



# Sarcomas of the mediastinum with epithelioid morphology

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**Abstract:** While soft tissue sarcomas typically have a spindled or pleomorphic appearance, a subset of malignant soft tissue neoplasms can have a prominent epithelioid morphology. In complex anatomic sites such as the mediastinum, such tumors can often be mistaken for a carcinoma or mesothelioma. Frequent expression of cytokeratin staining can further confound the diagnostic process and familiarity with these entities can help prevent an erroneous diagnosis. Particular entities that have been reported to occur in the mediastinum with such features include dedifferentiated liposarcoma, pleomorphic liposarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma, SMARCA4-deficient thoracic sarcoma, alveolar soft part sarcoma and clear cell sarcoma. Many of these tumors exhibit unique clinical, genetic, molecular or immunohistochemical features which allow for accurate characterization. For example, pleomorphic liposarcoma contains bizarre appearing lipoblasts and dedifferentiated liposarcoma exhibits *MDM2* gene amplification that is typically confirmed by fluorescence *in-situ* hybridization. Malignant peripheral nerve sheath tumor will often arise in association with a nerve or neurofibroma. Synovial sarcoma consistently exhibits rearrangements involving the *SS18* gene and SMARCA4-deficient thoracic sarcoma shows loss of SMARCA4 staining in the tumor cells. Alveolar soft part sarcoma demonstrates an *ASPL-TFE3* fusion transcript. Clear cell sarcoma often shows an *EWSRI-ATF1* fusion transcript. When encountering a sarcoma of the mediastinum with epithelioid features, familiarity with these and other characteristics can help insure a correct diagnosis.

**Keywords:** Soft tissue sarcoma; mediastinum; epithelioid; epithelioid-like; mesenchymal neoplasm

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## Introduction

Although soft tissue sarcomas are typically associated with spindled, pleomorphic or round cells, certain types of sarcomas can have features amazingly similar to epithelial neoplasms. The tumor cells in these “epithelial-like” sarcomas can have rounded to ovoid nuclei which can be vesicular in nature. The cells can be arranged in a tubular or “glandular-like” arrangements frequently seen in carcinomas, mesotheliomas or thymic tumors. Moreover, these sarcomas frequently exhibit immunohistochemical staining for broad spectrum cytokeratins or epithelial

membrane antigen (EMA), further emulating carcinomas. These overlapping features present a formidable diagnostic challenge to the pathologist who encounters a sarcoma with epithelioid morphology. When these tumors arise in locations removed from any epithelial structures (such as soft tissue of extremities for example), one can better consider a mesenchymal tumor with epithelioid morphology. As an anatomic site, however, the mediastinum hosts a wide variety of carcinomas which reflect the diversity of its organs and structures. Additionally, mesenchymal neoplasms comprise only a small percentage (approximately 5%) of primary tumors found in this location (1,2). In

the mediastinum, a sarcoma with epithelioid features is much more likely to be mistaken for a carcinoma or mesothelioma. Consequently, a familiarity with the specific characteristics of sarcomas with epithelioid features is essential for a correct diagnosis.

When suspecting a diagnosis of sarcoma with epithelioid features, all attributes should be taken into consideration during evaluation. The clinical and radiologic attributes, such as the size and progression of the lesion, association with adjacent anatomic structures, and patient's history of previous malignancy are particularly important to know. Histologically, the tumor cells should be assessed for cytologic features such as enlarged nuclei, prominent nucleoli and architectural findings such as a sheet, cord or tubular arrangement. Immunohistochemistry can be helpful; however, the pathologist needs to be aware of the sensitivity and specificity of the stains utilized. Many of these epithelioid-like sarcomas can be positive for specific cytokeratins, such as CK7. Of note, although historically utilized to identify mesenchymal differentiation, vimentin is no longer considered diagnostically useful in this respect, given its incredible lack of specificity.

The aim of this review is to provide an overview of sarcomas with epithelioid morphology that can be encountered in the mediastinum.

## Adipocytic tumors

### *Dedifferentiated liposarcoma with epithelial-like cells*

Well-differentiated liposarcoma typically arises in the deep soft tissue of the extremities or the retroperitoneum with approximately 2% presenting in the mediastinum (3). These low-grade sarcomas can grow quite large and typically exhibit some degree of adipocytic features which make classification relatively straightforward (4,5). They can occasionally, however, transition to higher grade dedifferentiated liposarcomas which no longer exhibit adipocytic features. Histologically, dedifferentiated liposarcomas are typically composed of highly atypical spindled cells which are arranged in a storiform architecture, sometimes emulating undifferentiated high-grade pleomorphic sarcoma (5). Rarely, these dedifferentiated liposarcomas have been found to have a spiraling arrangement of cells with associated bone or epithelioid-like cells that have been identified as meningothelial-like whorls. Sometimes these epithelioid-like cells can become prominent and extend beyond these meningothelial-like whorls in a nested or sheet like arrangement in the

background of fibrous tissue (*Figure 1A,B*). Typically, dedifferentiated liposarcoma will have an associated well-differentiated liposarcoma component that greatly facilitates diagnosis. In a needle core biopsy or in tumors without a low-grade component, identification of *MDM2* gene amplification by FISH can help confirm the diagnosis (4,6). Dedifferentiated liposarcomas will recur in 40% of cases and approximately 20% of these tumors metastasize (5).

