphatic structures usually associated with a lymphocytic infiltrate (*Figure 1C,1D*). Lymphocytic infiltrates are helpful in the distinction of lymphangiomas from hemangiomas which usually lack that feature. Vessels are empty or contain proteinaceous material possibly with lymphocytes, but without erythrocytes. Endothelial cells are low and flat. Like hemangioma, vessel-lining cells express ERG, CD31 (*Figure 1E*), and CD34; in addition, they express podoplanin (D2-40) (*Figure 1F*).

Angiosarcoma

Angiosarcoma is a rare malignant vascular tumor representing less than 1% of all sarcomas (17) and also less than 1% of all mediastinal tumors (2,18-20). They most commonly develop in the prevascular compartment. Patients present with symptoms including dyspnea, cough, hemothorax, and cardiac compression (21,22). They are more common in older men. Interestingly, in children, angiosarcomas most commonly occur in the mediastinum (23). A subset of angiosarcomas develops after radiotherapy; almost all of them harbor *MYC* amplification (24-27). Others arise in preexisting hemangiomas, after

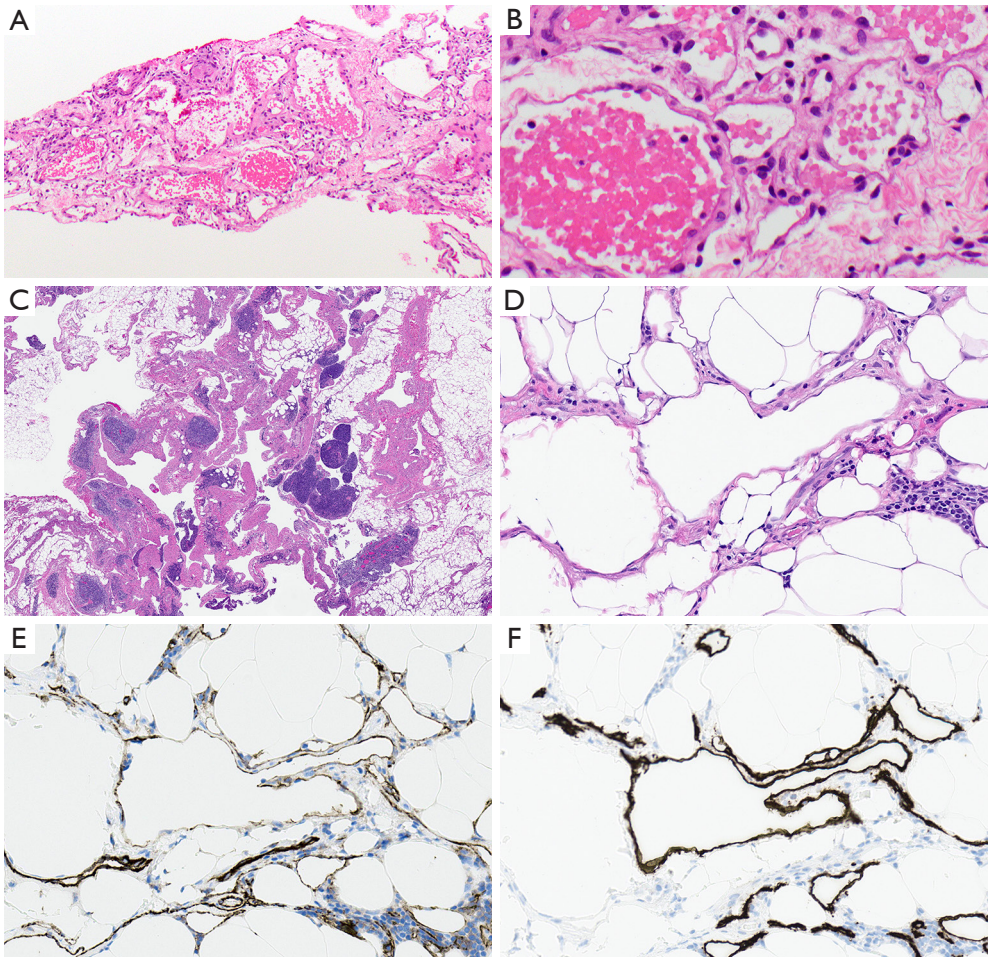

Figure 1 Hemangioma (A,B) and cystic lymphangioma (C-F). (A) Multiple thin-walled spaces are present many of which are filled with red blood cells. (B) The spaces are lined by bland endothelial cells. (C) Multiple thick and thin-walled spaces are together with lymphoid aggregates. (D) This empty thin-walled space is lined by flat, bland endothelial cells that express CD31 (E) and podoplanin (D2-40) (F). Magnification, H&E ×100 (A), ×400 (B), ×2 (C), ×400 (D), CD31 ×400 (E), D2-40 ×400 (F). H&E, hematoxylin-eosin.

surgery, or trauma. Various angiogenesis-associated genes are mutated in these tumors such as *VEGFR2*, *VEGFR3*, *TIE1*, *PLCG1*, *PTPRB*, and *KDR* (28-31).

Histologically angiosarcomas are characterized by the proliferation of neoplastic epithelioid and/or spindle cells, with vascular structures covered by atypical endothelial cells (*Figure 2A-2C*). High mitotic rate, necrosis, and hemorrhage are usually present. The neoplastic cells express CD31 (*Figure 2D*), ERG, Fli-1 (*Figure 2E*), and CD34 (32-34). Importantly, epithelioid cells can be positive for keratins (*Figure 2F*) which is a pitfall. Angiosarcoma with *MYC* amplification will also express MYC.

Features that are helpful in the differential diagnosis of spindle cell neoplasms in the prevascular mediastinum are summarized in *Table 4*.

Tumors of neurogenic origin

In the mediastinum neurogenic tumors arise from neural elements such as the sympathetic system, phrenic, and pneumogastric nerves. The great majority of these tumors (71–95%) occur in the paravertebral mediastinal compartment (2,45). They represent 4% to 34% of all mediastinal lesions; however, in the paravertebral mediastinum they represent 54% of all solitary lesions and are the most common solitary lesion in that compartment (2,7,46). Based on their origin tumors are classified as peripheral nerve sheath tumors [schwannoma, neurofibroma,

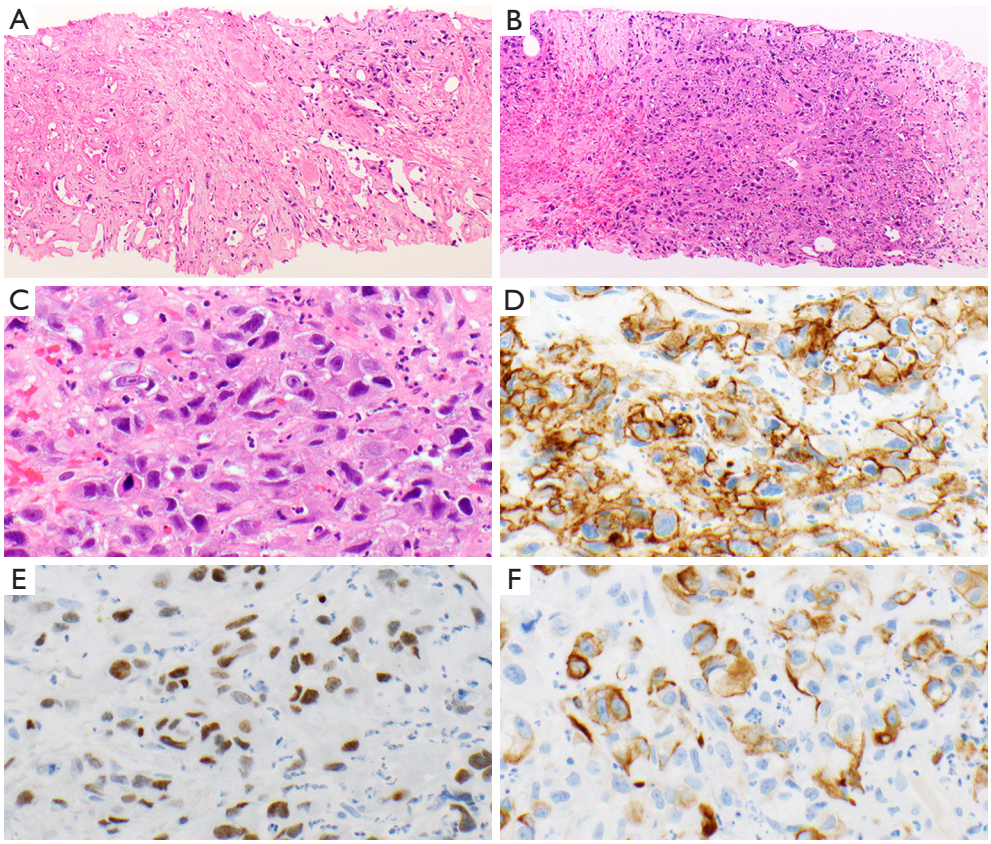

Figure 2 Angiosarcoma. (A) Irregular spaces are lined by plump epithelioid cells. (B,C) In other areas, there is a solid growth of epithelioid and spindle cells that are characterized by dark nuclear chromatin, prominent nucleoli, and pleomorphism. The neoplastic cells are diffusely positive for CD31 (D), and Fli1 (E), a subset of neoplastic cells expresses keratin AE1/AE3 (F). Magnification, H&E ×100 (A,B), ×400 (C), CD31 ×400 (D), Fli-1 ×400 (E), keratin AE1/AE3 ×400 (F). H&E, hematoxylin-eosin.

malignant peripheral nerve sheath tumor (MPNST)], neuroblastic tumors (ganglioneuroma, ganglioneuroblastoma, neuroblastoma), and paraganglia (paraganglioma). While many of the neurogenic tumors in the mediastinum are benign, 5% to 10% and 40% to 60% are considered malignant in adults and children, respectively (47). Patients are mostly asymptomatic. Generally, as a group, patients with neurogenic tumors in the mediastinum have a good prognosis after surgical removal.

Schwannoma

Schwannoma is a benign tumor composed almost exclusively of neoplastic Schwann cells. It is the most common neurogenic tumor of the mediastinum, representing approximately 50% of these tumors occurring at that site (7,46,48,49). They are usually encapsulated (4). Schwannomas are comprised of hypercellular (Antoni A) and hypocellular (Antoni B) areas (*Figure 3A*). The tumor cells are spindled, mostly uniform, with elongated nuclei (*Figure 3B*) that diffusely express S100 protein (nuclear and cytoplasmic, *Figure 3C*) and SOX-10 (35,36). Occasionally hyalinized blood vessels (*Figure 3D*), nuclear palisading (Verocay bodies, *Figure 3E*), and chronic inflammation with lymphoid aggregates are present. Up to 75% of schwannomas harbor an inactivating *NF2* mutation (50-53). Multiple schwannomas are the hallmark of neurofibromatosis type 2 and schwannomatosis.

