Chapter

Pathology of Alveolar Soft Part Sarcoma

Yves-Marie Robin

Abstract

Alveolar soft part sarcoma (ASPS) is a rare orphan sarcoma of uncertain differentiation according to the latest WHO classifcation 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: differentation, 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], gastrointestinal tract [8], breast [9], uterine corpus [10], cervix [11], and the bladder [12]. Some deeply 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 characteristic 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 established 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 following 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 nucleophosphoproteins 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 [28] 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 crystalloids 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 rhomboid 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 MCTI-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].

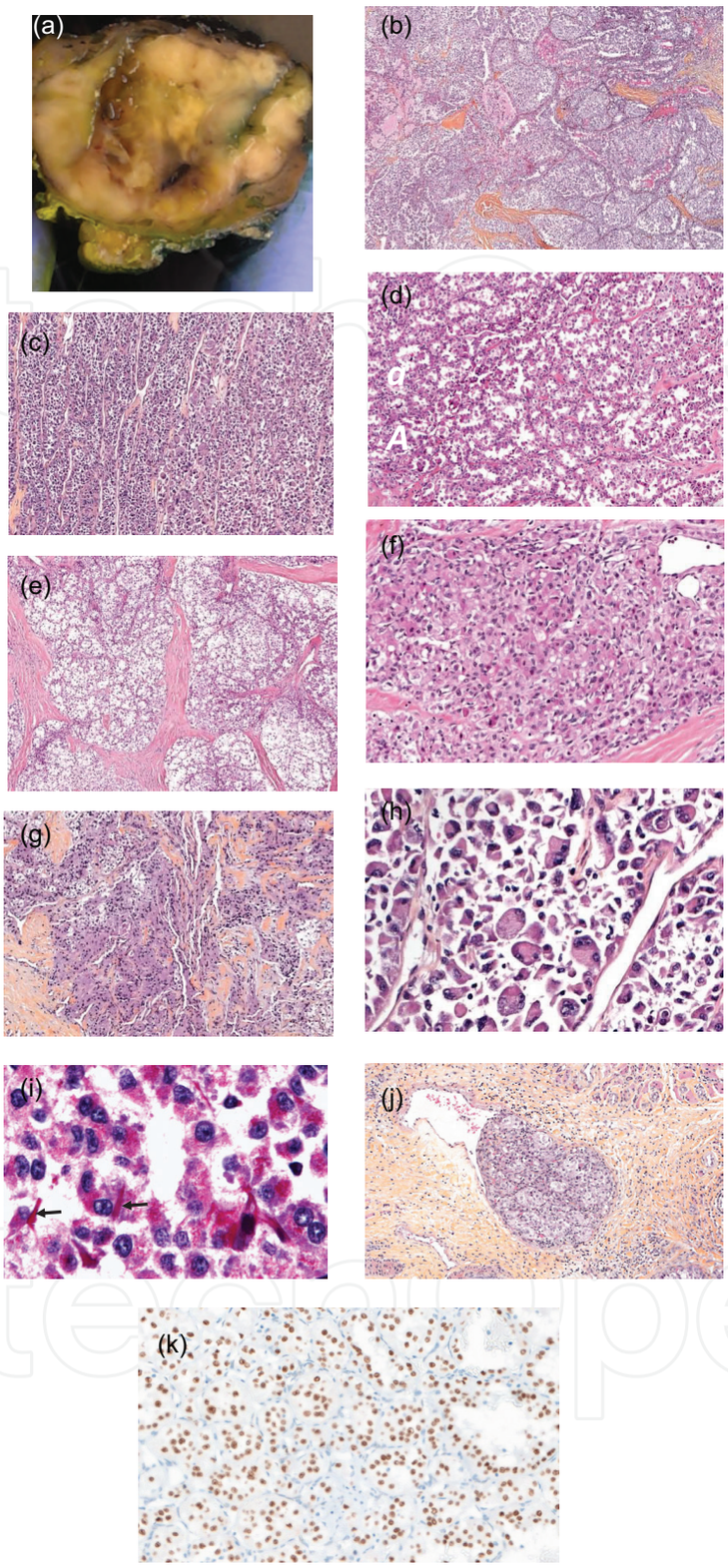

Figure 1.
ASPS : gross pathology (cut surface) (a), typical cytoarchitectural features (b-j) and TFE3 immunohistochemical nuclear staining (k).