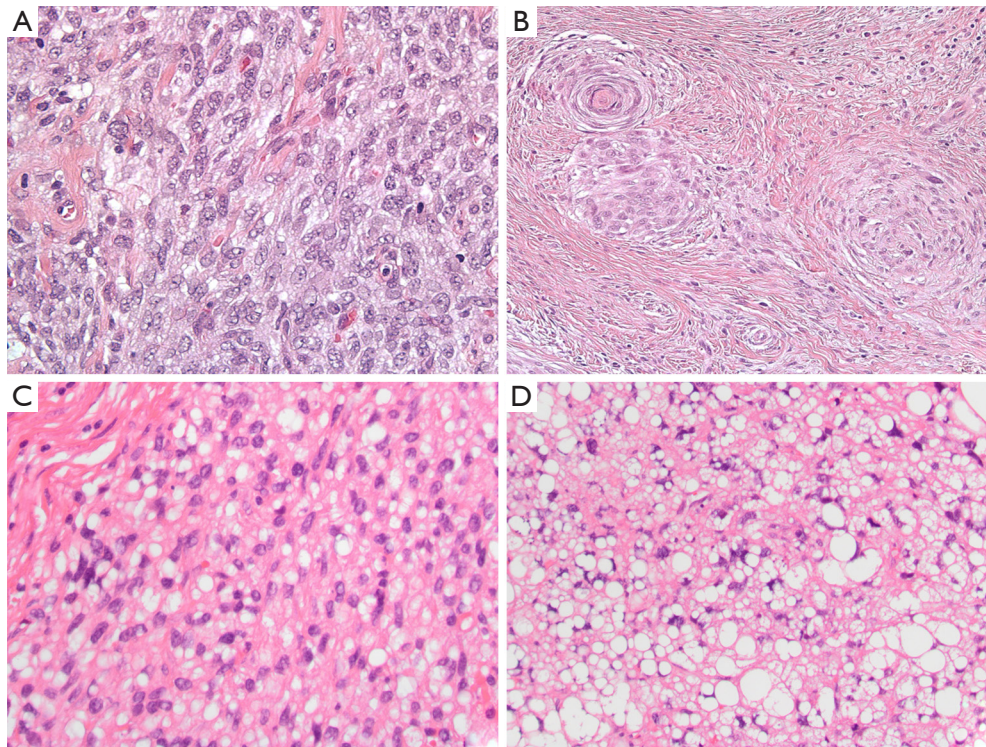
### *Pleomorphic liposarcoma with epithelioid-like features*

Pleomorphic liposarcoma is the least common variant of liposarcoma. Although a rare tumor in the mediastinum, it appears to have a predilection for this location relative to other sites (4,6-8). Histologically, it typically manifests as a high-grade sarcoma that contains at least a focal population of highly atypical cells which emulate the features of immature adipocytes (termed "lipoblasts"). Although these tumors are typically associated with a pleomorphic appearance, almost a third of pleomorphic liposarcomas can harbor more epithelioid-like cells which can mimic a renal cell carcinoma or adrenocortical carcinoma (*Figure 1C,D*). Of these tumors with epithelioid-like areas, nearly 40% will focally stain with a broad-spectrum cytokeratin (AE1/AE3) (9). Unlike other liposarcomas, they do not exhibit a characteristic genetic abnormality, such as *MDM2* gene amplification. After excluding dedifferentiated liposarcoma, the diagnosis is primarily based on morphologic features. Clinically, they usually have a quick and frequent rate of metastatic spread (approximately 32%) (4).