MPNST

MPNSTs are malignant spindle cell tumors, which can grow up to 27 cm. The majority of MPNSTs are associated with neurofibromatosis type 1, followed by sporadic and radiation-induced tumors (37,49). *NF1* gene mutations are often found in MPNST (54,55), as well as mutations

Table 4 Differential features of giant spindle cell tumors in the mediastinum (1,24-27,32-44)

Tumor	Morphologic characteristics	Anxillary testing
Angiosarcoma	• Vascular structures/channels lined by atypical endothelial cells which can be bland to very atypical • Neoplastic spindle and/or epithelioid cells • High mitotic activity, necrosis, and hemorrhage common	• IHC: vascular markers (CD31, CD34, ERG, Fli-1) Keratin in subset • *MYC* amplification in radiation-induced sarcoma
Schwannoma	• Usually encapsulated • Tumor cells spindled and uniform with elongated nuclei • Tumor cells arranged in Antoni A and B areas • Verocay bodies—hallmark of schwannoma • Hyalinized blood vessels	• IHC: S100 protein, SOX-10
MPNST	• Dense proliferation of atypical spindle or epithelioid cells with high mitotic activity and necrosis • Cartilage, bone, glandular structures, rhabdomyoblasts ("malignant Triton tumors") possible	• IHC: focal S100 protein, SOX-10; subset of tumors shows loss of expression of H3K27me3; epithelioid MPNST: subset shows loss of expression of INI-1, strong S100 protein and SOX-10 expression, intact H3K27me3
Synovial sarcoma	• Monophasic (spindle cells only) or biphasic (epithelial- and spindle-cell components in various proportions) • Epithelial cells can form nests, cords, or glands • Spindle cells: delicate, fairly uniform, relatively small, sparse cytoplasm, ovoid, bland but hyperchromatic nuclei with granular chromatin and inconspicuous nucleoli; growing in dense cellular sheets or vague fascicles • Poorly differentiated areas might be present	• IHC: SS18-SSX and SSX-C-terminus; epithelial cells: keratin; spindle cells: keratin (focal) in most cases • FISH or RT-PCR (only necessary if fusion-specific IHC not available): t(X;18)(p11;q11) (2/3 of cases *SS18-SSX1* fusion, 1/3 *SS18-SSX2* fusion, a few cases with *SS18-SSX4* fusion)
Liposarcoma	• Well-differentiated: adipose tissue with scattered atypical spindle cells with nuclear atypia and dark nuclear chromatin • Dedifferentiated: might harbor well-differentiated liposarcoma areas. Sheets of atypical spindle cells • Myxoid: small, round, stellate cells with variable small lipoblasts in a myxoid stroma • Pleomorphic: bizarre lipoblasts, multinucleated floret-type giant cells	• Well-differentiated: FISH: *MDM2* amplification • Well-differentiated, dedifferentiated: giant ring and marker chromosomes containing amplified sequences of chromosome region 12q13-15 for genes *MDM2, CDK4*, and *CPM* • Myxoid: *DDIT3* gene rearrangements
Desmoid-type fibromatosis	• Poorly circumscribed • Infiltrative • Elongated, slender spindle cells of uniform appearance • No nuclear hyperchromasia or cytologic atypia • Cells grow in long sweeping bundles • Variable mitotic rate • Collagenous stroma with variably prominent blood vessels	• Usually not necessary • IHC: variable staining for MSA, SMA, nuclear beta-catenin stain (70–75% of tumors) • Molecular: *CTNNB1* mutation (85% of tumors)
Solitary fibrous tumor	• Usually well-circumscribed • Spindle cells • Ropey collagen • Hemangiopericytoma-like vasculature	• IHC: STAT6, CD34 • Molecular: *NAB2–STAT6* gene fusion (usually not necessary)
Micronodular thymoma with lymphoid stroma	• Slightly spindled or oval bland appearing epithelial cells, no or low mitotic activity, forming nodules • Background of B cells forming scattered lymphoid follicles with germinal centers	• Usually not necessary in resection specimen • IHC: neoplastic cells: keratin AE1/AE3, p40, p63 B cells: CD20 Scattered TdT-positive thymocytes
Metaplastic thymoma	• Biphasic • Epithelial component: islands or trabeculae of oval or slightly spindled cells with moderate eosinophilic cytoplasm, very low mitotic activity • Fibroblast-like spindle cell component: Bland spindle cells with pale cytoplasm • Thymocytes absent	• IHC: epithelial cells: keratin AE1/AE3, p40, p63 Spindle cells: keratin AE1/AE3 +/–; p40/p63– • Molecular: *YAP1-MAML2* gene fusion in both components

IHC, immunohistochemistry; MPNST, malignant peripheral nerve sheath tumor; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase-polymerase chain reaction; MSA, muscle specific actin; SMA, smooth muscle actin.

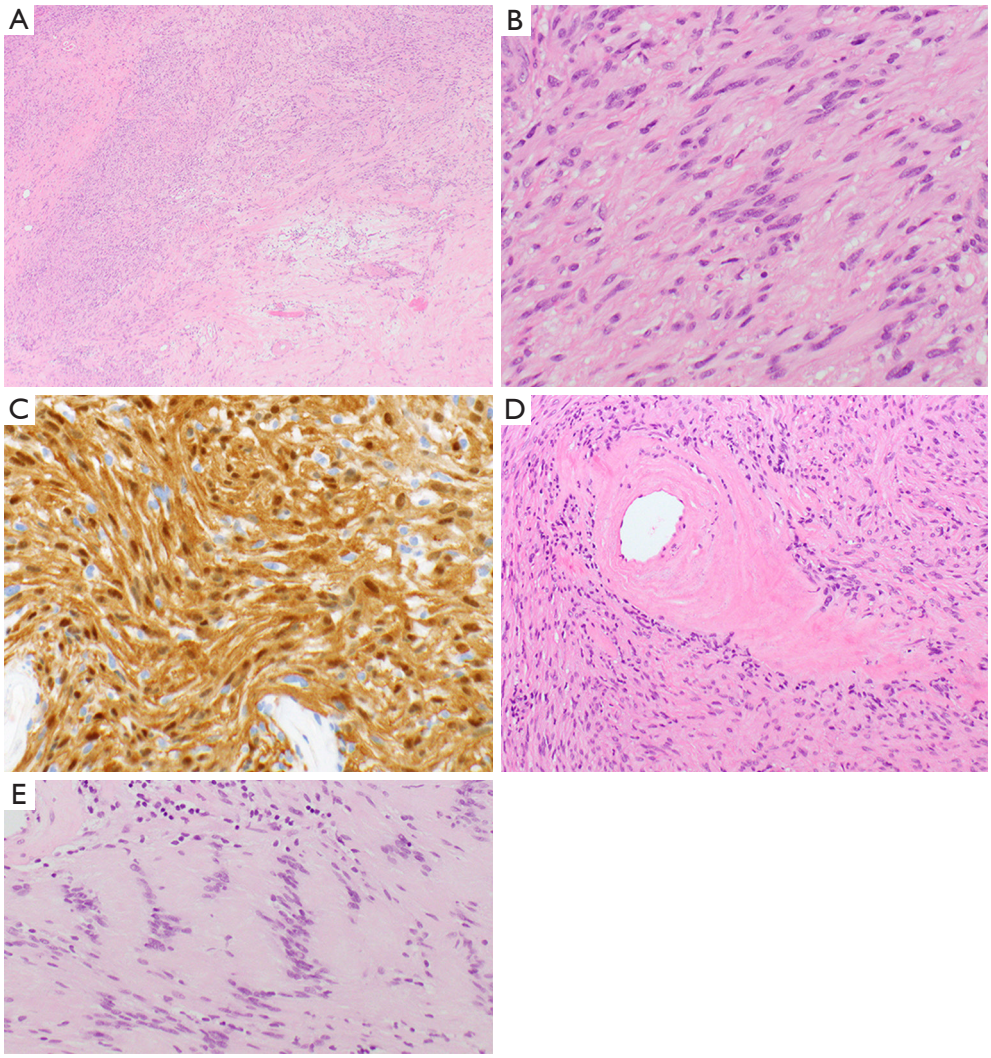

Figure 3 Schwannoma. (A) This spindle cell neoplasm is comprised of hypercellular (Antoni A, upper left) and hypocellular (Antoni B, lower right) areas. (B) The neoplasm is comprised of bland elongated neoplastic cells. (C) The neoplastic cells express S100 protein (nuclear and cytoplasmic). (D) Hyalinized vessels can be seen. (E) Verocay bodies, characterized by palisading spindle cells, are a hallmark of schwannomas. Magnification, H&E ×40 (A), ×400 (B), ×200 (D,E), S100 protein ×400 (C). H&E, hematoxylin-eosin.

in *CDKN2A/CDKN2B* and *EED* or *SUZ12* (56-59). These tumors are characterized by dense populations of spindle cells, high mitotic activity, and necrosis (*Figure 4A*,*4B*) (37). MPNSTs may also contain cartilage, bone, glandular structures, and/or rhabdomyoblasts ("malignant Triton tumors"). The neoplastic cells may focally express S100 protein and SOX-10 or are entirely negative for both. H3K27me3 (*Figure 4C*), if lost, can be helpful in the differential diagnosis (38). Seventy-five percent of epithelioid MPNSTs, a subtype of MPNST harbor an inactivating *SMARCB1* (INI1) mutation, demonstrated with loss of INI1 expression by IHC. They are also strongly S100 protein and SOX-10 positive, without loss of H3K27me3 (39). MPNST have a poor prognosis with a mortality of 60% (49,60).

Paraganglioma

Paragangliomas are rare neural crest neoplasms encompassing less than 1% of mediastinal lesions (2). They can occur in any of the mediastinal compartments (2,7,61). In the mediastinum they originate from the sympathetic

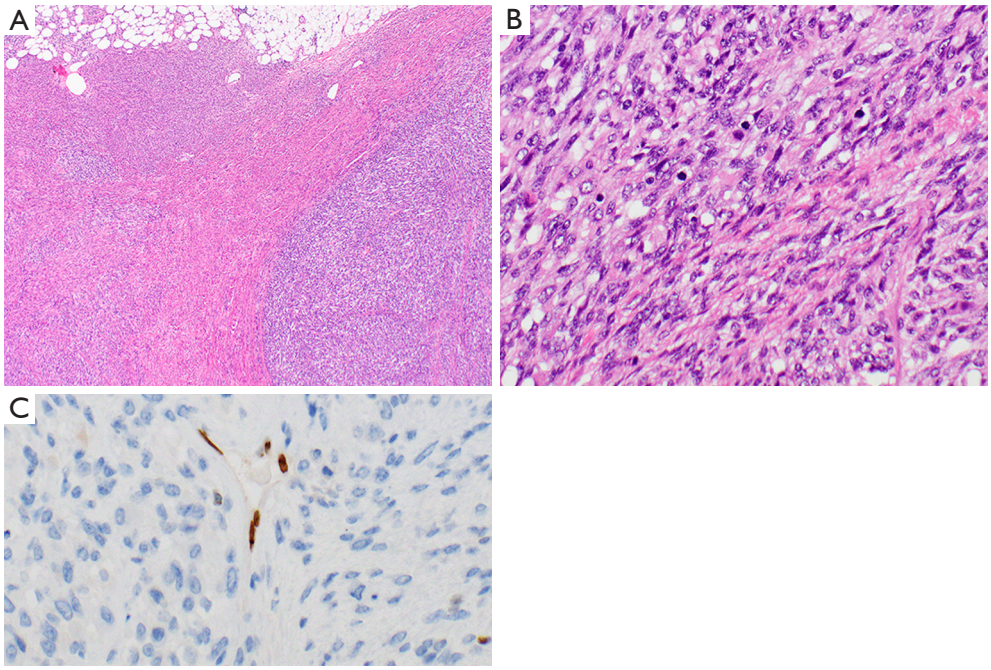

Figure 4 Malignant peripheral nerve sheath tumor. (A) Sheets of neoplastic spindle cells are invading adipose tissue. (B) The neoplastic cells are largely of spindled cytology, show some pleomorphism, and exhibit high mitotic activity. (C) The expression of H3k27me3 is lost in the neoplastic cells (note the preserved expression of H3k27me3 in benign endothelial cells serving as positive internal control). Magnification, H&E ×40 (A), ×400 (B), H3k27me3 ×400 (C). H&E, hematoxylin-eosin.

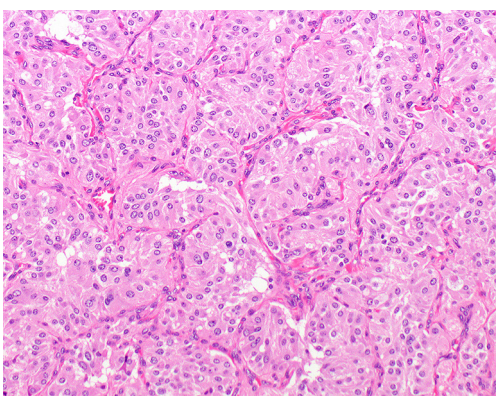

Figure 5 Paraganglioma. Nests of epithelioid cells that are characterized by ample cytoplasm and round nuclei are forming "Zellballen" that are surrounded by capillaries and sustentacular cells. Magnification, H&E ×200. H&E, hematoxylin-eosin.

ganglia. Paragangliomas are usually circumscribed and can sometimes be larger than 10 cm in diameter (62). Histologically they are recognized by epithelioid cells arranged in a nested pattern ("Zellballen"), where epithelioid tumor cells are surrounded by sustentacular cells (*Figure 5*). Nuclei may sometimes be pleomorphic, with occasionally pronounced nucleoli. Tumor cells have finely granular, eosinophilic, or basophilic cytoplasm. Mitotic activity can be seen in approximately half of paragangliomas (62). The tumor cells express neuroendocrine markers (chromogranin, synaptophysin, INSM1) and are characteristically negative for keratins. Sustentacular cells express S100 protein and GFAP. A subset of mediastinal paraganglioma has been found to harbor single or multiple mutations including *SDHB*, *SDHD*, *SDHC*, *ATRX*, *TERT*, and *TP53* mutations (62). In most of the patients, germline mutation analysis revealed the same succinate dehydrogenase mutation (or the lack thereof) as identified in the paraganglioma of that patient (62).

All above mentioned tumors of neurogenic origin may occur over a wide age range, but most commonly in adults.