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 [53].

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

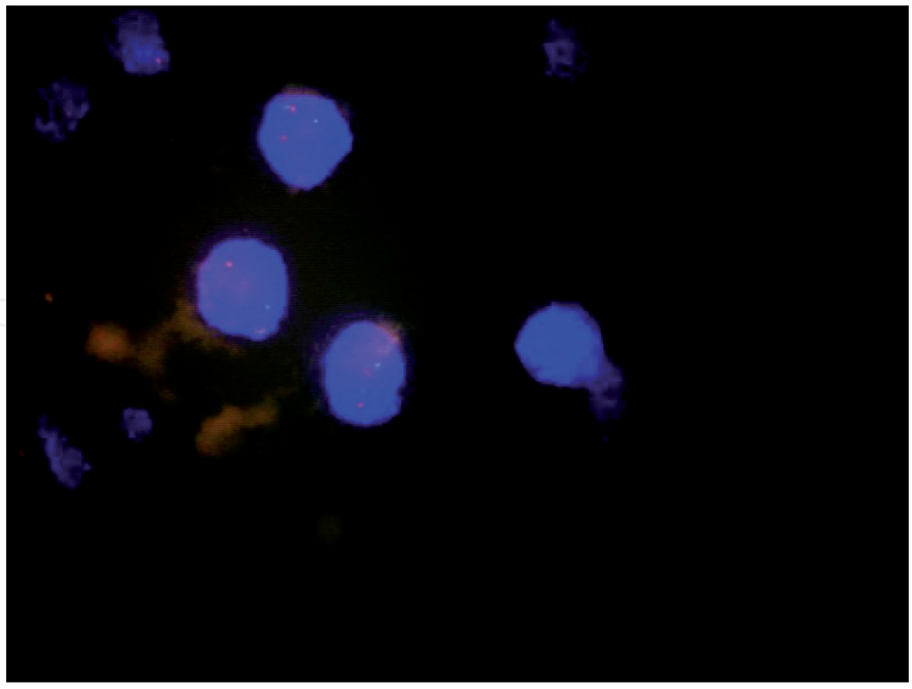

Figure 2.
Fluorescent in situ hybridization (FISH) using break-apart probes targeting the TFE3 gene. Cells in the upper left quadrant show rearrangement of the gene with a split between red and green signals.

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, PDFG, 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