## Vascular tumors

### *Epithelioid angiosarcoma*

Angiosarcoma is an aggressive malignant vascular neoplasm that can arise in the anterior mediastinum in young to older adults, reportedly ranging from 3 to 12 cm in greatest dimension (10). They are rare, representing approximately 4% of angiosarcomas of the soft tissue (11). Histologically, malignant endothelial cells form ill-formed vascular like spaces that infiltrate soft tissue (11). In the epithelioid variant of angiosarcoma, a substantial portion of the malignant endothelial cells are arranged in diffuse sheets of epithelioid like cells with violet or amphophilic cytoplasm and vesicular nuclei (*Figure 2A,B*). Some pseudoglandular-like spaces can be seen. This particular variant of angiosarcoma has a predilection for deep soft tissue sites such as retroperitoneum, abdomen

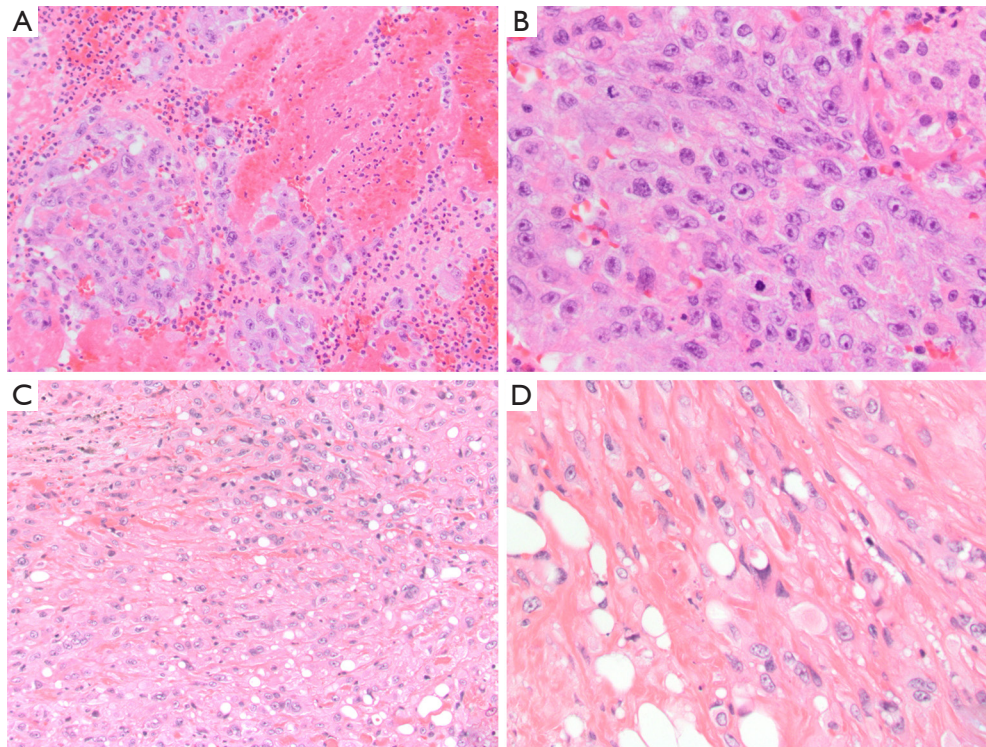


**Figure 1** Liposarcomas with epithelioid-like cells. (A) Relatively monomorphic epithelioid-like cells in a vague sheet like arrangement in a dedifferentiated liposarcoma [40× magnification, Hematoxylin and eosin stain (H&E)]; (B) the epithelioid-like cells in dedifferentiated liposarcoma are associated with meningotheelial-like whorls (10× magnification, H&E); (C) Sheets of epithelioid-like cells in a pleomorphic liposarcoma can mimic tumors such as renal cell carcinoma or adrenal cortical carcinoma (20× magnification, H&E); (D) Other area of this pleomorphic liposarcoma shows more characteristic highly atypical lipoblasts (20× magnification, H&E).

or thigh. These tumors have rarely been reported in the mediastinum (12-14). While these tumors will typically stain for vascular markers such as CD31, CD34 and ERG, a substantial portion of epithelioid angiosarcomas have been found to be positive for AE1/AE3 pancytokeratin (11,13,15,16). When making the diagnosis of epithelioid angiosarcoma, one should be careful to exclude other epithelioid vascular tumors such as epithelioid hemangioma or epithelioid hemangioendothelioma. These tumors exhibit more cytologic atypia than those found in an epithelioid hemangioma. The cells in an epithelioid hemangioendothelioma will exhibit a *WWTR1-CAMTA1* fusion transcript by sequencing or nuclear expression of CAMTA1 by immunohistochemistry. Given the rarity of angiosarcomas in the mediastinum, there is limited documentation of the clinical behavior of these tumors in this specific location. Generally, however, these are highly aggressive soft tissue tumors with patients exhibiting a median survival of approximately one year (11).