Neuroblastic tumors

Peripheral neuroblastic tumors (PNTs) of the thorax tend to occur in young patients. They include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. PNT of the thorax comprise 20% of all PNT, which are the most

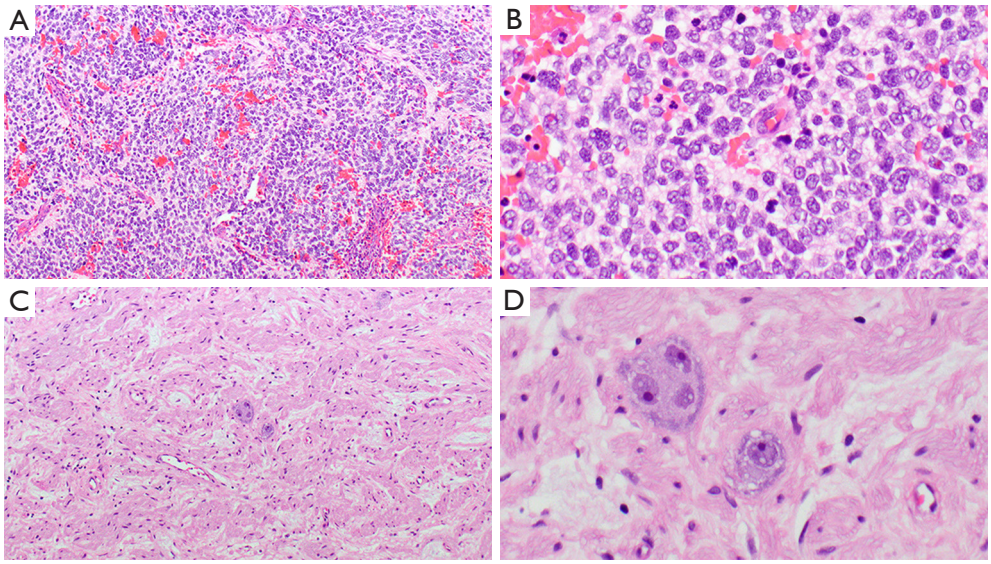

Figure 6 Schwannian stroma-poor neuroblastoma (A,B) and ganglioneuroma (C,D). (A) This hypercellular neoplasm is largely comprised of small round blue cells (B) with high mitotic activity and karyorrhexis, forming vague nests of cells. No Schwannian stroma is present. (C) Abundant Schwann cells are growing in fascicles with interspersed mature ganglion cells (also D). Magnification, H&E ×100 (A,C), ×400 (B,D). H&E, hematoxylin-eosin.

common neoplasms in the first year of life (4,63,64). Histologically, these neoplasms consist of ganglion cells in different stages of differentiation ranging from neuroblasts to mature ganglion cells. Various amounts of Schwann cells and stroma may also be present. Necrosis, hemorrhage, karyorrhexis, mitosis, calcification, and fibrosis are common. Based on the histologic features the International Neuroblastoma Pathology Committee recognizes four categories of neuroblastic tumors: neuroblastoma (Schwannian stroma-poor, *Figure 6A*,*6B*), ganglioneuroblastoma, intermixed (Schwannian stroma-rich), ganglioneuroma (Schwannian stroma-dominant, *Figure 6C*,*6D*), and ganglioneuroblastoma, nodular (Schwannian stroma-rich/dominant/poor) (65). The tumor cells are positive for NSE , chromogranin, synaptophysin, and CD56, which can aid in the diagnosis. However, while expressed in the tumor cells of neuroblastic tumors, NSE is not specific for these tumors and indeed is expressed in many other neoplasms, therefore this test is not very useful in the distinction of neuroblastic tumors from its mimickers. Molecular alterations in these tumors include *MYC* amplification, *ALK* mutation/amplification, *TERT* rearrangement, *ATRX* mutations, and various chromosomal aberrations (66-69). Since therapy is dependent on risk-stratification, and can vary from observation and surgery only (in the low-risk group) to multimodality treatments with surgery, chemotherapy, radiation, and anti-GD2 antibody-based immunotherapy, one universally accepted risk stratification system is needed (70-72). The International Neuroblastoma Risk Group (INRG) classification system takes into account the INRG stage, age, histologic category and grade, *MYCN* amplification status, and 11q aberration and ploidy (73). However, it is still not accepted as the only risk-stratification system (74).

Mesenchymal neoplasms

Synovial sarcoma

Synovial sarcomas are malignant tumors that are characterized by t(X;18)(p11;q11) resulting in *SS18-SSX* gene fusion in more than 95% of cases. In the thorax, these tumors most commonly occur in the pleura or lung; only 1.4% of all synovial sarcomas are in the prevascular or paravertebral mediastinum (75-78). The average tumor size in that location is 13.5 cm (range, 6–29 cm). There is a slight male predominance and the mean age of patients is 38 years (range, 14–75 years) (79). Patients are usually symptomatic at the time of presentation and are treated by resection (if possible) and chemotherapy and/or radiation.

Synovial sarcomas are comprised of a monomorphic

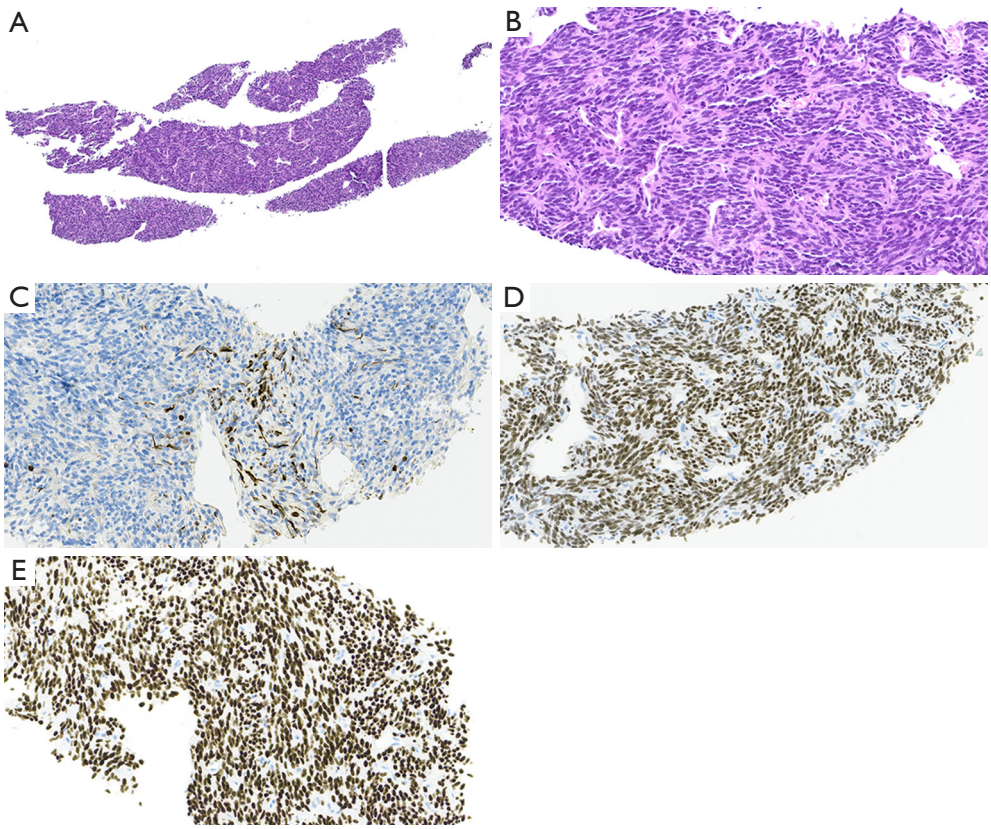

Figure 7 Synovial sarcoma, monophasic. (A,B) Sheets of monomorphic spindle cells are present with interspersed hemangiopericytoma-like (branching) vessels. (C) The neoplastic cells are focally positive for keratin AE1/AE3 and show diffuse nuclear staining for SS18-SSX (D) and SSX-C-terminus (E). Magnification, H&E ×40 (A), ×400 (B), keratin AE1/AE3 ×400 (C), SS18-SSX ×400 (D), SSX-C-terminus ×400 (E). H&E, hematoxylin-eosin.

spindle cell proliferation with (biphasic) or without (monophasic, *Figure 7A-7C*) an epithelial component. In the mediastinum, most of the synovial sarcomas appear to be monophasic, over half of them exhibit a poorly differentiated morphology with rounded or spindle cells that have higher nuclear grade, rhabdoid cytology, and high mitotic activity (76). Otherwise, these tumors show a hemangiopericytoma-like vasculature, wiry collagen, alternating zones of hyper- and hypocellularity, and mast cells in the stroma (76). In the lung/pleura entrapped pneumocytes may mimic a biphasic synovial sarcoma. Fusion-specific antibodies, SS18-SSX (*Figure 7D*) and SSX-C-terminus (*Figure 7E*) have recently been shown, especially in combination, to be highly specific and sensitive for synovial sarcoma (40,41). If not available, cytogenetic and molecular studies may also be used to confirm the diagnosis. The differential diagnosis includes other sarcomas, specifically leiomyosarcoma and MPNST, solitary fibrous tumor, sarcomatoid or biphasic mesothelioma, sarcomatoid carcinoma, melanoma, desmoid-type fibromatosis, and even type A thymomas among others.

Local recurrence or progressive disease has been reported in almost 90% of patients with mediastinal synovial sarcoma (76). Metastases occur in about half of the patients including to the lung, pericardium, diaphragm, soft tissue, and brain. In a series of 21 mediastinal synovial sarcomas 69% of patients died of the disease 5 to 32 months after diagnosis, the remaining patients were alive with disease (76). Tumor size of over 5 cm and locally recurrent disease have been shown to be independent risk factors for worse outcome (78).

Liposarcoma

Liposarcomas are rare in the mediastinum and comprise less than 1% of all mediastinal lesions (80). They are most

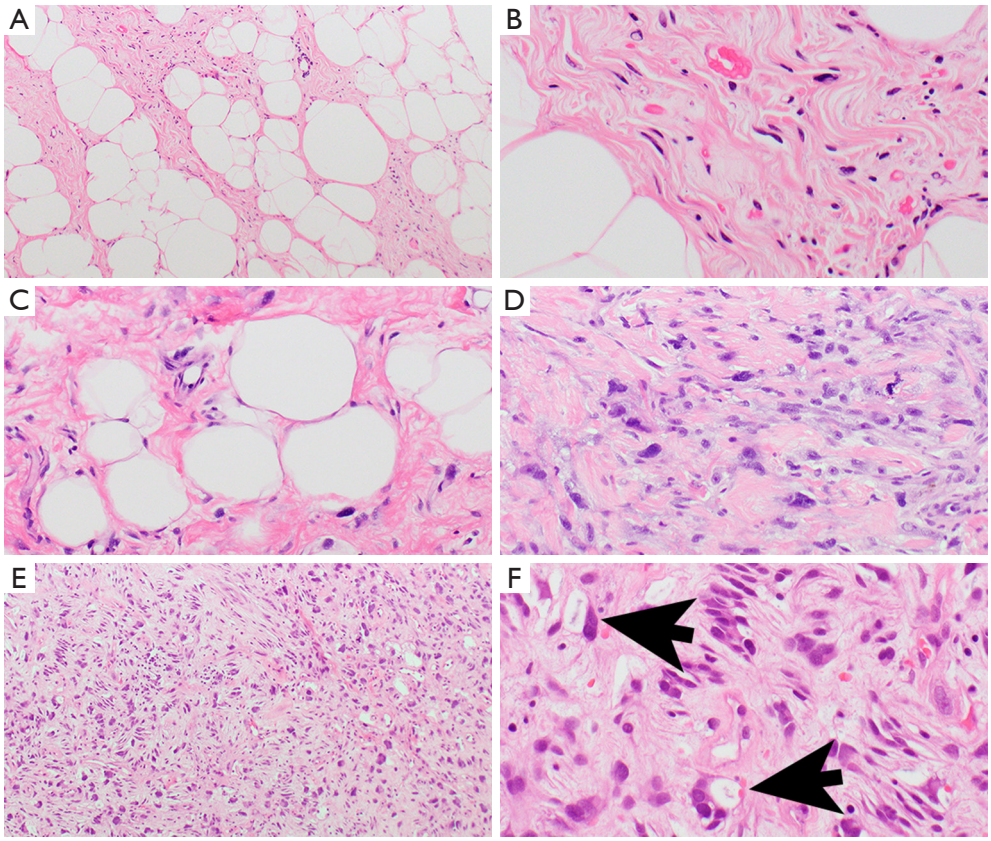

Figure 8 Well-differentiated (A,B), dedifferentiated (C,D) and pleomorphic liposarcoma (E,F). (A) An adipose neoplasm is characterized by intersecting fibrotic areas that contain atypical spindle cells with characteristic dark nuclear chromatin (B). Fluorescence in situ hybridization revealed *MDM2* rearrangement (not shown). (C) An area of well-differentiated liposarcoma with atypical spindle cells with dark nuclear chromatin is present. (D) Other areas of the neoplasm show sheets of large pleomorphic spindle cells with dark nuclear chromatin and mitotic activity. (E) This neoplasm is predominantly comprised of pleomorphic spindle cells and contains scattered pleomorphic lipoblasts (arrows F). Magnification, H&E ×100 (A,C,E), ×400 (B,D,F). H&E, hematoxylin-eosin.

commonly found in the paravertebral mediastinum followed by prevascular and visceral mediastinum (80). These tumors can grow up to at least 40 cm (42). The mean age of patients is 53 to 63 years without sex predilection (42,81).