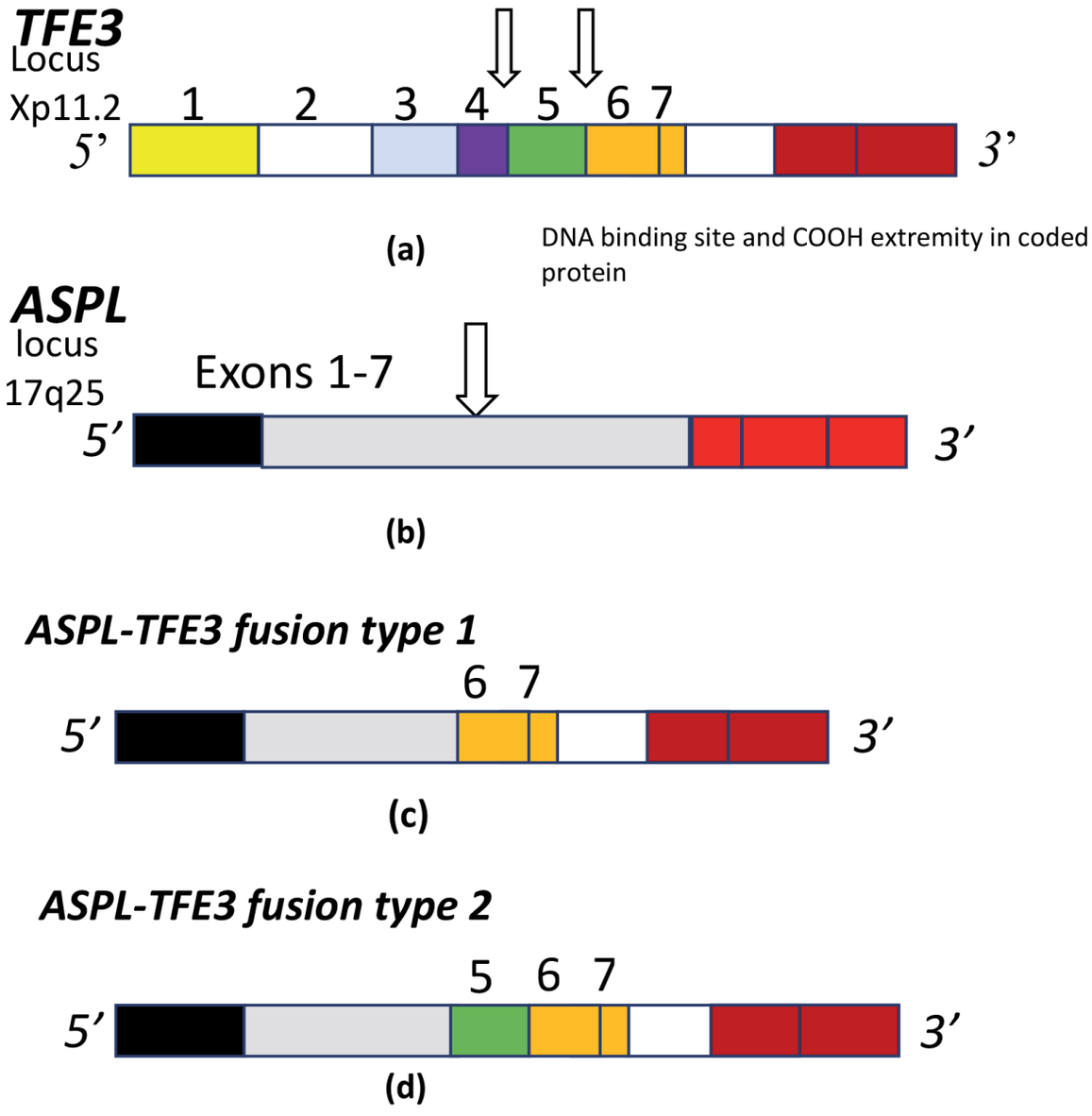

Figure 3.
Representations of TFE3 (a) and ASPL (b) genes with breakpoints indicated by arrows; bottom figures (c, d) correspond to the types 1 and 2 fusions respectively.

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

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.

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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Author details

Yves-Marie Robin
Biopathology Wing, Unit of Molecular and Morphological Pathology, Centre Oscar Lambret, Lille, France

*Address all correspondence to: ym-robin@o-lambret.fr

References

[1] Christopherson WM, Foote FW, Stewart FW. Alveolar soft-part sarcomas; structurally characteristic tumors of uncertain histogenesis. Cancer. 1952;**5**:100-111

[2] Lieberman PH, Brennan MF, Kimmel M, Erlandson RA, Garin-Chesa P, Flehinger BY. Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. Cancer. 1989;**63**:1-13

[3] Liebl LS, Elson F, Quaas A, Gawad KA, Izbicki JR. Value of repeat resection for survival in pulmonary metastases from soft tissue sarcoma. Anticancer Research. 2007;**27**:2897-2902

[4] Das KK, Singh RK, Jaiswal S, Agrawal V, Jaiswal AK, Behari S. Alveolar soft part sarcoma of the frontal calvarium and adjacent frontal lobe. Journal of Pediatric Neurosciences. 2012;**7**:36-39

[5] Ju HU, Seo KW, Jegal Y, Ahn J-J, Lee YJ, Kim YM, et al. A case of alveolar soft part sarcoma of the pleura. Journal of Korean Medical Science. 2013;**28**:331-335

[6] Shaddix KK, Fakhre GP, Nields WW, Steers JL, Hewitt WR, Menke DM. Primary alveolar soft-part sarcoma of the liver: Anomalous presentation of a rare disease. The American Surgeon. 2008;**74**:43-46

[7] Kim YD, Lee CH, Lee MK, Jeong YJ, Kim JY, Park DY, et al. Primary alveolar soft part sarcoma of the lung. Journal of Korean Medical Science. 2007;**22**:369-372

[8] Yaziji H, Ranaldi R, Verdolini R, Morroni M, Haggitt R, Bearzi I. Primary alveolar soft part sarcoma of the stomach: A case report and review. Pathology, Research and Practice. 2000;**196**:519-525