#### *Epithelioid hemangioendothelioma*

Epithelioid hemangioendothelioma is another vascular tumor which is considered malignant but not as aggressive as angiosarcoma. Clinically, these tumors can vary in size and often arise as a well-circumscribed or locally infiltrative mass in the anterior mediastinum. True to their name, they are composed of varying amount of epithelioid-like endothelial cells with cytoplasmic vacuolization in a background of hyalinized fibrosis (*Figure 2C,D*). Sometimes, erythrocytes can be found in the vacuoles of the cells (17). Similar to epithelioid angiosarcoma, epithelioid hemangioendotheliomas will stain for endothelial markers such as CD31, CD34 and ERG. Immunohistochemical staining of CAMTA1 is considered to be relatively specific, consistent with the *WWTR1-CAMTA1* fusion transcript associated with this tumor. The diagnosis of epithelioid hemangioendothelioma can sometimes be difficult since up to one third of these tumors can show focal staining for



**Figure 2** Vascular tumors with epithelioid-like cells. (A) Epithelioid-like cells with associated blood in an epithelioid angiosarcoma (10× magnification, H&E); (B) The tumor cells in epithelioid angiosarcoma show enlarged nuclei with prominent nucleoli (40× magnification, H&E); (C) Epithelioid hemangioendothelioma shows epithelioid-like cells with scattered cytoplasmic vacuoles in a background of hyalinized fibrosis (10× magnification, H&E); (D) Occasional erythrocytes are seen in the cytoplasmic vacuoles of epithelioid hemangioendothelioma (20× magnification, H&E).

AE1/AE3 which can mislead a pathologist into making an erroneous diagnosis of metastatic carcinoma (13). When exhibiting higher grade cytologic features, epithelioid hemangioendothelioma can morphologically overlap with an angiosarcoma with epithelioid features. Epithelioid angiosarcomas, however, lack the *WWTR1-CAMTA1* fusion transcript associated with this entity (13,18). Of epithelioid hemangioendotheliomas in the soft tissue, approximately 20% metastasize. Larger tumors with increased mitoses have a more aggressive clinical course (19). Although the data is limited, patients with epithelioid hemangioendotheliomas arising in the mediastinum have done well (17).

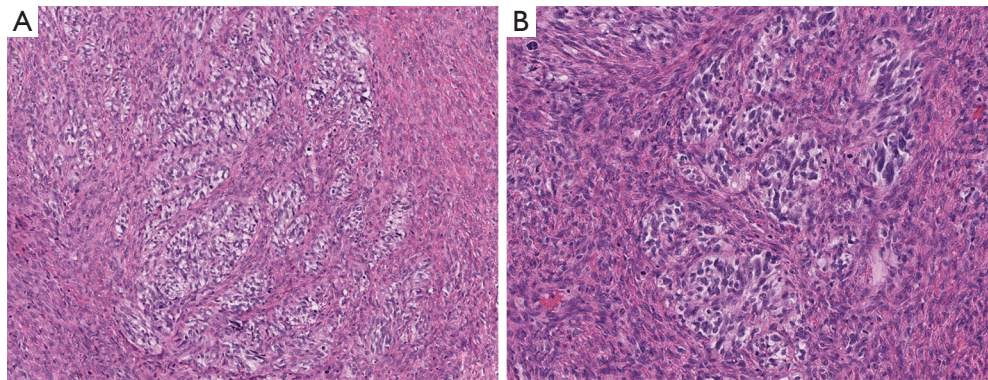
### Peripheral nerve sheath tumors

#### *Malignant peripheral nerve sheath tumor with divergent glandular differentiation*

Malignant peripheral nerve sheath tumor is typically a

high-grade malignant neoplasm that frequently arises in association with a neurofibroma or a peripheral nerve. Approximately half of these tumors will arise in patients with neurofibromatosis. (20). Microscopically, malignant peripheral nerve sheath tumor typically appears like a high-grade malignant spindle cell proliferation with areas of coagulative necrosis and numerous mitoses. Very rarely, malignant peripheral nerve sheath tumor can have heterologous components such as skeletal muscle, or clusters of glandular cells. In the latter entity, the glands lack cytologic atypia and can be columnar or cuboidal in appearance and often contain mucin. These glands typically are in the background of a more conventional malignant peripheral nerve sheath tumor with a spindled morphology (Figure 3). Immunohistochemically, the glandular elements in this tumor are positive for keratin and CEA and even express neuroendocrine markers such as synaptophysin (21,22).

Malignant peripheral nerve sheath tumors with glandular differentiation are extraordinarily rare and most typically



**Figure 3** Malignant peripheral nerve sheath tumor with divergent glandular differentiation. (A) The tumor has a dual population of spindled and epithelioid cells (10× magnification, H&E); (B) higher magnification shows distinct nests of cuboidal epithelioid cells (20× magnification, H&E).

arise in the retroperitoneum. A case was recently reported in the mediastinum (21). The glandular elements are generally thought to be an incidental finding that does not change the generally grim prognosis of these tumors.