Any of the liposarcoma subtypes can occur in the mediastinum (80). Well-differentiated liposarcomas are the most common subtype in the mediastinum followed by dedifferentiated liposarcoma (80). Pleomorphic liposarcomas appear to be disproportional and more common in the mediastinum than in the soft tissue (42). Myxoid liposarcomas may also occur. Unusual morphologic variants such as lipoleiomyosarcoma, dedifferentiated liposarcoma with "meningothelial"-like dedifferentiation, differentiated myxoid liposarcoma mimicking well-differentiated liposarcoma, and pleomorphic liposarcoma with epithelioid and myxoid change have also been described in this location (42).

Well-differentiated liposarcomas are characterized by adipose tissue with scattered atypical spindle cells with nuclear atypia and dark nuclear chromatin (*Figure 8A,8B*). Sometimes the distinction from lipoma can be challenging. In these circumstances, *MDM2* amplification by fluorescence in situ hybridization (FISH) confirms liposarcoma (43). Dedifferentiated liposarcomas are often arising from well-differentiated liposarcomas and therefore usually harbor well-differentiated areas (*Figure 8C*). Otherwise, these tumors are comprised of sheets of atypical spindle cells (*Figure 8D*). Myxoid liposarcomas are composed of small, round, stellate cells with variable small lipoblasts in a myxoid stroma. Pleomorphic liposarcomas are characterized by

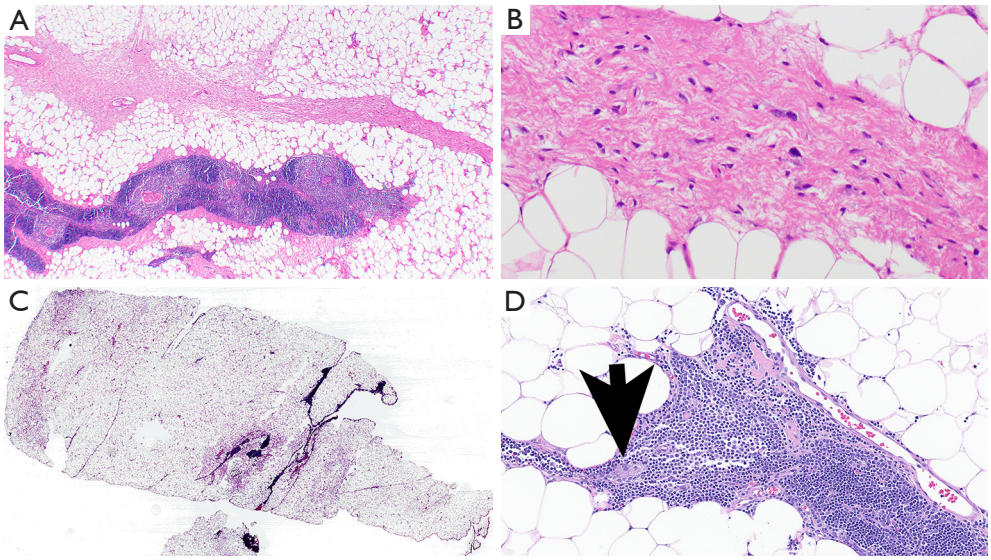

Figure 9 Thymoliposarcoma (A,B) and thymolipoma (C,D). (A) Thymic gland tissue with preserved architecture including a darker cortex and paler medulla harboring Hassall corpuscles is in a background of adipose tissue with intersecting fibrosis. (B) Within the fibrosis there are atypical spindle cells with dark nuclear chromatin. (C) This lesion is predominantly comprised of benign adipose tissue with occasional strands of thymic tissue (D, note remnant Hassall corpuscle, arrow). Magnification, H&E ×20 (A), ×200 (B), ×2 (C), ×20 (D). The case of thymoliposarcoma was contributed by Dr. Andrew L. Folpe, Mayo Clinic Rochester. H&E, hematoxylin-eosin.

bizarre lipoblasts (*Figure 8E,8F*) and possibly multinucleated floret-type giant cells.

Well-differentiated and dedifferentiated liposarcomas harbor characteristic giant ring and marker chromosomes containing amplified sequences of chromosome region 12q13-15 for genes *MDM2*, *CDK4*, and *CPM*, which can be helpful in the diagnosis (42,43). Myxoid liposarcomas do not carry these amplifications but often harbor *DDIT3* gene rearrangements (42).

In the mediastinum, the differential diagnosis of liposarcoma includes lipoma, thymoliposarcoma, thymolipoma, lipofibroadenoma, lipoblastoma (which in general occurs in children less than 3 years old), other sarcomas, and melanoma.

The outcome of liposarcomas is associated with the histologic subtype with worse outcomes of myxoid liposarcomas, followed by pleomorphic liposarcomas (42). Well-differentiated liposarcomas have the best prognosis. Primary mediastinal liposarcomas have a recurrence rate of 10% to 50% after resection; they can metastasize to the lungs, liver, soft tissues, bone, and brain (42).

Thymoliposarcoma

Thymoliposarcomas are extremely rare but are in the differential diagnosis of thymomas, liposarcomas, and thymolipomas. Thymoliposarcomas are usually large tumors ranging from 9 to 35 cm (82,83). Grossly these tumors are described as fatty masses and are usually encapsulated and lobulated (82). On microscopy, lobules of thymic tissue are embedded in the adipose tissue (*Figure 9A*). The adipose tissue is comprised of benign-appearing and atypical adipocytes, the latter are characterized by hyperchromatic, pleomorphic, and irregular nuclei (*Figure 9B*). Atypical spindle cells are reported scattered in the adipose tissue and thymic cortex. *MDM2* amplification has been reported in one case (83). In a series of 11 cases, the mean age of the patients was 55.8 years (range, 31–77 years) with a slight male predominance (82). Most of the reported cases had a favorable outcome with 4 patients experiencing recurrence and/or metastasis to a vertebra, lymph nodes, and/or lung.

Thymolipoma

Thymolipoma is another rare tumor of the thymus which occurs in the prevascular mediastinum and is classified under mesenchymal neoplasms (adipocytic tumors) in the 2021 WHO classification (4). Thymolipomas have been reported to range in size from 3 cm to more than 30 cm. Since the first description in 1916 (84) less than 300 cases were reported in the English literature. The current name was

assigned in 1949 by Hall (85) who described a mixed tumor composed of fat and thymic tissue. Thymolipomas constitute 2% to 9% of thymic tumors and occur over a wide age range (6 months to 82 years), but are more commonly found in younger patients with equal gender distribution (86). In most patients, they will be detected as incidental findings. If symptomatic, patients can present with dyspnea, chronic cough, weight loss, respiratory infections, and even vomiting. Up to 50% of thymolipomas are associated with myasthenia gravis (87,88). They occur very often at the cardiophrenic angle and weigh over 500 g, with a maximal reported weight of 16 kg (88,89). Macroscopically they are usually yellow, soft masses, with a capsule and lobulated appearance. Histologically, most of the tumor (50–95%) is composed of mature adipose tissue (*Figure 9C*), without any morphologic signs of malignancy. The remainder is comprised of benign, usually involuted thymic parenchyma (*Figure 9D*) (86,90). A single thymolipoma was described to harbor a t(12,14)(q15q32) (91) suggestive of a dysregulation in the *HMGA2* gene which has been identified in the majority of lipomas. If possible, complete surgical resection is curative, without recurrence.

Thoracic SMARCA4-deficient undifferentiated tumor

Thoracic SMARCA4-deficient undifferentiated tumors (SMARCA4-DUT) are very aggressive tumors (92-94). *SMARCA4* encodes BRG1, a tumor suppressor, which is a catalytic subunit of the SWI/SNF (BAF) chromatin-remodeling complex. The SWI/SNF complex is involved in the regulation of transcription and the promotion of cell differentiation (94-96). SMARCA4-DUT are characterized by inactivating mutations of *SMARCA4* resulting in loss of BRG1 expression in neoplastic cells (97). In general, these tumors also show loss of BRM1 (encoded by *SMARCA2*, another catalytic subunit of SWI/SNF) although a study of SMARCA4-DUT in the lung showed preserved expression of BRM1 in 18% of the cases (93,98).

The reported median age of these patients ranges between 39 and 59 years (range, 27–82 years) (92,93,95,98,99). There is a male predominance with a male-to-female ratio of up to 9:1. Most patients are smokers. Patients most commonly present with dyspnea, chest pain, and SVC syndrome (92). Tumors are often large at presentation with reported median tumor sizes of 12 to 13 cm (range, 2.2–27 cm). In the thorax, most SMARCA4-DUT are found in the prevascular mediastinum followed by pleura and lung.

These tumors are characterized by poorly differentiated cytology with medium-sized epithelioid cells with irregular nuclear borders and often conspicuous nucleoli (*Figure 10A*). Sometimes, at least focally, rhabdoid cytology is appreciated (*Figure 10B*). Focal myxoid stroma or desmoplastic small round cell tumor features are described in 7% of the tumors (99). Mitotic activity is high and extensive necrosis is usually noted. While the tumor cells are forming clusters and sheets, they are growing in a somewhat discohesive pattern. The immunophenotype can vary, however, these tumors show no or only focal keratin expression (*Figure 10C*) (93,98,99). Loss of expression of BRG1 (*Figure 10D*) is the hallmark of SMARCA4-DUT. Diffuse expression of SOX2 is reported in almost all cases (94,95,99). About one-third of the cases express CD34 and/or SALL4. Synaptophysin can also be expressed in a subset of cases. Rare tumors focally express claudin 4 and TTF-1. SMARCA4-DUT are negative for desmin, nuclear protein in testis (NUT), S100 protein, WT-1, and p40 (93,98,99). In 69% to 88% of cases a *TP53* mutation is identified (93,94).

The pathogenesis of SMARCA4-DUT is not entirely clear. Evidence suggests that these tumors may represent de-differentiated non-small cell carcinomas (93) although some features indicate that they are more closely related to other BAF-deficient tumors such as malignant rhabdoid tumor and small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) (94).

The differential diagnosis of SMARCA4-DUT includes malignant rhabdoid tumor and atypical teratoid/rhabdoid tumor, metastatic SCCOHT, non-small cell lung carcinoma, NUT carcinoma, GCT, lymphoma, malignant melanoma, mesothelioma, and sarcoma (99). Loss of BRG1 expression by itself is not specific for SMARCA4-DUT as it can also be seen in carcinomas including those of lung origin, SCCOHT, and a subset of malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors.

