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Chapter
Pathology of Alveolar Soft Part Sarcoma

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Abstract

Alveolar soft part sarcoma (ASPS) is a rare orphan sarcoma of uncertain differentiation according to the latest WHO classification of soft tissue tumors with a somewhat indolent clinical course. The common histomorphological alveolar-type presentation is unique. It is usually not graded according to the French Federation of Cancer Centers grading system, but nonetheless defined as a high-grade sarcoma. The tumor adopts a clinical pattern with a distinctive natural history marked by local recurrences up to 50% of cases and a high prevalence of metastases in such diverse sites such as the lung, liver, brain, bone that can occur more than 10 years after the primary event. ASPS is driven by a specific recurrent nonreciprocal translocation der(17)t(X;17)(p11;q25). This chimeric gene fusion is also found (albeit in the balanced mode) in a subset of renal cell carcinomas in the young. Nevertheless, its high specificity and sensitivity in ASPS is a recognized feature and accurate diagnosis requires trained pathologists and molecular testing. Prognostication is based on age, size of tumor, primary site, and the presence or not of metastasis.

Keywords: differentiation, immunohistochemistry, transcription factor E3, fluorescent in situ hybridization, genetics, translocation, differential diagnoses

1. Introduction

Alveolar soft part sarcoma (ASPS) is a rare orphan malignant soft tissue tumor of uncertain cellular lineage representing 0.5–1% among soft tissue sarcomas and with a somewhat indolent yet lethal clinical course. It was first described in 1952 by Christopherson, a fellow in surgical pathology at Memorial Sloan Kettering Cancer Center, who reported 12 cases with similar clinical and pathology features [1]. It occurs mainly in adolescents and young adults between 15 and 40 years of age. For localized disease, the survival rate is 71% at 5 years and falls at 20% at 5 years for metastatic disease [2].

2. Clinical features

At diagnosis, a patient with ASPS describes a slow-growing mass in the extremities. Tumors in adults are most frequently involved located in the deep soft tissue of the lower extremities, especially the thigh and buttock [2]. This stands in contrast to
the pediatric population where the tumor clearly has a predilection for the head and
neck, and in particular the tongue and orbit [3]. ASPS has also been described as a
rare primary lesion of the calvarium [4] and the pleura [5]. In the viscera, occurrences
have been reported in such diverse anatomic sites as liver [6], lung [7], gastrointesti-
nal tract [8], breast [9], uterine corpus [10], cervix [11], and the bladder [12]. Some
deply seated tumors may be quite large whereas those located in the head and neck
area and viscera usually measure much less.

Preferential sites of metastatic sites are lung, bone, and frequently the brain.
Metastases have been reported even 15 years after primary tumor diagnosis [2].

3. Pathology

3.1 Broad considerations

ASPS consists of nests of large rounded cells sometimes associated with charac-
teristic crystalloids and embedded in a finely capillarized stromal background. The
molecular genetics aspect involves the recurrent unbalanced translocation der(17)
t(X;17)(p11;q25) [13]. The female predominance could theoretically be based on the
statistical observation that the risk of a translocation involving the X chromosome
present in two copies is greater in women [14]. No differentiation lineage is estab-
lished according to the WHO classification of soft tissue tumors [15] although as is
well-known differentiation patterns are the basis of most of the histopathological
classifications of sarcomas.

