Alveolar Soft Part Sarcoma

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• This article provides an overview of the pathology of alveolar soft part sarcoma, focused on its morphology, special stains useful in diagnosis, and the clinical and radiographic features of the disease. Alveolar soft part sarcoma is a rare neoplasm of unknown histogenesis with poor prognosis. Although there are several immunohistochemical stains available to help reach the diagnosis, the morphology of the tumor should be considered the main diagnostic feature. The periodic acid–Schiff stain is the best single stain that supports the diagnosis.

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Alveolar soft part sarcoma (ASPS) is a rare malignant soft tissue tumor that was first described and named by Christopherson and Stewart in 1952.[1] Despite numerous studies, there is still uncertainty about this tumor's exact cell of origin.

CLINICAL FEATURES

Most ASPSs occur in adolescents and young adults between 15 and 35 years of age. There is a predilection for females especially during the first 2 decades of life.[2] In adults it most commonly involves the muscle and deep soft tissue of the extremities, trunk, head and neck, and retroperitoneum. In children and adolescents, this tumor most commonly occurs in the head and neck region.[3]

This tumor accounts for about 1% of all soft tissue sarcomas.[4] The etiology is unknown, although cases have been reported to occur 20 years after radiation therapy.[5] Trauma may direct attention to the mass. It usually presents as a soft, painless, slow-growing mass that rarely causes functional impairment.[4] Erosion or destruction of the underlying bone can occur. The majority of patients have metastatic disease at the time of diagnosis.[6] The most common metastatic sites are lung, bone, central nervous system, and liver. Metastasis has been reported as long as 15 years after removal of the tumor. Computed tomographic scan and angiography of the tumor reveal its hypervascularity, prominent draining veins, and prolonged capillary staining[7] (the angiographic dye remains in the capillary longer than usual). Three-phase bone scan with administration of 26.4 mCi and Tc-99m oxidronate sodium (Tc-99m HDP) can also be used to show the vascularity of the tumor. Magnetic resonance imaging typically exhibits high signal intensity of tumor on both T1- and T2-weighted images.[8]

PATHOLOGY

Gross Features

On gross examination the tumor is usually yellow to gray with variable firm and friable areas. Although it is typically well circumscribed, no definite capsule is present. On cross section it is generally white-tan to gray-red with large areas of necrosis and hemorrhage. Frequently, it is surrounded by many tortuous large vessels.

Microscopic Features

In spite of apparent gross circumscription, microscopically cells can be seen to infiltrate the adjacent structures. The tumor cells are separated by fibrous trabeculae into well-defined nests of uniformly large, round-to-polygonal cells. Individual nests are separated from each other by thin-walled, sinusoidal vascular channels lined by a single layer of flattened endothelial cells. Some dilated thin-walled vessels may be present, and a hemangiopericytoma-like pattern may be seen.[9]

The individual cells show little variation in size and have distinct cell borders. One or more vesicular nuclei with small nucleoli are evident, and the cytoplasm is abundant with a granular, eosinophilic, and sometimes vacuolated appearance. Mitotic figures are rare.[4,10] Frequently, the cells contain eosinophilic crystalline or rod-shaped inclusions, faintly visible in hematoxylin-eosin–stained tissue sections.[9] On periodic acid–Schiff (PAS) stains, intracytoplasmic glycogen and characteristic PAS-positive, diastase-resistant rhomboid or rod-shaped crystals are present. Typical crystalline material is seen in at least 80% of cases, and PAS-positive granules are present in almost all cases.[4] It has been shown that the precrystalline cytoplasmic granules of ASPS contain monocarboxylate transporter 1 and CD147.[11]

Immunohistochemistry

The constituent cells of ASPS typically are immunoreactive for vimentin, muscle-specific actin, and desmin but do not stain with antibodies against cytokeratin, epithelial membrane antigen, neurofilaments, glial fibrillary acidic protein, serotonin, or synaptophysin. Rarely, S100 protein and neuron-specific enolase may be positive in tumor cells. There have been inconsistent reports on detection of nuclear MyoD1 in ASPS, and many reports have shown positive cytoplasmic staining of MyoD1, a finding that has