The majority of patients with SMARCA4-DUT has metastases at time of presentation including to lymph nodes (59–91% of patients), adrenal gland (27–48%), lung (29%), and bone (24–55%) (92,93). The median survival of these patients is only 4 to 7 months (range, 1–13 months). Disease progression or relapse occurs in essentially all patients and patients in general die of their disease, mostly due to local complications (92,94). Response to chemotherapy and surgery is limited (92). However, promising preclinical studies and early clinical trials with the H3K27 histone methyltransferase EZH2 inhibitor are underway in tumors related to the SWI/SNF complex emphasizing the importance of an accurate

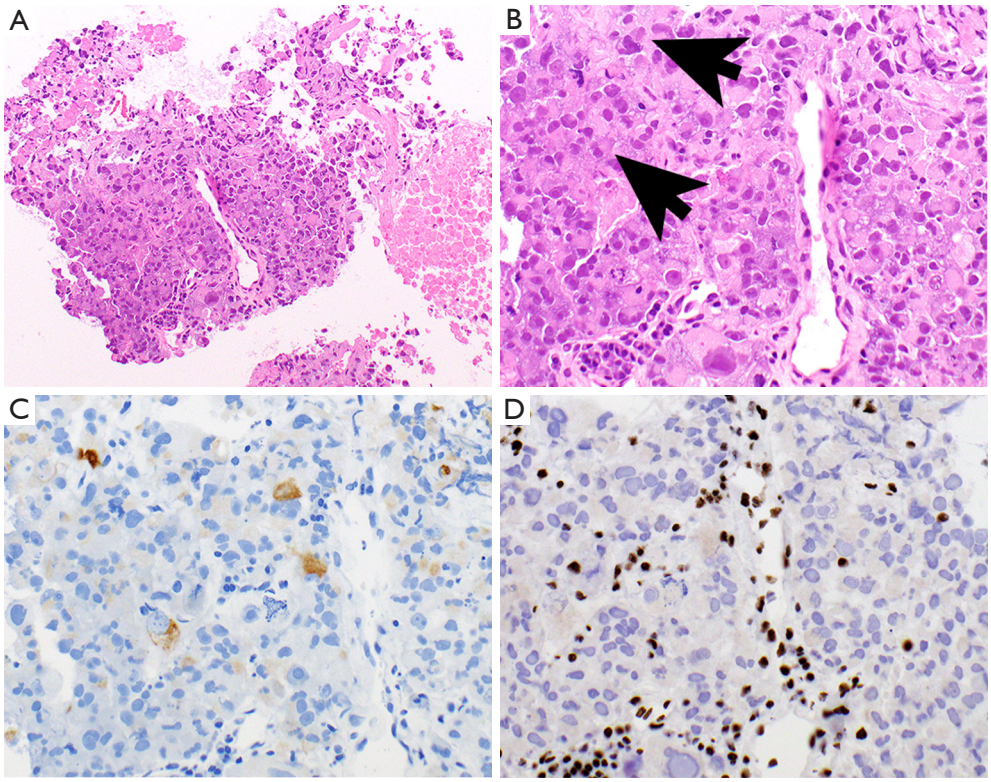

Figure 10 SMARCA4-deficient undifferentiated tumor. (A) Tumor cells are growing in sheets although they are discohesive in some areas. Large areas of necrosis are also present. (B) The neoplastic cells are epithelioid with prominent nucleoli. Some exhibit rhabdoid features as characterized by eccentric nuclei with prominent nucleoli and eosinophilic cytoplasm (arrows points toward two examples of tumor cells with rhabdoid features). (C) Only rare tumor cells express weakly OSCAR keratin. (D) BRG1 (SMARCA4) expression is lost in the tumor cells (note nuclear staining of benign cells which serves as internal positive control). Magnification, H&E ×100 (A), ×400 (B), OSCAR keratin ×400 (C), BRG1 ×400 (D). OSCAR, broad spectrum anti-cytokeratin antibody; H&E, hematoxylin-eosin.

diagnosis of this tumor (94,100). In addition, a few patients with SMARCA4-DUT showed prolonged partial response following treatment with pembrolizumab, an anti-PD-1 antibody (101,102).

Desmoid-type fibromatosis

Desmoid-type fibromatosis is uncommon in the thorax. In a study of 47 such patients, the median age was 45 years (range, 4–96 years) with a female predominance and a median tumor diameter of 6.5 cm (range, 2.2–13 cm) (103). While the lesions were most commonly located in the chest wall (43%), they also occurred in the supraclavicular area, shoulder, axillary area, and mediastinum. Most patients (75%) underwent resection, some in combination with chemotherapy and/or radiation.

Desmoid-type fibromatosis are poorly circumscribed neoplasms that grow in an infiltrative pattern. The neoplastic spindle cells are bland, elongated, and slender of uniform appearance and are growing in interlacing bundles/long sweeping fascicles in a collagenous stroma with variably prominent blood vessels (*Figure 11A,11B*). In general, there is no nuclear hyperchromasia or cytologic atypia. The mitotic rate can vary. In 70% to 100% of cases, the tumor cells show nuclear beta-catenin staining due to *CTNNB1* mutation that is seen in 85% of these tumors or, in a few cases, mutations in the *APC* gene (104,105). SMA expression is found in a large subset of fibromatoses (103). The tumor cells are negative for CD34, desmin, and S100 protein (103). The Ki-67 labeling index is low with 1 to 3% of tumor cell nuclei staining (103).

Desmoid-type fibromatosis may recur but does not metastasize; in the study of 47 patients with thoracic fibromatosis 28% of patients had recurrence and 13%

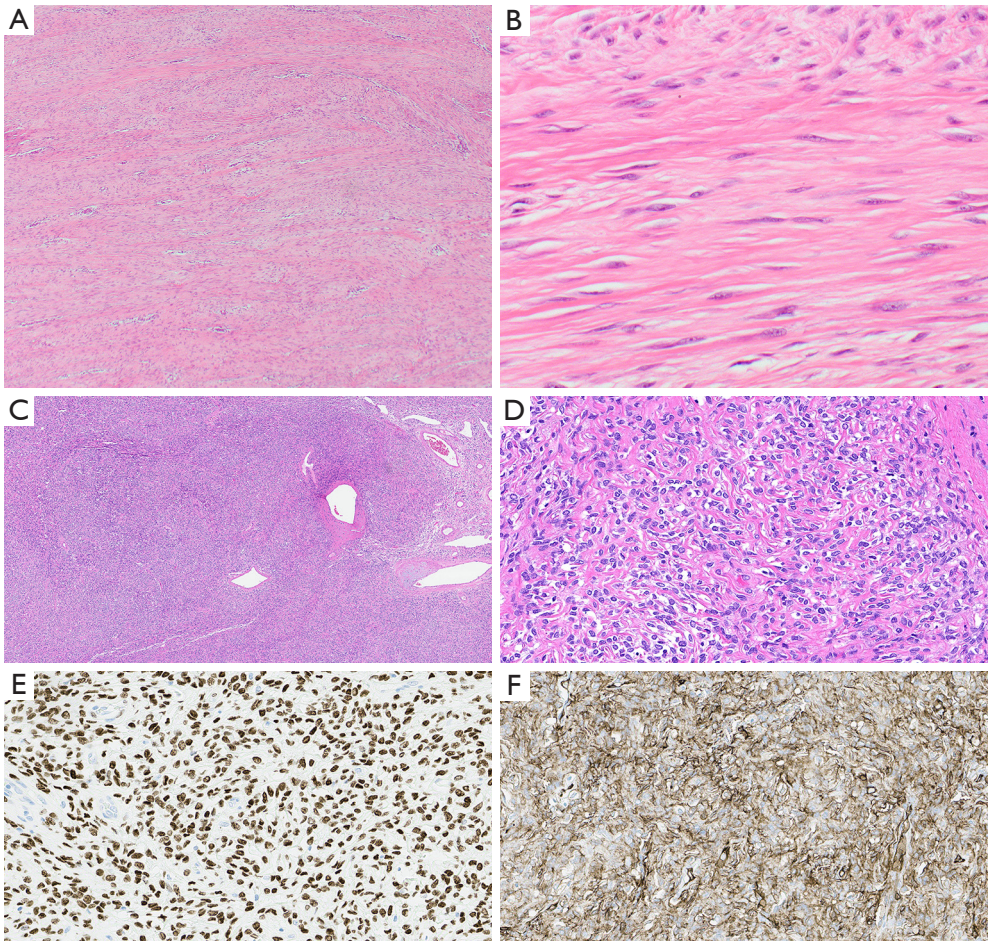

Figure 11 Desmoid-type fibromatosis (A,B) and solitary fibrous tumor (C-F). (A) Spindle cells are growing in long, sweeping fascicles. (B) The spindle cells are elongated and bland and have ample cytoplasm. (C) This neoplasm is characterized by a cellular spindle cell proliferation with scattered vessels some of which have a hyalinized wall. (D) The neoplastic spindle cells are bland and associated with ropey collagen. The neoplastic cells are positive for STAT6 (E) and CD34 (F). Magnification, H&E ×40 (A,C), ×400 (B,D), STAT6 ×400 (E), CD34 ×400 (F). H&E, hematoxylin-eosin.

progressed (103).

The differential diagnosis of desmoid-type fibromatosis includes solitary fibrous tumor, synovial sarcoma, and desmoplastic mesothelioma.

Solitary fibrous tumor

The solitary fibrous tumor is a spindle cell neoplasm that is usually slow growing, well circumscribed, and only rarely occurs as a primary tumor in the mediastinum. It may be pedunculated. In a study of 70 resected thoracic solitary fibrous tumors only 23% originated from the mediastinum (106). While approximately 30% of all solitary fibrous tumors occur in the thoracic cavity, most of those arise in the pleura (107). Patient's symptoms are usually due to the mass effect on vital structures. However, patients may also become hypoglycemic and acromegalic due to the production of IGF2 by the tumor (108).

Solitary fibrous tumors are comprised of bland oval and spindled cells growing in a patternless pattern with cells intersected by ropey collagen (*Figure 11C*,*11D*). Hemangiopericytoma-like vasculature is characterized by branching or antler-like vessels which are often hyalinized (*Figure 11C*). Mitotic activity and necrosis are variable. The neoplastic cells express STAT6 (*Figure 11E*), CD34 (*Figure 11F*), and Bcl2. Keratins, desmin, SMA, SOX10,

and S100 protein are negative. Resected solitary fibrous tumors are stratified based on their risk to metastasize. While various risk stratifications are proposed, the authors use the risk stratification model proposed and refined by Demicco *et al.* (109) that includes patient age, tumor size, mitotic activity, and the presence or absence of necrosis. Evidence suggests that mediastinal solitary fibrous tumors behave more aggressively than their pleural counterpart although the numbers are small. Studies also have shown that *TERT* promoter mutations in solitary fibrous tumors are associated with increased *TERT* mRNA expression and older age, larger tumor size, higher risk classification, and worse event-free survival (110).

The pathogenesis of solitary fibrous tumors appears to be related to a *NAB2-STAT6* fusion gene due to paracentric inversion on chromosome 12q13 (111).

In the mediastinum, especially in the prevascular mediastinum, solitary fibrous tumors need to be differentiated from type A thymoma, monophasic synovial sarcoma, localized sarcomatoid mesothelioma, desmoid fibromatosis, and carcinoid tumor.

TET

Thymoma

Thymomas are rare malignant neoplasms that comprise 38% of all solitary prevascular mediastinal lesions in adults (2). They are part of a spectrum of epithelial neoplasms of the thymus. They commonly occur in the 5th to 6th decade of life, although reported age distribution is from 6 to 83 years old, with female predominance. Thymomas comprise up to 85% of TET in adults (112,113).

Thymomas most commonly occur in the prevascular mediastinum. On imaging, they are well-demarcated, usually homogeneous, and round/lobulated. Occasionally they infiltrate surrounding structures. The size of most thymomas is on average less than 10 cm. However, micronodular thymoma with lymphoid stroma (MNTLS) and metaplastic thymoma can reach 15 and 18 cm, respectively. Since only these fulfill our defined size limit of 10 cm, we will discuss them in more detail below.

Patients with thymoma are staged according to the American Joint Committee of Cancer (AJCC)/International Union Against Cancer (UICC) TNM staging system (114), although the Masaoka-Koga system is still often reported as well (115). In many studies, staging and complete resection have been shown to be the most important prognostic factor (113,115-117). Although the overall prognosis is often favorable, thymomas are regarded as malignant due to their invasive and metastatic potential.

MNTLS occurs in older patients, with a slight male predominance. Patients are usually asymptomatic (118,119). On gross examination, tumors are well demarcated, with a capsule. The cut surface is soft and tan. Morphologically these neoplasms are defined by slightly spindled or oval bland appearing epithelial cells without atypia and no or low mitotic activity comprising small nodules in a background of B cells forming scattered lymphoid follicles with germinal centers (*Figure 12A,12B*). Scattered TdT-positive thymocytes are usually located at the interface between the epithelial cell nodules and the lymphocytic component. Occasionally cystic changes and rosette-like structures can occur. In up to 30% of MNTLS a component of type A thymoma is also present (119-121). The prognosis is very good, with currently no reported tumor-related deaths, recurrences, or metastases, after surgical removal (119). MNTLS needs to be distinguished from micronodular thymic carcinoma with lymphoid stroma, lymphoepithelial carcinoma, and type AB thymoma.

Metaplastic thymoma is a biphasic thymic tumor. It is reported in patients with an age range from 28 to 71 years old and is more common in women. Patients are usually asymptomatic (122-125). Macroscopically these neoplasms are well-demarcated and sometimes have a capsule. The cut surface is grey-white or yellow and solid. Histologically metaplastic thymomas are composed of two more or less well-separated components. The epithelial component comprises islands or trabeculae of oval or slightly spindle cells (*Figure 12C,12D*). The cytoplasm is moderate and eosinophilic. Mitotic activity is very low. In these areas there is commonly eosinophilic hyaline material present. The other cell component is comprised of fibroblast-like spindle cells with pale cytoplasm. Plasma cells may be present, but thymocytes are usually absent. The majority of metaplastic thymomas does not show invasion and metastases are not reported. After complete surgical resection overall survival is very good (123,126,127). Rare metaplastic thymomas have been reported to transform into sarcomatoid carcinomas (128,129).

YAP1-MAML2 gene fusions have been identified in metaplastic thymoma (44,130).