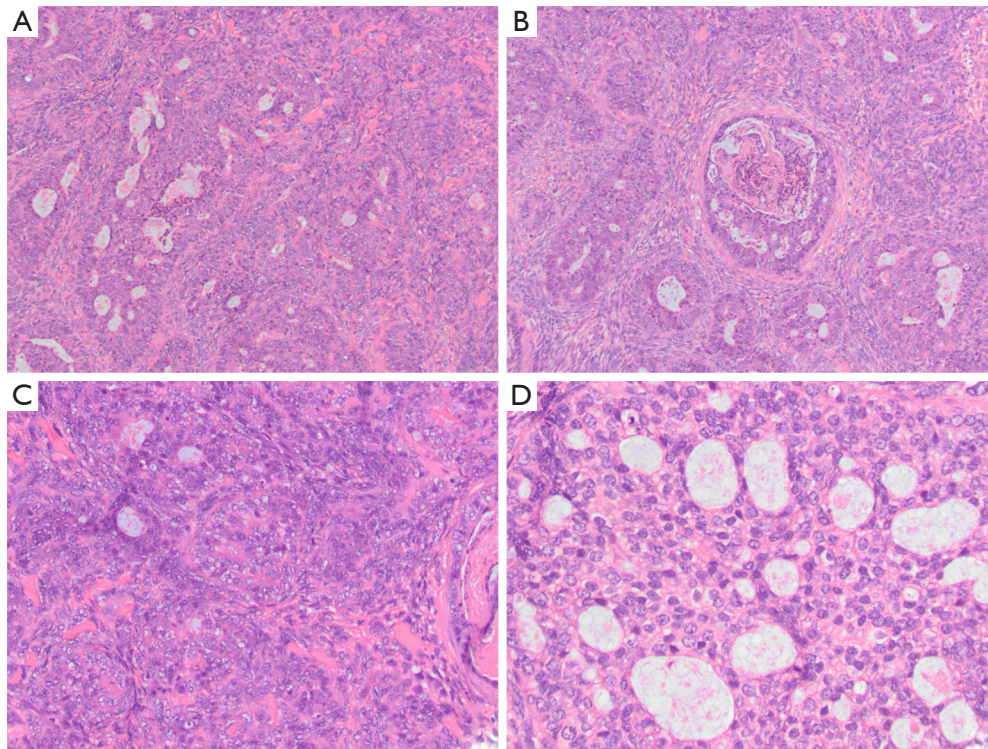
### Other sarcomas with epithelioid morphology

#### *Synovial sarcoma with prominent epithelial component*

Synovial sarcomas are mesenchymal tumors that can have prominent and complex arrangements of epithelial-like cells. Despite the name, the tumor exhibits no credible features of synovial differentiation. Although commonly arising in the extremities, these tumors can arise in a broad diversity of locations, including the mediastinum (16,23). They occur over a broad age range of and can arise in either the anterior or posterior mediastinum, often growing quite large prior to identification and diagnosis (23,24). Histologically, synovial sarcomas can exhibit a broad range of morphologic features. Classically, there is an intimate admixture of both epithelioid-like and spindled cells that have varying amounts of associated collagen and sometimes calcifications. This is typically referred to as the biphasic type of synovial sarcoma. In the monophasic variant of synovial sarcoma, the tumor is exclusively composed of spindled cells with no obvious epithelial or glandular elements. Poorly differentiated synovial sarcomas emulate “round cell” sarcomas and typically exhibit substantial mitoses and necrosis (25). Occasionally, a synovial sarcoma can contain an overwhelming portion of epithelial-like cells which some have described as a monophasic epithelial-type synovial sarcoma or synovial sarcoma, epithelial/glandular

variant. These epithelioid cells can be arranged in sheets, nests and even complex cribriform formations (Figure 4).

It is unclear whether a monophasic epithelial synovial sarcoma truly exists or if it simply represents a “epithelial-cell” predominant biphasic synovial sarcoma. Ultimately, this distinction has little clinical significance as long as pathologists and clinicians who treat the patient understand that the epithelial component of a synovial sarcoma can mimic entities such as carcinoma or mesothelioma when seen in the mediastinum. Synovial sarcoma expresses antigens frequently associated with carcinomas, including EMA and many cytokeratins, such as AE1/AE3, CK7, CK19, CK8/18, and high- and low-molecular weight cytokeratins (16,26). Over the past few years, a TLE-1 stain has been found to have high sensitivity for synovial sarcomas. However, this stain can also be positive in histologic mimickers of this tumor, including malignant peripheral nerve sheath tumor and solitary fibrous tumor. As almost all mesotheliomas are positive for TLE-1, this stain provides little utility for confirmation of synovial sarcoma in the mediastinum. Recently reported SS18-SSX fusion specific antibodies could potentially provide more specific clinically available stains for synovial sarcoma in the near future (27). Synovial sarcomas harbor a distinct *SS18-SSX1* or *SS18-SSX2* gene fusion that can be detected by FISH, RT-PCR or next generation sequencing (25). Primary pulmonary and mediastinal synovial sarcomas have been observed to have more aggressive behavior when compared to tumors in other soft tissue sites (28). Of patients with synovial sarcoma of the mediastinum, approximately 67% had disease progression with a median



**Figure 4** Synovial sarcoma with prominent epithelioid component. (A,B) The epithelial-like cells show prominent nests that occasionally form a cribriform architecture (2× magnification and 4× magnification, H&E); (C,D) the nests of epithelioid cells have vesicular nuclei with occasional nucleoli (10× magnification and 20× magnification, H&E).