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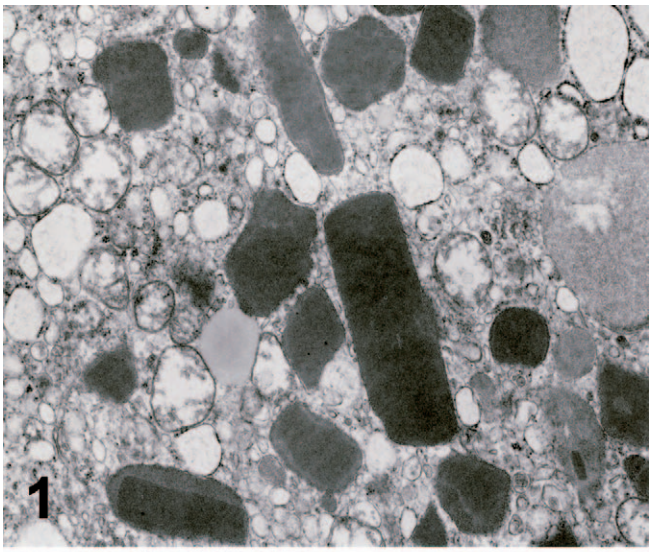

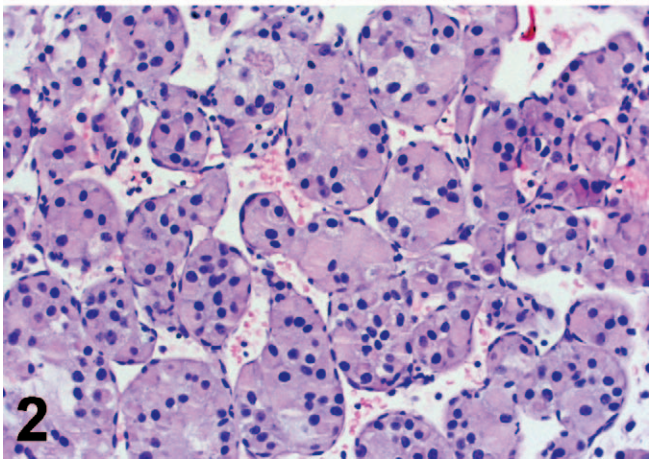

Figure 1. *Electron microscopy, characteristic rhomboid crystals with a regular lattice pattern (original magnification ×24 000). (Courtesy of N. G. Ordonez, MD, M. D. Anderson Cancer Center, Houston, Tex.)*

Figure 2. *Hematoxylin-eosin stain of the core biopsy specimen shows large and round-to-polygonal tumor cells with abundant granular eosinophilic cytoplasm; one mitotic figure is present (original magnification ×400).*

been rationalized as an occurrence of cross-reactivity with an undetermined cytoplasmic antigen.[12] Alveolar soft part sarcoma is usually negative for myogenin.

Electron Microscopic Features

Ultrastructurally, tumor cells have numerous mitochondria, a prominent smooth endoplasmic reticulum, glycogen, and a well-developed Golgi apparatus. Characteristically, there are rhomboid, rod-shaped, or spicular crystals with a regular lattice pattern and sparse electron-dense secretory granules (Figure 1).[4]

Cytogenesis

Alveolar soft part sarcoma is characterized cytogenetically by a chromosomal translocation resulting in der(17)t(X;17)(p11;25).[13,14] This translocation causes the fusion of the *TEF3* (transcription factor binding to immunoglobulin heavy constant μ enhancer 3) with a novel gene at 17q25, named *ASPL*. The *TEF3* gene is located on Xp11.22 and encodes a member of the tripartite motif family, whose members are involved in diverse cellular functions such as developmental patterning and oncogenesis. Translocation between chromosomes X and 17 is seen in all the tested cases, implicating transcriptional deregulation in the pathogenesis of this tumor.[15] It has been suggested that ASPL might serve as a reasonably specific marker for ASPS. It has been proposed that the female predominance observed in ASPS occurs because the translocation fusion gene is not subject to inactivation of the X chromosome. Therefore, female possession of an extra X chromosome doubles the likelihood of developing ASPS.[16] An antibody to the carboxy-terminal portion of TEF3 has been developed and shows a strong nuclear staining in ASPS, which can be used for diagnosis.[17] (This antibody is now commercially available.)