Lipofibroadenoma of the thymus

Lipofibroadenoma is another rare tumor occurring in the

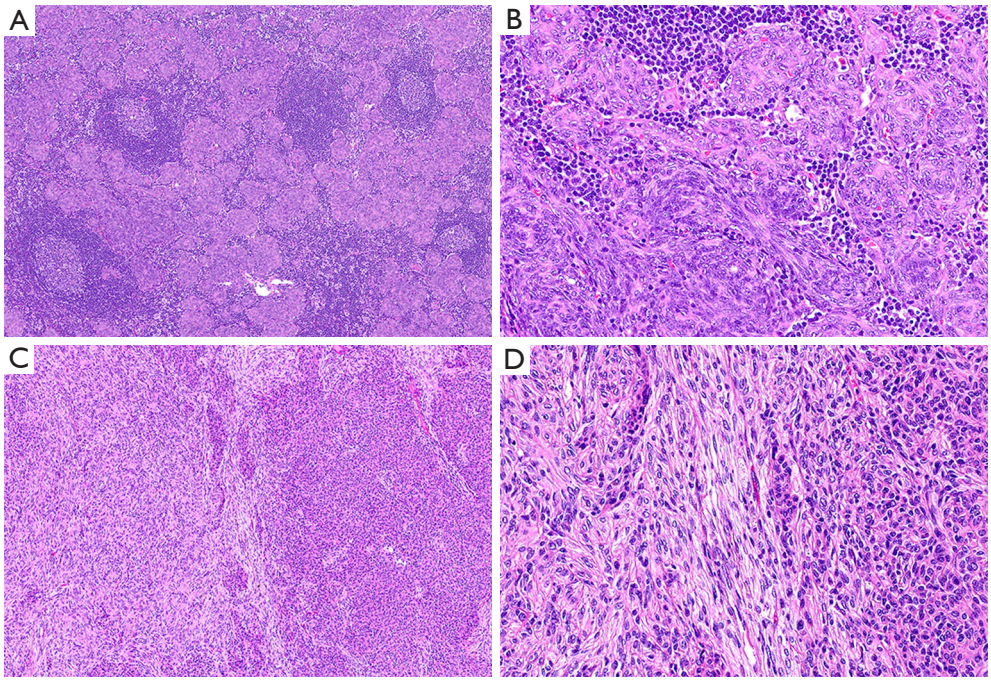

Figure 12 Micronodular thymoma with lymphoid stroma (A,B) and metaplastic thymoma (C,D). (A) Nests of neoplastic cells are in a background of follicular hyperplasia with scattered lymphoid follicles containing reactive germinal centers. (B) The neoplastic cells are bland, oval to slightly elongated with inconspicuous nucleoli. (C) This biphasic neoplasm is comprised of darker (right side) and paler (predominantly left side) areas. (D) The darker cells are plumper and have less cytoplasm which is eosinophilic while the paler cells are more elongated and larger with pale cytoplasm. Magnification, H&E ×10 (A,C), ×40 (B,D). H&E, hematoxylin-eosin.

prevascular mediastinum and classified under TET in the 2021 WHO. It is composed of adipose, fibroelastotic, and thymic tissue (*Figure 13A-13D*). Only case reports of patients with these tumors are available (131-135). Patients are usually asymptomatic, although fever, cough, and night sweats were reported (135). Lipofibroadenomas have been reported up to 23 cm in size (135). Histologically lipofibroadenomas are similar to thymolipomas and fibroadenomas of the breast. It is not clear if this tumor represents a hamartoma or a true neoplasm. It is regarded as a benign tumor, with an excellent prognosis if completely resected.

Thymic carcinoma

Thymic carcinomas encompass 7% of all solitary prevascular mediastinal lesions in adults (2). These tumors are usually large and infiltrative and while their mean or median tumor size has been reported between 5.4 and 8.7 cm, they may become as large as 17 cm (136-138). The age range is quite broad with reported median age ranging from 54 to 66 years old (2,136,137,139-143). Thymic carcinoma can be of various subtypes with the most common being squamous cell carcinoma (*Figure 14A,14B*) (144). Other subtypes include basaloid carcinoma, lymphoepithelial carcinoma, NUT carcinoma (see below), clear cell carcinoma including thymic hyalinizing clear cell carcinoma with *EWSR1* translocation, low-grade papillary adenocarcinoma, adenocarcinoma not otherwise specified (NOS), mucoepidermoid carcinoma, thymic carcinoma with adenoid cystic carcinoma-like features, enteric-type adenocarcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, undifferentiated carcinoma, and thymic carcinoma NOS.

NUT carcinoma

NUT carcinomas are very aggressive tumors that most commonly occur in the midline of the thorax where 51% of all cases are located followed by head and neck (41%) and other sites (145,146). A few NUT carcinomas have been reported outside of the midline. The median age ranges between 16 and 50 years (range, 0.1–80 years). Fifty-one to

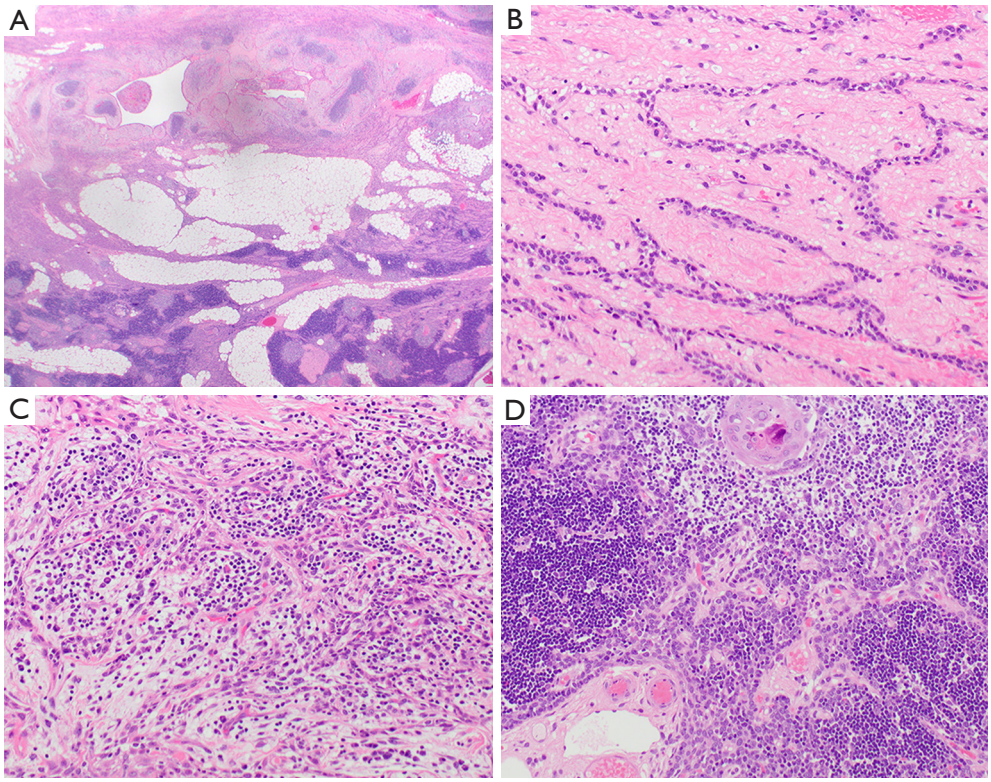

Figure 13 Lipofibroadenoma. (A) Fibroelastotic tissue (upper part), morphologically reminiscent of a fibroadenoma of the breast, is intimately associated with adipose tissue and thymic tissue (lower part). (B) Bland epithelial cells form trabecula in a fibroelastotic and inflamed (C) background. (D) The thymic parenchyma is architecturally preserved with a paler medulla containing Hassall corpuscles (upper part) and a darker cortex. Magnification, H&E ×12.5 (A), ×200 (B-D). H&E, hematoxylin-eosin.

sixty-seven percent of patients have metastases at the time of presentation. Most commonly a *BRD4-NUT* fusion due to t(15;19)(q14;p13.1) has been identified although other fusion partners of *NUT* have also been reported (146-148). This tumor is considered an aggressive subset of squamous cell carcinomas.

Morphologically NUT carcinomas are characterized by a rather monotonous population of epithelioid cells with an increased nuclear-to-cytoplasmic ratio, prominent nucleoli, and open chromatin (*Figure 14C*,*14D*). An abrupt squamous differentiation may be noted in a subset of cases (*Figure 14D*). Specifically in small biopsies there can be crush artifacts leading to a potential misdiagnosis of small cell carcinoma. Large areas of necrosis are usually apparent. The immunoprofile varies; typically, the neoplastic cells are positive for keratin and markers of squamous differentiation such as p40 (*Figure 14E*) and CK5; they may also express TTF-1 and CD34. NUT immunostain shows a characteristic nuclear stippled expression pattern (*Figure 14F*) and is 100% specific (after exclusion of a GCT) and 87% sensitive for NUT carcinoma (149). While other assays such as cytogenetics and reverse transcription-polymerase chain reaction (RT-PCR) are available, they are not necessary if the immunostain is positive.

The outcome is usually fatal with a median overall survival of 4.7 to 6.7 months with only rare patients surviving for several years (150,151). The median overall survival is significantly worse in thoracic *BRD4-NUTM1* NUT carcinomas (4.4 months) compared with non-thoracic *BRD4-NUTM1* NUT carcinomas (10 months) and non-thoracic, non-*BRD4-NUTM1* NUT carcinomas (36.5 months) (152). Complete surgical resection and/or initial radiotherapy may be associated with increased progression-free and overall survival (150,153). Clinical trials have been performed or are ongoing using for instance bromodomain and extraterminal domain (BET) family inhibitors to target the BRD4-NUT protein (154,155).

The differential diagnosis includes small cell carcinoma,

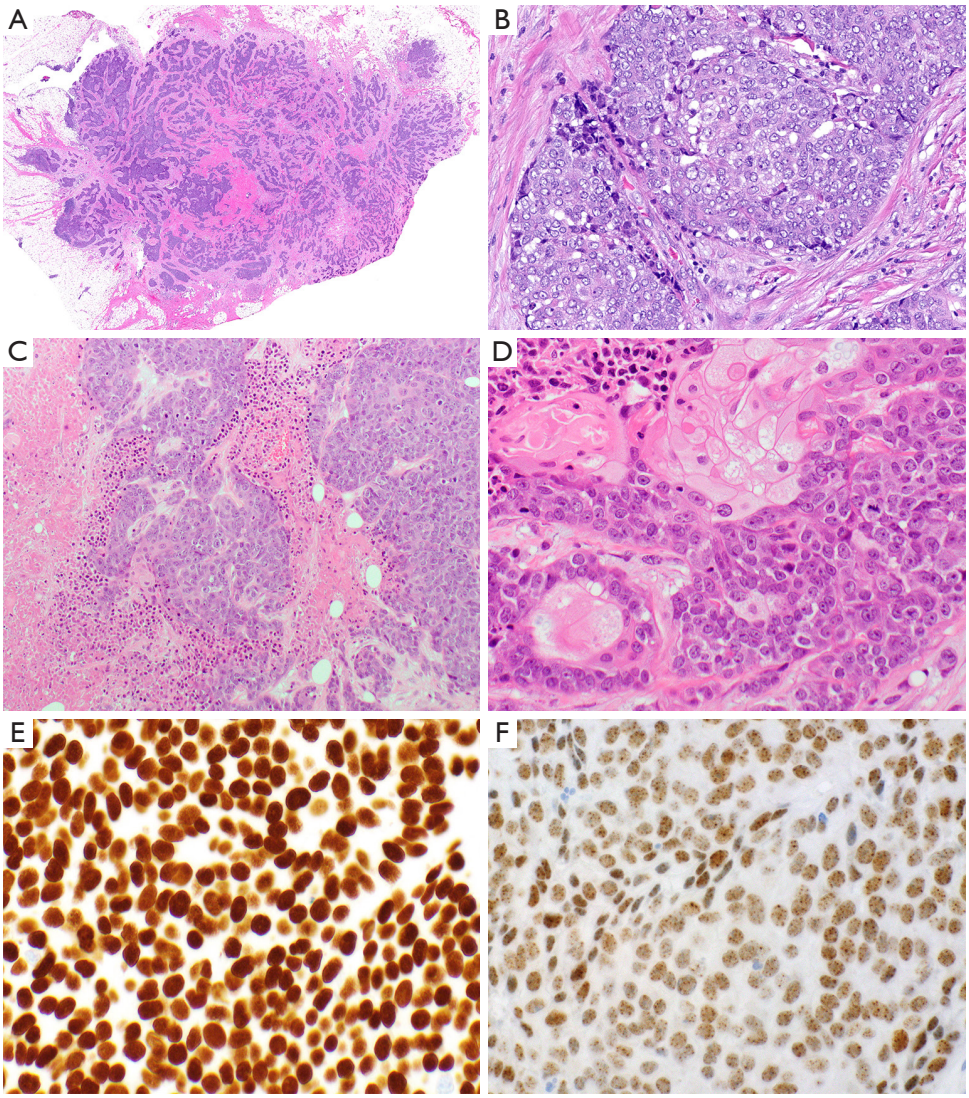

Figure 14 Thymic squamous cell carcinoma (A,B) and NUT carcinoma (C-F). (A) Irregular nests of tumor cells are within a fibrotic stroma and invade adjacent adipose tissue. (B) The tumor cells are large, have round nuclei with more conspicuous nucleoli, and grow in a desmoplastic stromal reaction. The tumor cells are positive for p40 and negative for NUT and EBV in situ hybridization (not shown). (C) Sheets of neoplastic cells and large areas of necrosis are present. (D) The neoplastic cells have a monotonous cytology characterized by round-to-slightly-oval cells with only a small amount of cytoplasm and conspicuous nucleoli. There is an abrupt squamous differentiation. The tumor cells are positive for p40 (E) and NUT (F) (note the characteristic stippled nuclear staining pattern of NUT). Magnification, H&E ×2 (A), ×40 (B), ×100 (C), ×400 (D), p40 ×400 (E), NUT ×400 (F). NUT, nuclear protein in testis; EBV, Epstein-Barr virus; H&E, hematoxylin-eosin.

squamous cell carcinoma, lymphoma, and SMARCA4-DUT.