After the original description of the lesion, one of the prevailing hypotheses,
now totally abandoned, concerned its alleged myogenic phenotype which had
fueled the unresolved question of its histogenesis. Masson had first numbered
this tumor among muscle lesions [16]. Much data then seemed to uphold striated
muscle differentiation based on different observations. Immunohistochemistry
and immunofluorescent techniques showed cytoplasmic expression of muscle-
associated proteins, such as desmin, muscle-specific actin, MM isozyme of creatine
kinase [17–25], and nuclear expression of the skeletal muscle-specific regulatory
protein MyoD1 [23]. The myogenic hypothesis was ultimately set aside for the fol-
lowing reasons. Desmin is not considered a reliable marker of skeletal muscle tissue
differentiation and can be found expressed as well in smooth muscle proliferation,
rhabdoid tumors, Ewing sarcoma, or neuroblastoma [26]. As for the nucleophos-
phoproteins MyoD1 and myogenin, no subsequent studies confirmed positivity.
In the 12 cases reported by Wang et al. [27] and the 19 cases reported by Gomez
et al. immunohistochemical nuclear expression was completely absent. These
authors observed nonspecific granular cytoplasmic staining linked to aberrant
cross-reactions with unrelated antigens. In their studies, western blotting failed to
highlight the 45-kd band of MyoD1, and MyoD1 transcript has not been detected
by northern blot analysis [20]. Neither had ultrastructural myofilaments been
observed in alveolar soft part sarcoma [27, 29]. The ultrastructure of the crystal-
loids supposedly composed of Z-band tropomyosin B, similar to rod structures
seen in rhabdomyoma [30] seemed to favor muscle differentiation but new data
demonstrated the absence of tropomyosin [31]. Some subsequent gene expression
profiling studies momentarily revived the concept of muscle cell differentiation
with the identification of differentially expressed genes [32, 33]. But later studies
failed to validate these findings [34].
One report of expression profiling analysis suggested a neural differentiation because of marked expression of the transcription factor PAX6, an activator of neural genes [35, 36]. Curiously a neural crest origin had already been speculated [37]. DeSchryver-Kecskemeti et al. described ASPS as “malignant angioReninoma.” Indeed fluorescein-tagged antirenin antibodies in tumor cell were detected [38]. However, patient arterial hypertension was missing, and no tumor renin secretion (whether active or inactive) was biochemically revealed [31]. ASPS had also been labeled, albeit incorrectly as “malignant myoblastoma,” “granular cell myoblastoma,” “malignant granular cell myoblastoma” [39–41], or as “malignant tumor of the non-chromaffin paraganglia” [42].

3.2 Gross morphology

When excised, ASPS has a soft consistency with encapsulated borders. The cut surface has a white to yellow–brownish color tinged with hemorrhagic spilling or central necrosis in large tumors (Figure 1a).

3.3 Light microscopy

ASPS shows a distinctive recognizable morphology in most cases with nests or trabeculae (Figure 1b, c, and e) of large epithelioid round cells displaying an alveolar (Figure 1d) and sometimes dyscohesive appearance (Figure 1d and h). The stroma has a delicate vasculature with frequent lymphovascular invasions (Figure 1j). Typical cytoarchitectural aspects include individual monomorphic tumor cells with an abundant granular eosinophilic or clear glycogen-rich cytoplasm, sharp cytoplasmic borders, no striations, and an eccentric vesicular nucleus containing a prominent central nucleolus. In some cases, sheets of contiguous tumor cells may appear solid (Figure 1f and g), a finding more conspicuous in children. Cells can be multinucleated (Figure 1h). Mitoses are few and necrosis rare. Other possible aspects are nuclear pseudoinclusions, cystic or myxoid changes, stromal sclerosis, calcification, and chronic inflammatory infiltrate [2, 13, 42–50]. Rarely, some tumors display a high mitotic rate, polymorphism, spindling, and xanthomatous changes [9]. Special stains, such as periodic acid-Schiff with diastase can highlight crystalloids, rod-like or rhombid diastase-resistant membrane-bound intracytoplasmic crystalline formations originally noted by Masson [16] (Figure 1i—arrows). Ladanyi et al. were able to conclude that these are complexes of monocarboxylate transporter 1 (MCT1) interacting with a CD 147, a chaperone protein [51]. Their microscopic detection may be time-consuming and inconclusive. Some cases show simply a granular substance instead of crystals which could be a pre-crystalline formation of the MCT1-CD147 complex [51].

3.4 Ultrastructure

In electron microscopy, ASPS cells are poor in desmosomes and are lined by incomplete basement membranes in contact with capillaries [43, 47]. The cytoplasmic endoplasmic reticulum is as a rule sparse, mitochondria are numerous, and Golgi apparatus is greatly developed [43]. The latter is associated with crystalloids or pre-crystallized electron-dense granules mentioned above both of which are membrane-bound [31, 43, 47].
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3.5 Immunohistochemistry

Immunostaining is, in most cases, unnecessary for diagnosis. Transcription factor TFE3 expression (Figure 1k) is linked to the gene fusion ASPL-TFE3 (Figure 2) but is
not specific to ASPS as it can also be seen in subsets of epithelioid hemangioendotheliomas and PEComas [52], in granular cell tumor, malignant melanoma and pediatric renal cell carcinoma [33].

This contrasts with sensitivity which is high (92%) Nevertheless, staining can also be weak or even absent in some cases, particularly in pre-analytically ill-prepared samples [54].