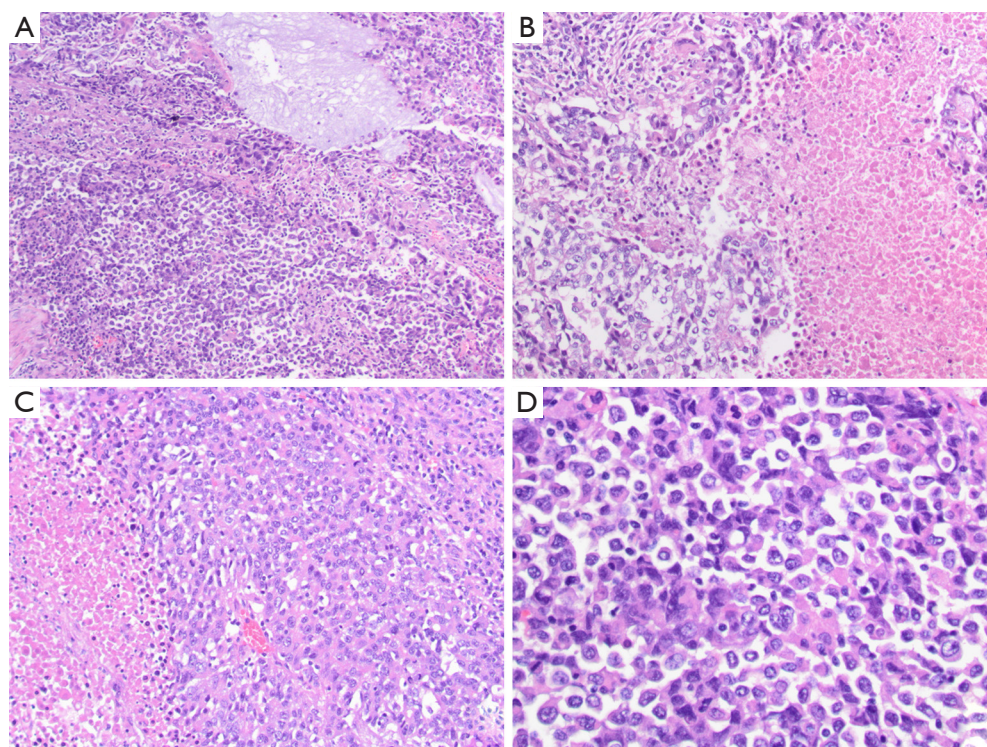
time to progression of 18 months. Complete excision is associated with increased overall survival (23).

#### ***SMARCA4-deficient thoracic sarcoma***

The *SMARCA4* gene is responsible for the BRG1 protein which forms one of the subunits of the switch/sucrose-nonfermenting chromatin-remodeling complex (SWI/SNF). Inactivation of *SMARCA4* has recently been described in various malignancies with a “rhabdoid” morphology, including small cell carcinoma of the ovary and a subset of atypical teratoid rhabdoid tumors found in the central nervous system (29). Recently, similar *SMARCA4* inactivation was identified in a group of undifferentiated thoracic malignancies but were felt to be similar to other sarcomas with similar histologic and immunohistochemical features (29-31). These aggressive thoracic tumors often involve the mediastinum. Typically, they are quite large, precluding resection. Although initially described as arising in younger adults, these tumors can arise in a broad age range of patients spanning between the second to eighth

decade of life (30). Metastasis (to sites such as the lymph nodes, bone and adrenal glands) are typically present at the time of diagnosis (29,32). Clinically, these tumors are extraordinarily aggressive with patient’s typically expiring within one year of diagnosis (31). Histologically, the tumor contains sheets and nests of syncytial or discohesive epithelioid to round cells with mildly eosinophilic to amphophilic cytoplasm. Focal areas of tumor cells have more monomorphic morphology with round and vesicular nuclei and prominent nucleoli. Rhabdoid cells, which have more abundant and glassy eosinophilic cytoplasm, can be usually be focally or rarely seen. Substantial mitoses and abundant necrosis are present (*Figure 5*) (6,30). Immunohistochemically, these tumors typically show at focal weak to moderate AE1/AE3 expression. The tumor cells can also stain for EMA, CD34, SALL4 and SOX2. While SMARCB1 is typically retained, SMARCA4 and SMARCA2 are lost in the tumor cells. The tumor cells are negative for NUT, S100 and desmin staining (30).