Primary GCTs of mediastinum

GCTs most commonly occur in gonads. In the mediastinum of adults and children, they comprise up to 5–15% or 20% of neoplasms, respectively (2,156). Although the mediastinum is the most common site of extragonadal GCTs, they only account for 2% to 7% of all GCTs (157,158). Almost all primary mediastinal GCT (PMGCT) develop in the prevascular mediastinum (2,159,160). Evidence suggests that PMGCT arise from primordial

germ cells that underwent an aberrant migration during embryogenesis or possibly from stem cells in the thymus (161-164). The incidence of PMGCT abruptly increases with puberty (157,165). While teratomas and yolk sac tumors predominate in prepubertal patients, in postpubertal males a third of the PMGCT are seminomas, a third are teratomas, and a third are mixed GCT, yolk sac tumors, embryonal carcinomas, or choriocarcinomas. In postpubertal females in general only teratomas are found. PMGCT share most of the immunophenotypical and genetic characteristics with gonadal GCT such as the presence of isochromosome 12p or 12p amplification. Unique features include rare *PDGFR* mutations that only occur in mediastinal, but not in gonadal seminomas (166). Furthermore, PMGCT can be associated with Klinefelter syndrome (167-169). In addition, hematologic malignancies are more commonly associated with PMGCT than GCT elsewhere (170,171). PMGCT often present when they are large at which time the patients experience chest pain, cough, and dyspnea.

Microscopically PMGCT are identical to gonadal counterparts. They are divided into seminomas, non-seminomatous tumors, and teratomas. The most common PMGCT are teratomas, encompassing 43% to 74% of all PMGCTs, followed by seminomas (10–37%) (172,173). Useful immunostains have been presented by Fichtner *et al.* (174).

Here the most common PMGCT will be shortly presented: teratoma, seminoma, yolk sac tumor, and embryonal carcinoma.

Seminomas occur in postpubertal males usually after the age of 10 years old. Seminomas can grow up to 20 cm in diameter and patients are generally symptomatic. Histologically seminomas are composed of sheets or clusters of uniform, polygonal cells with round nuclei and prominent nucleoli (*Figure 15A,15B*). The cytoplasm is glycogen-rich, clear to dense eosinophilic. Cell borders are distinct. Usually, there is a background of lymphocytes forming lymphoid follicles with germinal centers (166). Poorly formed non-necrotizing granulomas are often present and can mask the tumor cells leading to a potential wrong assumption of infection (175). In addition, seminomas can present with a lobulated architecture and fibrous bands, features that are similar to thymoma and classic Hodgkin lymphoma, nodular sclerosis type. Lastly, seminomas can be associated with a cyst and therefore the evaluation of the wall of any cyst in the mediastinum is important (176). Indeed, many tumors in the mediastinum can be associated with a cyst including but not limited to seminoma, thymoma, and lymphoma.

Yolk sac tumors are characterized by various patterns such as glandular-alveolar, solid, hepatoid, macrocystic, microcystic (reticular), endodermal sinus, myxomatous, enteric, polyvesicular-vitelline, and spindle, that often occur together in a single tumor (*Figure 15C-15F*). Schiller Duval bodies are the hallmarks of yolk sac tumors although they are not always present.

Embryonal carcinoma is an infiltrative malignant tumor growing up to 22 cm, with a poor prognosis. Histologically embryonal carcinoma can also present with various growth patterns, including solid, glandular, and papillary (177), usually with necrotic areas and hemorrhage. Tumor cells are large and polygonal, with clear to eosinophilic and basophilic cytoplasm, prominent nucleoli, and high numbers of mitoses.

Teratomas occur in both sexes and all age groups and can reach up to 25 cm in diameter. While the majority of mediastinal teratomas are mature (*Figure 16A,16B*), immature teratomas and teratomas with other malignant component(s) such as another GCT, sarcoma, carcinoma, or hematologic malignancy also occur. Pure teratomas derived from nontransformed precursor cells show normal 12p copy numbers and no cytologic atypia and are considered benign (type I GCT). Those teratomas occur in children, females, and some males (178). In postpubertal males, pure teratomas identified in resection specimens post-neoadjuvant chemotherapy in patients who had elevated serum markers including AFP or beta-HCG before neoadjuvant therapy are suggested to derive from malignantly transformed precursor cells, commonly harbor increased 12p copy numbers and show cytologic atypia and are regarded as malignant (type II GCT) (178).

Some PMGCT may be combined with somatic-type malignancies (*Figure 16C-16H*), or they occur as a combination of two or more PMGCT (mixed GCTs of the mediastinum).

Seminomas have an excellent cure rate with cisplatin-based chemotherapy with 5-year overall survival of 72% to 100%. Five-year overall survival is much worse for patients with non-seminomatous tumors, being only 45% to 60% which is also worse in comparison to similar tumors in other locations (179-181).

Non-neoplastic mediastinal cysts

Mediastinal cysts are rare benign lesions that comprise 12% to 24% of solitary lesions in the mediastinum (2,182). While most mediastinal cysts are identified incidentally, some

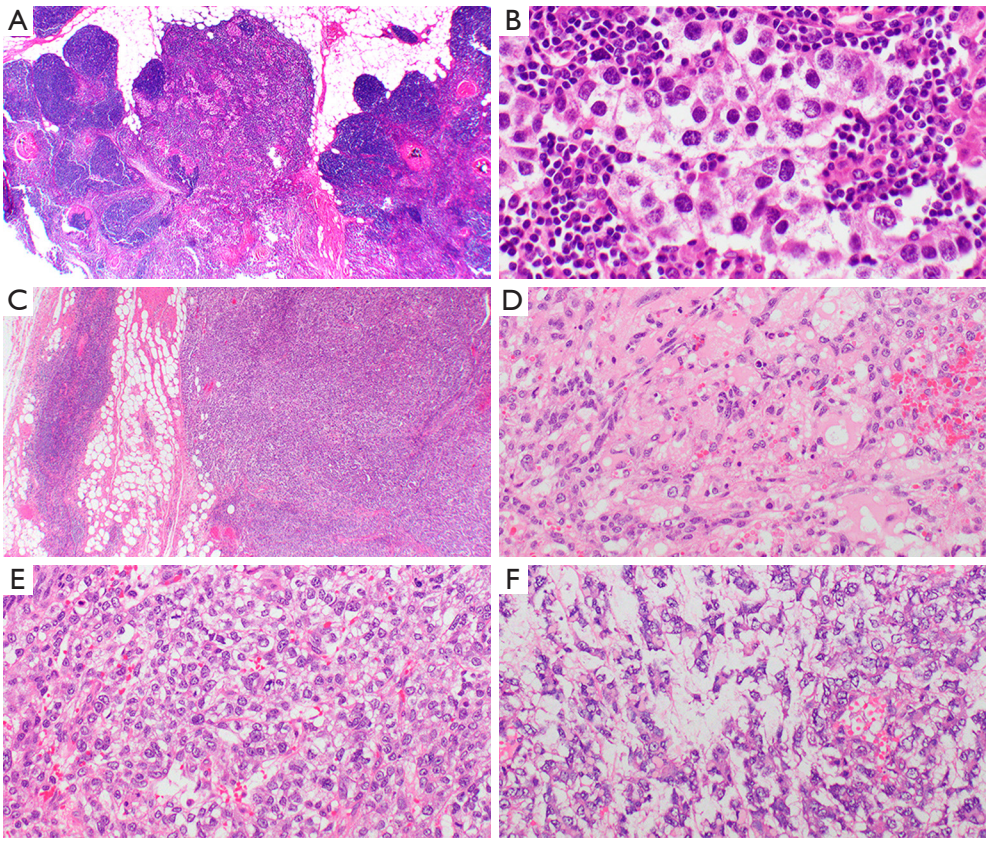

Figure 15 Seminoma (A,B) and yolk sac tumor (C-F). (A) Seminoma (middle of the picture) appears to arise in the thymic gland (note thymic gland with Hassall corpuscles on both sides of the picture). (B) Clusters of polygonal neoplastic cells with clear cytoplasm, distinct cellular borders, and round nuclei with prominent nucleoli (seminoma cells) are in a background of small lymphocytes. (C) A neoplasm (right) is invading adipose tissue. An unremarkable thymic gland is also present (left side). This neoplasm is characterized by various morphologic patterns including microcystic (D) and solid (E) and focal myxoid stroma (F). Magnification, H&E ×20 (A,C), ×400 (B), ×200 (D-F). H&E, hematoxylin-eosin.

patients present with symptoms, especially as these cysts can reach as much as 18 cm in diameter (2,183). It is important to differentiate benign cysts from cystic neoplasms or neoplasms that are associated with a mediastinal cyst. Therefore, cystic lesions should be sampled extensively especially if any solid areas or cyst wall irregularities are noted. Based on the pathogenesis mediastinal cysts are classified as derived from embryonic foregut (bronchogenic and enteric cysts), mesothelial derived (pleural and pericardial cysts), thymic cysts, and rare cysts (thoracic duct cyst, mediastinal parathyroid cyst, and cyst with Muellerian differentiation) (182). While the majority of mediastinal cysts are congenital, multilocular thymic cysts, some thoracic duct cysts, and rarely pleuropericardial cysts are acquired (184).

All cysts occur equally in both females and males, except cysts with Muellerian differentiation which occur exclusively in females (184,185).

Bronchogenic cysts are usually unilocular cysts with a smooth surface, and up to 12 cm in diameter (186). They are filled with gelatinous, mucinous, or serous material. The cyst wall is lined by a respiratory type of ciliated pseudostratified epithelium, with or without squamous metaplasia. The cyst wall usually harbors cartilage, seromucinous glands, and/or smooth muscle, and rarely nerves and fat reminiscent of components of a large airway (*Figure 17A,17B*).