Useful Immunohistochemical Stains in Differential Diagnosis of Alveolar Soft Part Sarcoma (ASPS)*

	EMA	HMB-45	Melan-A	S100	Pan-CK	Hep-Par1
ASPS	−†	−	N/A	+/−	−	−
Paraganglioma	−	−	−/+	+	−/+	−/+
Melanoma	−	+	+	+	−	−/+
Granular cell tumor	−	−	−	+	−	−
Renal cell carcinoma	+	−	−	+/−	+	−
Hepatocellular carcinoma	+/−	N/A	−	−	+	+
Adrenal cortical carcinoma	−	−	+	−	−/+	−/+

* This table was prepared using ImmunoQuery (http://www.immunoquery.com) and PubMed (http://www.ncbi.nlm.nih.gov/PubMed/). EMA indicates epithelial membrane antigen; HMB, human melanoma black; Pan-CK, pancytokeratin; Hep-Par1, hepatocyte paraffin 1; and N/A, the stain was not reported to be tested.

† Immunoreactivity is considered negative if it is positive in <5%, −/+ if it is positive in 5 to 15%, and +/− if it is positive in 16 to 30% of the cases reported. All the tests marked positive in this table have been reported to be positive in more than 78% of the cases tested.

Differential Diagnosis

The differential diagnosis of ASPS includes paraganglioma, granular cell tumor, renal cell carcinoma, malignant melanoma, hepatocellular carcinoma, and adrenal cortical carcinoma (Table).[18–40] Malignant melanoma and primary or metastatic renal cell carcinoma closely simulate the histologic appearance of ASPS, but in most cases they can be differentiated from ASPS by the absence of the characteristic PAS-positive crystalline material and the presence of HMB-45 and epithelial membrane antigen, respectively, in these tumors. (Epithelial membrane antigen is rarely present in ASPS, and HMB-45 has not been reported to be positive in ASPS.) Tumor cells of hepatocellular carcinoma have prominent nuclei and nucleoli and often show intranuclear pseudoinclusions. They may also produce bile. Hepatocyte paraffin 1 is positive in hepatocellular carcinoma but has not been reported to be positive in ASPS. Unlike ASPS, adrenal cortical carcinoma typically exhibits nuclear hyperchromasia and mitotic activity. When in doubt, immunohistochemical stains for inhibin, calretinin, synaptophysin, and Melan-A may be of help as these are often positive in adrenal cortical carcinoma. Glycogen is present in both ASPS and renal cell carcinoma but is absent in