[9] Wu J, Brinker DA, Haas M, Montgomery EA, Argani P. Primary alveolar soft part sarcoma (ASPS) of the breast: Report of a deceptive case with xanthomatous features confirmed by TFE3 immunohistochemistry and electron microscopy. International Journal of Surgical Pathology. 2005;**13**:81-85

[10] Zhang L, Tang Q, Wang Z, Zhang X. Alveolar soft part sarcoma of the uterine corpus with pelvic lymph node metastasis: Case report and literature review. International Journal of Clinical and Experimental Pathology. 2012;**5**:715-719

[11] Roma AA, Yang B, Senior ME, Goldblum JR. TFE3 immunoreactivity in alveolar soft part sarcoma of the uterine cervix: Case report. International Journal of Gynecological Pathology Official Journal of International Society of Gynecological Pathologists. 2005;**24**:131-135

[12] Amin MB, Patel RM, Oliveira P, Cabrera R, Carneiro V, Preto M, et al. Alveolar soft-part sarcoma of the urinary bladder with urethral recurrence: A unique case with emphasis on differential diagnoses and diagnostic utility of an immunohistochemical panel including TFE3. The American Journal of Surgical Pathology. 2006;**30**:1322-1325

[13] Folpe AL, Deyrup AT. Alveolar soft-part sarcoma: A review and update. Journal of Clinical Pathology. 2006;**59**:1127-1132

[14] Ladanyi M, Lui MY, Antonescu CR, et al. The der(17)t(X;17)(p11;q25) of

human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene. 2001;**20**:48-57

[15] International Agency for Research. WHO Classification of Tumours of Soft Tissue and Bone. 5th Edition. Lyon, France: WHO Edition; 2020

[16] Masson P. Tumeurs humaines. Librairie Maloine. Tech. 1956;**213**: 1956-1968

[17] Persson S, Willems JS, Kindblom LG, Angervall L. Alveolar soft part sarcoma. An immunohistochemical, cytologic and electron-microscopic study and a quantitative DNA analysis. Virchows Archiv. A, Pathological Anatomy and Histopathology. 1988;**412**:499-513

[18] Mukai M, Torikata C, Iri H, Mikata A, Hanaoka H, Kato K, et al. Histogenesis of alveolar soft part sarcoma. An immunohistochemical and biochemical study. The American Journal of Surgical Pathology. 1986;**10**:212-218

[19] Mukai M, Torikata C, Shimoda T, Iri H. Alveolar soft part sarcoma. Assessment of immunohistochemical demonstration of desmin using paraffin sections and frozen sections. Virchows Archiv. A, Pathological Anatomy and Histopathology. 1989;**414**:503-509

[20] Denk H, Krepler R, Artlieb U, Gabbiani G, Rungger-Brändle E, Leoncini P, et al. Proteins of intermediate filaments. An immunohistochemical and biochemical approach to the classification of soft tissue tumors. The American Journal of Pathology. 1983;**110**:193-208

[21] Foschini MP, Ceccarelli C, Eusebi V, Skalli O, Gabbiani G. Alveolar soft part sarcoma: Immunological evidence of rhabdomyoblastic differentiation. Histopathology. 1988;**13**:101-108

[22] Matsuno Y, Mukai K, Itabashi M, Yamauchi Y, Hirota T, Nakajima T, et al. Alveolar soft part sarcoma. A clinicopathologic and immunohistochemical study of 12 cases. Pathology International. 1990;**40**:199-205

[23] Rosai J, Dias P, Parham DM, Shapiro DN, Houghton P. MyoD1 protein expression in alveolar soft part sarcoma as confirmatory evidence of its skeletal muscle nature. The American Journal of Surgical Pathology. 1991;**15**:974-981

[24] Miettinen M, Ekfors T. Alveolar soft part sarcoma. Immunohistochemical evidence for muscle cell differentiation. American Journal of Clinical Pathology. 1990;**93**:32-38

[25] Sciot R, Dal Cin P, De Vos R, Van Damme B, De Wever I, Van den Berghe H, et al. Alveolar soft-part sarcoma: Evidence for its myogenic origin and for the involvement of 17q25. Histopathology. 1993;**23**:439-444

[26] Goldblum JR, Weiss SW, Folpe AL. Enzinger and Weiss's Soft Tissue Tumors. 6th ed. Elsevier. 2019. Available from: https://www.elsevier.com/books/enzinger-and-weisss-soft-tissue-tumors/goldblum/978-0-323-08834-3 Accessed: December 2, 2017

[27] Wang NP, Bacchi CE, Jiang JJ, McNutt MA, Gown AM. Does alveolar soft-part sarcoma exhibit skeletal muscle differentiation? An immunocytochemical and biochemical study of myogenic regulatory protein expression. Modern Pathology Official Journal of United States and Canadian Academy of Pathology Inc. 1996;**9**:496-506

[28] Gómez JA, Amin MB, Ro JY, Linden MD, Lee MW, Zarbo RJ.