CD147/EMMPRIN, a glycoprotein of the immunoglobulin superfamily, is considered a marker of poor prognosis as well as for some authors a potential therapeutic target [54, 55]. Secreted by the cancer cells as a conjugate protein of MCT1, a lactate transporter, it induces matrix metalloproteinases production by neighboring stromal fibroblasts hence facilitating local tumor progression and ultimately metastasis [15, 54, 55]. Its expression is not limited to ASPS but has also been signaled in other lesions, such as granular cell tumor and clear cell renal cell carcinoma [54].

Diffuse cytoplasmic immunostaining with cathepsin K, a protease activated by the microphthalmia transcription factor (MITF) in osteoclasts, is fairly constant. But it is also seen in melanoma, clear cell sarcoma, granular cell tumor, and PEComa [56, 57].

Other possibly expressed markers with little significance in ASPS include desmin, actin [5–12, 14], S-100 protein [21], NKIC3 [22], histiocytic marker CD68 KP1 [58], and vimentin [24]. Nuclear myogenin and MyoD1, cytokeratin, epithelial membrane antigen (EMA), chromogranin, synaptophysin, neurofilament, and glial fibrillary acidic protein (GFAP) are always negative [24, 47, 50]. The eventual clinical utility of standard immune complementary immunohistochemical tests in ASPS is yet to be determined. As mentioned earlier, lymphocytic infiltrate is rare. However, Goldberg et al. reported having identified activation of the PD-1 (programmed death-1) pathway with cell immunoreactivity for PD-L1 (PD-ligand 1) and individual CD8+ tumor-infiltrating T cells expressing PD-1 [59]. This, however, needs to be confirmed.

3.6 Molecular genetics

The unbalanced translocation der(17)t(X;17)(p11;q25) and its consequential fusion gene, a marker specific as well as sensitive [54], is the exhibited molecular label of ASPS. Cullinane et al. first reportedly identified this alteration cytogenetically [60]. This paved the way for the description of the two breakpoints on Xp11.2 and 17q25 [61] leading to the characterization of the two involved genes [14], the transcription factor TFE3 on Xp11.2 and a novel gene with no yet known function, ASPL/ASPSCR1 (alveolar soft part sarcoma locus/alveolar soft part sarcoma chromosomal region 1) on 17q25 (Figure 3a and b). In the encoded protein, there is conservation of the COOH-extremity and the DNA-binding domain of TFE3. Contrariwise its N-terminal sequences are occupied by ASPL which alters TFE3 normal activity. The oncoprotein then shifts to the nucleus where it behaves as a transcriptional driver.

Two published cases show a reciprocal translocation however [14, 62]. Further, two mutually exclusive translocation variants have been identified although with no known clinical consequence at present. The ASPL gene has a unique breakpoint whereas the TFE3 gene possesses two possible breakpoints with two possible fusion types. According to Ladanyi et al., in type 1 fusion, the ASPL gene is joined in frame to TFE3 exon four (exon 3 is excluded). In type 2, it links with exon 3. Aulmann et al. [63] emphasized that under the later reference sequence (GenBank NM_006521) with a modified nomenclature (with no biological consequence) since Ladanyi’s publication [14], in type 1, the
shortened ASPL gene (exons 1–7) joins directly with exon 6 of TFE3 (exon 5 is excluded) and in type 2 with exon 5 (Figure 3c and d).

Rapid diagnosis is usually achieved by fluorescent in situ hybridization (FISH) using break-apart TFE3 gene target probes (Figure 2). RT-PCR analysis (reverse transcription-polymerase chain reaction), is also satisfactory [56, 63, 64]. NGS being multiplex is more and more in use in specialized establishments.

The molecular mechanisms driven by the ASPL-TFE3 oncoprotein are not entirely known. Senescence promotion through p21 up-regulation wielding a mechanism of tumor progression by senescence-associated secretory phenotype (SASP) via proinflammatory cytokines secretion has been proposed [65–68].

In gene expression profiling analysis, MET acts as a transcriptional target of the ASPL-TFE3 fusion. The latter binds to the activated promoter, induces MET tyrosine kinase autophosphorylation increasing MET protein expression in the presence of its ligand hepatocyte growth factor (HGF), and upregulates downstream signaling, to promote cell proliferation, growth, and invasion. MET appears to be a possible candidate for targeted therapy in [69, 70].

Other actions of TFE3 aim at targeting hypoxia-inducible factor (HIF-1a) which activates angiogenesis via factors, such as VEGFA, PDGF, or angiopoietin [32, 35, 71–74], findings useful for antiangiogenic therapy investigations.