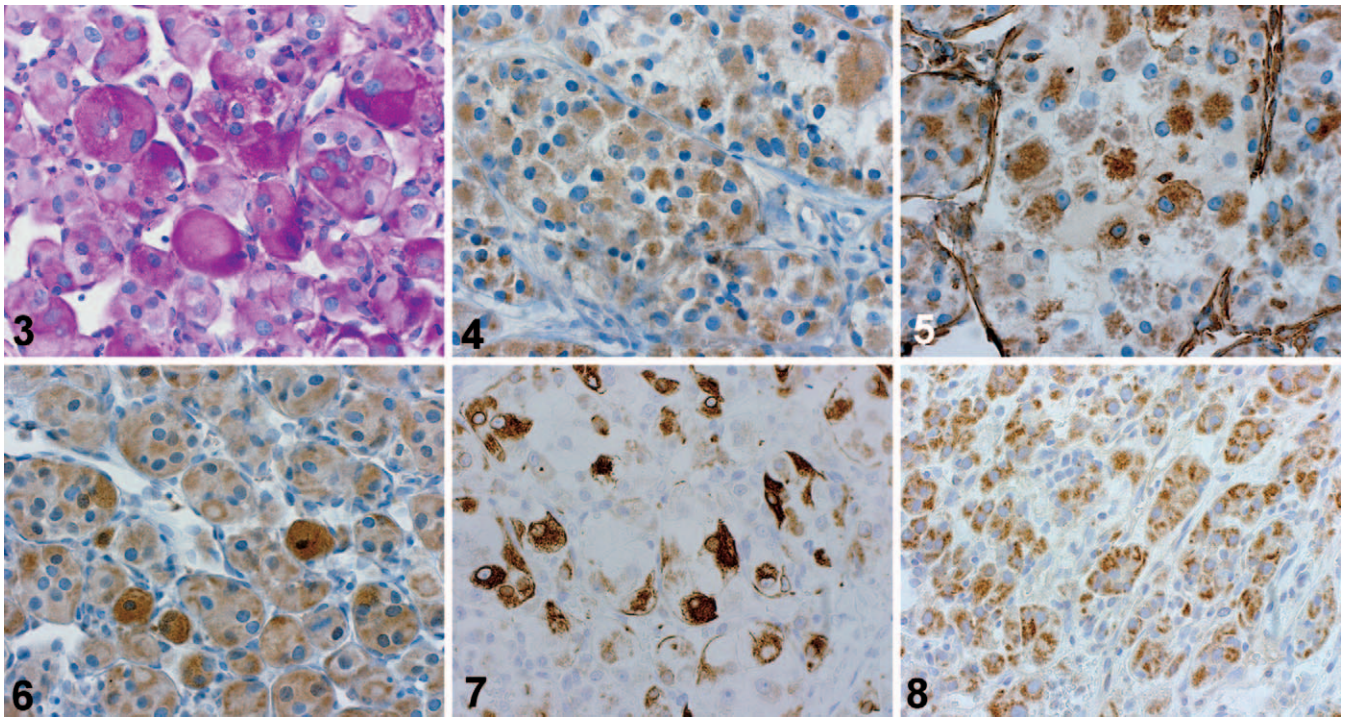

Figure 3. *Periodic acid–Schiff, variable cytoplasmic staining of the tumor cells (original magnification ×400).*

Figure 4. *Synaptophysin, variable cytoplasmic staining of the tumor cells (original magnification ×400).*

Figure 5. *Vimentin, moderate to strong cytoplasmic staining of the tumor cells (original magnification ×400).*

Figure 6. *Neuron-specific enolase, variable cytoplasmic staining of the tumor cells (original magnification ×400).*

Figure 7. *Desmin, strong focal cytoplasmic staining of the tumor cells (original magnification ×400).*

Figure 8. *MyoD1, variable cytoplasmic staining of the tumor cells (original magnification ×400).*

granular cell tumor and paraganglioma. Furthermore, the cells of granular cell tumor are less well defined, have a distinct granular cytoplasm, and are strongly positive for S100. They are also not as vascular as ASPS is. The high vascularity of ASPS occasionally dominates the presenting symptoms, varying from a localized ateriovenous malformation to heart failure. Although ASPS can mimic an arteriovenous malformation on angiography, magnetic resonance imaging usually reveals solid soft tissue components as well as tortuous vessels. Rarely, biopsy may be essential to differentiate ASPS from arteriovenous malformation.[8,41,42]

Treatment

The prognosis is generally poor. The most important prognostic factors are the age at diagnosis (younger patients have a better prognosis), size of the tumor (larger tumors have a worse prognosis), and the presence of metastatic disease at presentation.[4] Treatment is not very promising. Radical resection is the therapy of choice. Excision of lung and brain metastasis in selected patients has shown favorable results, with prolonged survival.[43] Multiple pulmonary metastases in 2 patients have responded to interferon alfa-2a and decreased in number and size.[44,45]

COMMENT

Alveolar soft part sarcoma is an unusual tumor with characteristic histopathologic and ultrastructural findings, controversial histogenesis, and often cryptic behavior. Several studies have been done using a variety of immunohistochemical stains, mainly to identify the cell of origin of the ASPS. Early investigators related ASPS to granular cell tumor and considered the Schwann cell as a possible origin. Some have proposed a relationship with paraganglioma.[46] Many have suggested that ASPS might have a myogenic derivation, but the cell of origin of ASPS remains unknown. At present ASPS is categorized as a ''malignant soft tissue tumor of uncertain type.''[4]

Diagnosis of ASPS, like other soft tissue tumors, can be challenging; immunohistochemistry can play a key role in these cases. The immunohistochemical stains are usually reactive for vimentin, muscle-specific actin, desmin, and cytoplasmic MyoD1. The tumor cells are usually nonreactive for pancytokeratin, synaptophysin, chromogranin, and myogenin (Figures 2 through 8).

Although immunohistochemistry can be helpful in diagnosis of ASPS, the diagnosis should rest mainly on morphology (which can be accentuated by CD34 or smooth muscle actin). The diagnosis is supported by diastase-resistant, PAS-positive cytoplasmic crystals or granules, or by demonstration of the characteristic rhomboid inclusions by electron microscopy.

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