Thymic cysts can be unilocular or multilocular, reaching 18 cm in diameter (187,188). Both unilocular and multilocular cysts have smooth surfaces and contain

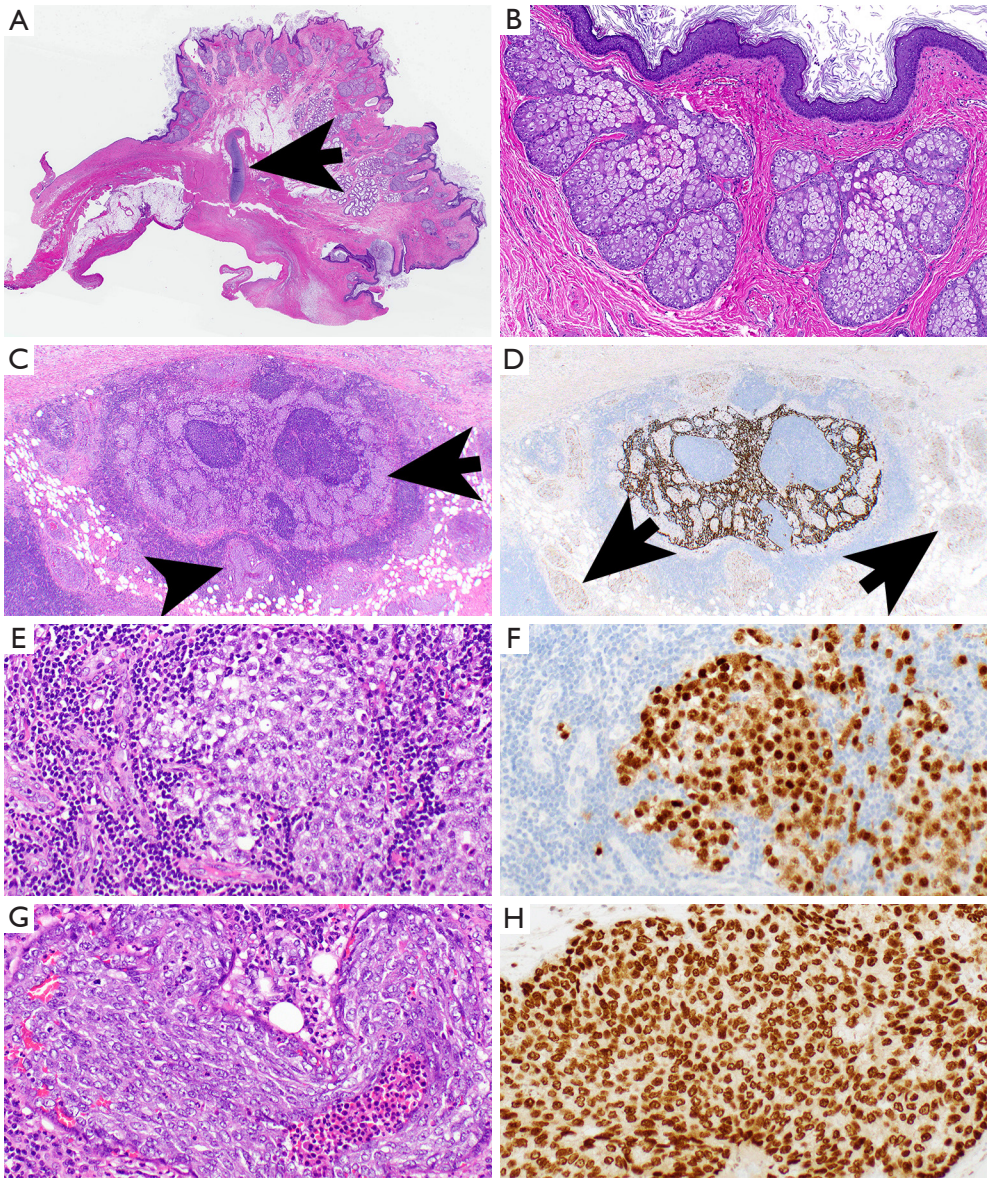

Figure 16 Mature teratoma (A,B) and angiosarcoma arising in a seminoma in the background of thymic gland (C-H). (A) This lesion is comprised of various mature tissues including keratinizing squamous epithelium with associated sebaceous glands (high magnification, B) and dermal glandular structures, cartilage (arrow), and adipose tissue. (C) Nests of tumor cells (arrow and arrowhead) are in an inflammatory background and adipose tissue. (D) Keratin AE1/AE3 highlights the epithelial component of the thymic gland. It also shows weak staining in tumor cells (arrows point toward some of the nests of tumor cells with weak keratin expression). (E) High magnification of a tumor cell nest indicated by the arrow in (C) reveals round cells that have clear or eosinophilic cytoplasm and prominent nucleoli, morphologic features suggestive of seminoma which was confirmed by the expression of OCT3/4 (F). (G) High magnification of a tumor cell nest indicated by the arrowhead in (C) shows slightly spindled cells with oval nuclei and prominent nucleoli. The neoplastic cells are associated with necrosis. (H) The tumor cells express ERG and other vascular markers (not shown), consistent with an angiosarcoma indicating a somatic malignancy arising in a germ cell tumor. Magnification, H&E ×2 (A), ×10 (B), ×20 (C), ×200 (E,G), keratin AE1/AE3 ×20 (D), OCT3/4 ×200 (F), ERG ×200 (H). H&E, hematoxylin-eosin.

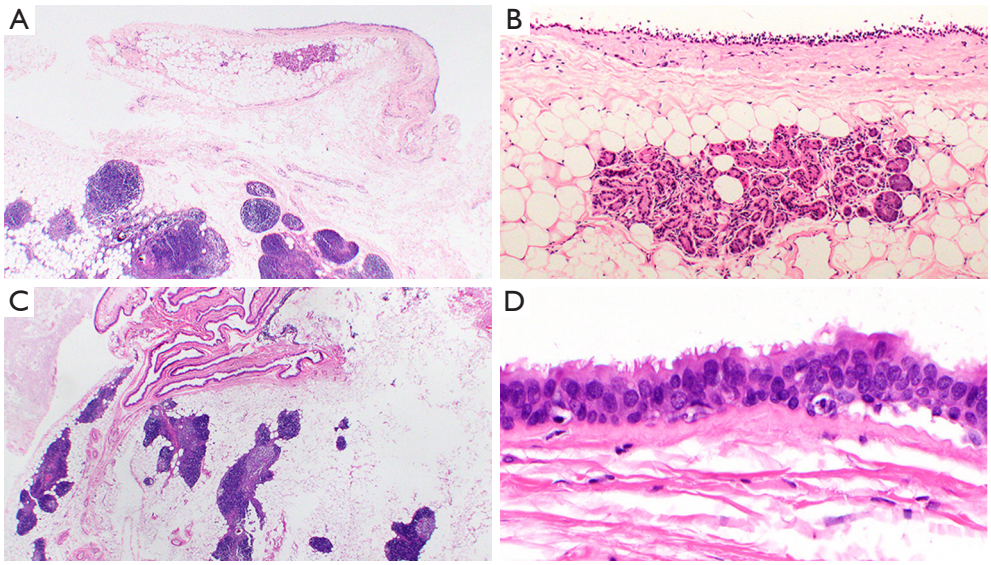

Figure 17 Bronchogenic (A,B) and thymic cyst (C,D). (A) A cyst lining is seen in the upper part of the picture with a nest of glandular structures below. In the lower part of the picture, there is benign thymic gland. (B) The cyst is lined by respiratory epithelium. Underneath the cyst lining, in the adipose tissue, there is a cluster of seromucinous glands. (C) A cyst is present in the background of thymic gland. (D) The cyst lining is comprised of stratified ciliated epithelium. Magnification, H&E ×20 (A), ×100 (B), ×12.5 (C), ×400 (D). H&E, hematoxylin-eosin.

serous material, however, multilocular cysts can also present with hemorrhagic content. In the cyst wall, there must be thymic tissue. The cyst lining may be comprised of flat, columnar, ciliated, or cuboidal cells, with areas of squamous epithelium (*Figure 17C,17D*). In multilocular cysts, there are often additional degenerative changes (fibrosis, cholesterol cleft granulomas), inflammation (including lymphoid follicles), and granulation tissue. Since these cysts may be associated with thymic epithelial neoplasms, lymphomas, and PMGCT, thorough sampling is essential (172,187-189).

Enteric cysts (esophageal duplication cyst, gastroenteric and neurenteric cyst) are usually found around the esophagus or in its wall. They can be associated with various congenital anomalies such as tracheoesophageal fistula, esophageal atresia, or congenital pulmonary airway malformation and vertebral malformations (neurenteric cyst) (190,191). Their wall has double-layered smooth muscle, covered with stratified squamous epithelium with or without esophageal glands (esophageal duplication cyst), or gastric/intestinal-type epithelium (gastroenteric cyst).

Mesothelial cysts (celomic, pleuropericardial cysts) also have a smooth surface, usually with a thin wall covered with mesothelial cells. They can also be multilocular and reach a size of up to 18 cm (192).

The therapy of choice for all non-neoplastic mediastinal cysts is complete surgical removal or observation.

Small biopsies

Large lesions in the mediastinum can lead to life-threatening situations due to compression or infiltration of vital structures such as the heart, large airways, lungs, aorta, and SVC. Therefore, the correct diagnosis is important for immediate treatment and management which differs greatly based on the tumor type and possibly clinical stage. Imaging studies together with clinical findings can suffice in some lesions. For instance, in a young male patient with a prevascular mediastinal mass, a high AFP or beta-HCG by serology (>100 IU/L) is virtually diagnostic of a non-seminomatous GCT and a biopsy is not required to start treatment (157,180). Furthermore, a diagnosis of thymoma is often highly suspected based on clinical and imaging features and patients usually undergo resection of that mass without prior biopsy. However, if for instance a lymphoma is suspected, a tissue biopsy to establish the diagnosis is required. Because of the potential heterogeneity of mediastinal lesions, especially given their potentially large size, the results of the biopsy need to be put in

context to findings on imaging and clinical impression. For instance, if a biopsy was performed in a young male with a prevascular mediastinal mass and high AFP by serology, however, a biopsy only shows mature teratoma, sampling bias should be suspected as a yolk sac tumor component was probably just not sampled. Similarly, thymomas are in general not subtyped on a biopsy because these tumors can harbor multiple components, and even though a biopsy shows for instance type B2 thymoma, there could be a type A component that was not sampled. Moreover, in thymomas, the initial treatment is in general independent of the subtype and largely relies on the clinical stage of the tumor. However, if there is a suspicion for invasion based on imaging or clinical assessment, and the patient will not undergo primary resection of the tumor, a biopsy should be performed before treatment is initiated. Indeed, with the exception of the above-mentioned young male with non-seminomatous GCT, a biopsy of any tumor that will not be primarily resected but treated with neoadjuvant or adjuvant therapy, should be performed. Biopsies of cysts potentially lack the cyst wall and only show cyst content such as necrotic debris resulting in a "non-diagnostic" biopsy. To minimize sampling bias, multiple needle cores or sampling via mediastinoscopy could be considered. Furthermore, sampling of various areas of the tumor could be helpful to additionally alleviate sampling bias. Because there is increasing potential for targeted therapy for some of the mediastinal lesions requiring testing on paraffin embedded tissue, biopsy specimens should be distributed into multiple tissue cassettes.

Taken together, in large mediastinal lesions, prebiopsy clinical impression and imaging analysis are important to critically evaluate the results of a biopsy and to consider sampling bias. A multidisciplinary discussion is important in the workup of any patient with a mediastinal mass.

Conclusions

A large variety of lesions can present as a giant mass in the mediastinum potentially leading to life-threatening situations given the vital structures in the vicinity. The correct diagnosis of these lesions is important as treatment and management differ substantially from resection of benign cysts for instance to chemotherapy for certain GCTs. In some patients, clinical assessment and imaging are sufficient for a diagnosis, for instance in a young male with a prevascular mediastinal mass and high serologic tumor markers, however, in most patients, a biopsy will be required. Given the potential heterogeneity of lesions, biopsy results must be critically reviewed in the clinical and radiologic context given potential sampling bias.

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Footnote

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Supplementary

Table S1 The search terms used

Mediastinum OR Mediastinal AND Thymolipoma
Mediastinum OR Mediastinal AND Liposarcoma
Mediastinum OR Mediastinal AND Thymoliposarcoma
Mediastinum OR Mediastinal AND Lipofibroadenoma
Mediastinum OR Mediastinal AND Desmoid fibromatosis
Mediastinum OR Mediastinal AND Solitary fibrous tumor
Mediastinum OR Mediastinal AND Hemangioma
Mediastinum OR Mediastinal AND Lymphangioma
Mediastinum OR Mediastinal AND Angiosarcoma
Mediastinum OR Mediastinal AND Paraganglioma
Mediastinum OR Mediastinal AND Schwannoma
Mediastinum OR Mediastinal AND Malignant peripheral nerve sheath tumor
Mediastinum OR Mediastinal AND Ganglioneuroma
Mediastinum OR Mediastinal AND Ganglioneuroblastoma
Mediastinum OR Mediastinal AND Neuroblastoma
Mediastinum OR Mediastinal AND Synovial sarcoma
Mediastinum OR Mediastinal AND SMARCA4-deficient undifferentiated tumors
Thymoma
Thymic carcinoma
Mediastinum OR Mediastinal AND NUT carcinoma
Mediastinum OR Mediastinal AND Germ cell tumors AND Primary
Mediastinum OR Mediastinal AND Teratoma AND Primary
Mediastinum OR Mediastinal AND Mixed germ cell tumors AND Primary
Mediastinum OR Mediastinal AND Seminoma AND Primary
Mediastinum OR Mediastinal AND Embryonal carcinoma AND Primary
Mediastinum OR Mediastinal AND Yolk sac tumor AND Primary
Mediastinum OR Mediastinal AND Choriocarcinoma AND Primary
Bronchogenic cyst
Thymic cyst
Enteric cyst
Esophageal duplication cyst
Gastroenteric cyst
Neurenteric cyst
Mesothelial cyst
Celomic cyst
Pleuropericardial cyst

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