Although historically designated as sarcomas, the true nature of these SMARCA4-deficient tumors has been



**Figure 5** SMARCA4-deficient thoracic sarcoma. (A) this SMARCA4-deficient thoracic sarcoma shows sheets of epithelioid cells with an increased nuclear-to-cytoplasmic ratio (10× magnification, H&E); (B) areas of cellular necrosis are seen (20× magnification, H&E); (C) the tumor cells are often somewhat discohesive (20× magnification, H&E); (D) scattered cells with “glassy” eosinophilic cytoplasm can be seen (40× magnification, H&E).

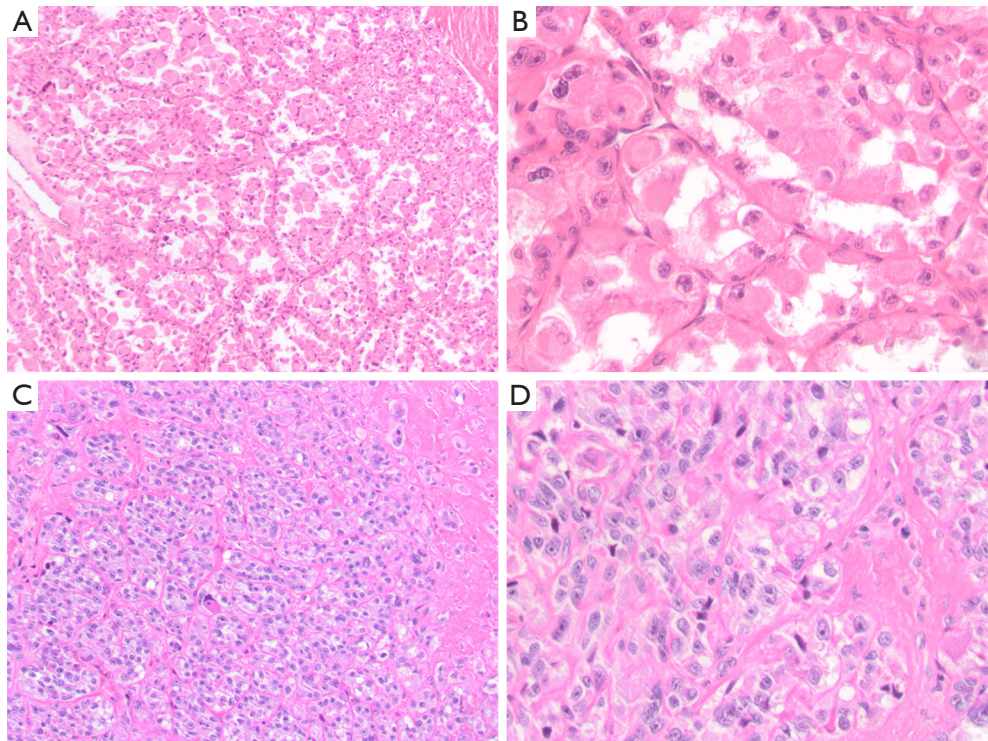
a topic of enthusiastic discussion. In a recent paper by Rekhtman *et al.*, the authors identified SMARCA4-deficient tumors which contained an associated component of non-small cell lung carcinoma or focal expression of TTF-1 or p40. From these and other findings, it was proposed these SMARCA4-deficient thoracic sarcomatoid tumors actually represent undifferentiated or dedifferentiated carcinomas rather than primary sarcomas (32). As the clinical and molecular characteristics of these tumors becomes better understood, this will continue to be a subject of intense interest.

#### *Alveolar soft part sarcoma*

Alveolar soft part sarcoma is a soft tissue neoplasm that frequently arises in the proximal extremity in adolescents or young adults. In infants and children, it is more frequently associated with the head and neck area (33-35). There are also reports of less common anatomic sites, such as the genitourinary tract (36-39). There are only a handful of

reports documenting alveolar soft part sarcoma arising in the mediastinum (40,41). Typically, these tumors are slow growing and can be quite large by the time they are identified. A substantial percentage of patients (20–70%) will have metastatic disease (e.g., lung, brain and bone) (42).