Further, melanoma inhibitor of apoptosis (ML-IAP), a factor of cell survival in melanoma targeted by MITF, is proven to be overexpressed in ASPS gene expression profiling [71, 75]. Both MITF and TFE3 are members of the basic helix–loop–helix leucine zipper transcription factors family and lock on to the same DNA motif, the E-box DNA consensus segment CANNTG [65, 76, 77].

CGH array studies show complex anomalies at multiple levels—gains of 1q, 8q, 16q, and Xp11-pter [78] with translocations, deletions, trisomy 12, trisomy 8, and loss of chromosome 17 after chemotherapy [79]. Updated results with high-resolution aCGH
reported by Selvarajah et al. have confirmed these observations and suggested increased genomic instability in the metastatic setting with still more gains and losses [35].

Recent literature relative to immunogenicity in ASPS mentions significantly increased expression of host response factors to the lesion involving the innate activating receptors TLR2 and TLR9 [59].

3.7 Differential diagnoses

In our experience, ASPS can have overlapping morphological features to some degree with other lesions of which the most frequent are listed in Table 1, but these mimics lack the specific recurrent nonreciprocal translocation found in ASPS. Key cytoarchitectural aspects, such as severe atypia, spindling, or pleomorphism generally are not in favor of ASPS. Moreover, the latter belongs to different clinical and immunohistochemical contexts. Generally, paragangliomas fit older patients [50] and
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Clear cell sarcoma of soft tissue
Metastatic melanoma
Clear cell renal carcinoma
Liver cell carcinoma
Granular cell tumor
PEComa
Paraganglioma
Rhabdomyosarcoma

Table 1.
Some basic differential diagnoses of ASPS.

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are not readily observed in limbs. Unlike in ASPS, tumor cells are void of cytoplasmic glycogen. More importantly, they show neuroendocrine differentiation with the accompanying sustentacular cells being immunoreactive with anti-S-100 protein [57]. Clear cell sarcoma of soft tissue and metastatic melanoma consistently express melanocytic markers, such as HMB45 and Melan A, as well as S100 protein. Equivocally in metastatic melanoma, those antigens may be lost and like in ASPS, Cathepsin K can be immunopositive. Clear cell sarcoma of soft tissue may likewise express focally cathepsin K but harbors a reciprocal translocation t(12,22) resulting in the fusion of EWSR1-ATF1 in most cases [57]. Granular cell tumors, like in ASPS, may immunostain with TFE3 and cathepsin K but unlike ASPS they are also consistently reactive with anti-PS100, anti-SOX 10, and anti-inhibin antibodies [57, 80].

Renal cell carcinoma in children shares with ASPS the same fusion gene resulting from identical breakpoints [81–83] but here translocation is reciprocal. Reciprocity can be assessed using the right primers to the nonfunctional fusion site [72]. Contrary to ASPS, renal cell carcinomas immunostain with cytokeratin, epithelial membrane antigen (EMA), and PAX8 and do not express cathepsin K. They can harbor other fusion partners of TFE3, such as DVL2 and PRCC. These fusion genes, DVLE2-TFE3 and PRCC-TTF3 as well as the newly identified chimeric HNRNPH3-TTF3 have been detected in ASPS also [84].

Liver cell carcinoma can morphologically represent an important diagnostic pitfall, the liver being a possible primary site of ASPS. Hepatocarcinoma cells are immunopositive for hepatocyte paraffin 1 (Hep-Par1), glypican-3, and polyclonal carcinoembryonic antigen (P-CEA) [57].

Neuroendocrine or endocrine tumors, contrary to ASPS, stain with antibodies against chromogranin, synaptophysin, and CD56.

PEComas are most often located in the pelvis, gynecologic tract, and retroperitoneum. Like ASPS, a subset expresses TFE3 but with a double differentiation pattern, smooth muscle and melanocytic, staining with h-Caldesmon, HMB45, less often Melan A., all of which are negative in ASPS [85]. Adrenocortical carcinomas express Melan A or inhibin. Rhabdomyosarcomas are consistently positive for skeletal muscle differentiation markers (desmin, nuclear myogenin or MyoD1). A number of other lesions are perhaps not likely to be confused with ASPS but can nevertheless, because of their epithelioid cell morphology and abundant cytoplasm, be considered as differential diagnoses of the tumor in its less frequent solid appearance without alveolar configuration. These include epithelioid sarcoma, epithelioid angiosarcoma, epithelioid hemangioendothelioma, myoepithelioma, chordoma, meningioma, or even histiocytic sarcoma. But these present immunohistochemical and molecular profiles inconsistent with ASPS.
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