Histologically, these tumors display a consistent monomorphic population of epithelioid cells arranged in a trabecular, nested or alveolar architecture. The cells typically contain eosinophilic cytoplasm but they can exhibit focal clearing. The nuclei are vesicular and often contain prominent nucleoli (*Figure 6A,B*) (38). Immunohistochemically, the tumor cells are usually positive for TFE3 and CD68 and are generally negative for cytokeratins, EMA, S100 and HMB45. A Periodic acid-Schiff (PAS) stain can demonstrate rhomboid or rod-shaped crystals in the cytoplasm of the tumor cells (43). Next generation sequencing, RT-PCR or FISH studies can be utilized to demonstrate the characteristic *ASPL-TFE3* fusion transcript associated with this tumor (44). Given the epithelioid nature of alveolar soft part sarcomas,



**Figure 6** Other soft tissue tumors with epithelioid-like cells. (A) This alveolar soft part sarcoma displays a classic alveolar arrangement of tumor cells portioned by small capillaries (20× magnification, H&E); (B) High-power examination shows the tumor cells to have epithelioid features with enlarged round nuclei and conspicuous nucleoli (40× magnification, H&E); (C) Clear cells sarcoma shows epithelioid cells in the background of dense hyaline fibrosis (10× magnification, H&E); (D). The cells have enlarged nuclei and prominent nucleoli (20× magnification, H&E).

the differential diagnosis frequently includes metastatic carcinoma or melanoma. The lack of keratin or S100 staining helps exclude these two possibilities, respectively. Of note, certain types of renal cell carcinoma will be positive for TFE3; however, alveolar soft part sarcomas will typically lack PAX8 staining associated with these tumors (45). PEComas have been demonstrated to stain for TFE3 by immunohistochemistry; however, they will not exhibit the *ASPL-TFE3* fusion transcript associated with alveolar soft part sarcoma. Although alveolar soft part sarcomas are slow growing tumors, they have a long-term clinically aggressive course. While survival in patients without metastasis at initial presentation was 77% at 2 years, it was only 38% and 15% at 10 year and 20 years, respectively (46). The tumors are typically resistant to chemotherapy and radiation therapy and local control with adequate surgical excision is the mainstay of treatment (33).

#### *Clear cell sarcoma of soft tissue*

Clear cell sarcoma of soft tissue is a tumor which most commonly arises in the distal extremities in association with a tendon or aponeurosis in young adults (previously designed as clear cell sarcoma of the tendon sheath). While these tumors typically show a prominent spindled morphology, some tumors can exhibit a predominantly epithelioid appearance. The tumors frequently have an indolent presentation and can be clinically present many years before histologic diagnosis (47,48). A handful of these tumors have been reported as large masses arising in the mediastinum with the tumor cells exhibiting epithelioid features (13,49,50). Histologically, clear cell sarcomas are characterized by epithelioid to spindled cells with eosinophilic or clear cytoplasm. The nuclei are enlarged and contain prominent nucleoli. The cells are



typically in the background of fibrotic stroma with dense fibrosis. Multinucleated tumor giant cells and melanin pigment deposition can be seen (*Figure 6C,D*) (16,48). Immunohistochemically, these tumors have a similar staining pattern to melanomas, with the tumor cells being positive for S100, SOX10, HMB-45 and Melan A. Unlike melanomas, however, these tumors exhibit an *EWSR1-ATF1* fusion transcript. Interestingly *EWSR1-ATF1* is not specific for this tumor, as this fusion has been identified in completely unrelated entities such as angiomatoid fibrous histiocytoma, hyalinizing clear cell carcinoma of the salivary gland and primary pulmonary myxoid sarcoma (51). The diversity of tumors harboring a similar fusion transcript emphasizes the importance of a holistic diagnostic approach when investigating a soft tissue sarcoma. In addition to melanoma, the morphologic differential includes other entities which can include epithelioid to spindled cells such as synovial sarcoma or perhaps malignant peripheral nerve sheath tumor. The presence of strong S100, HMB45 and Melan-A staining (with the concurrent presence of *EWSR1-ATF1* fusion transcript) easily distinguishes clear cell sarcoma of soft tissue from these histological mimickers. The limited occurrence of clear cell sarcoma in the mediastinum precludes site specific assessment of prognosis. Generally, although clear cell sarcoma typically has an indolent presentation, the long-term clinical outcome is poor. While the 5-year survival rate is 67%, the 20-year survival rate is 10%. Increased tumor size is associated with a poorer prognosis (48).

## Conclusions

In the mediastinum, the diagnosis of soft tissue sarcomas with epithelioid morphology can be a difficult endeavor. Not only do these tumors morphologically emulate the features of carcinoma or mesothelioma more frequently found in this location, but they also frequently stain for EMA and cytokeratin stains typically associated with epithelial neoplasms. As sarcomas and carcinoma typically have unique adjuvant treatment regimens, the diagnosis is clinically relevant. A holistic diagnostic approach and familiarity with the specific morphologic, immunohistochemical and molecular findings associated with these soft tissue neoplasms can help assure accurate diagnosis.

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