Immunohistochemical profile of myogenin and MyoD1 does not support skeletal muscle lineage in alveolar soft part sarcoma. Archives of Pathology & Laboratory Medicine. 1999;**123**:503-507

[29] Mukai M, Torikata C, Iri H, Mikata A, Sakamoto T, Hanaoka H, et al. Alveolar soft part sarcoma. An elaboration of a three-dimensional configuration of the crystalloids by digital image processing. The American Journal of Pathology. 1984;**116**:398-406

[30] Fisher ER, Reidbord H. Electron microscopic evidence suggesting the myogenous derivation of the so-called alveolar soft part sarcoma. Cancer. 1971;**27**:150-159

[31] Mukai M, Iri H, Nakajima T, Hirose S, Torikata C, Kageyama K, et al. Alveolar soft-part sarcoma. A review on its histogenesis and further studies based on electron microscopy, immunohistochemistry, and biochemistry. The American Journal of Surgical Pathology. 1983;**7**:679-689

[32] Stockwin LH, Vistica DT, Kenney S, Schrump DS, Butcher DO, Raffeld M, et al. Gene expression profiling of alveolar soft-part sarcoma (ASPS). BMC Cancer. 2009;**9**:22

[33] Nakano H, Tateishi A, Imamura T, et al. RT-PCR suggests human skeletal muscle origin of alveolar soft-part sarcoma. Oncology. 2000;**58**:319-323

[34] Hoshino M, Ogose A, Kawashima H, et al. Molecular analyses of cell origin and detection of circulating tumor cells in the peripheral blood in alveolar soft part sarcoma. Cancer Genetics and Cytogenetics. 2009;**190**:75-80

[35] Selvarajah S, Pyne S, Chen E, Sompallae R, Ligon AH, Nielsen GP, et al. High-resolution array CGH and gene expression profiling of alveolar soft part sarcoma. Clinical Cancer Research. 2014;**20**:1521-1530

[36] Zhang X, Huang CT, Chen J, et al. Pax6 is a human neuroectoderm cell fate determinant. Cell Stem Cell. 2010;**7**:90-100

[37] Mathew T. Evidence supporting neural crest origin of an alveolar soft part sarcoma: An ultrastructural study. Cancer. 1982;**50**:507-514

[38] DeSchryver-Kecskemeti K, Kraus FT, Engleman W, Lacy PE. Alveolar soft-part sarcoma--a malignant angioreninoma: Histochemical, immunocytochemical, and electron-microscopic study of four cases. The American Journal of Surgical Pathology. 1982;**6**:5-18

[39] Ackerman LV, Phelps CR. Malignant granular cell myoblastoma of the gluteal region. Surgery. 1946;**20**:511-519

[40] Khanolkar VR. Granular cell myoblastoma. The American Journal of Pathology. 1947;**23**:721-739

[41] Ravich A, Stout AP, Ravich RA. Malignant granular cell myoblastoma involving the urinary bladder. Annals of Surgery. 1945;**121**:361-372

[42] Smetana HF, Scott WF. Malignant tumors of nonchromaffin paraganglia. Military Surgeon. 1951;**109**:330-349

[43] Shipkey FH, Lieberman PH, Foote FW, Stewart FW. Ultrastructure of alveolar soft part sarcoma. Cancer. 1964;**17**:821-830

[44] Pappo AS, Parham DM, Cain A, Luo X, Bowman LC, Furman WL, et al. Alveolar soft part sarcoma in children and adolescents: Clinical features and outcome of 11 patients. Medical and Pediatric Oncology. 1996;**26**:81-84

[45] Jong R, Kandel R, Fornasier V, Bell R, Bedard Y. Alveolar soft part sarcoma: Review of nine cases including two cases with unusual histology. Histopathology. 1998;**32**:63-68

[46] Ordóñez NG, Mackay B. Alveolar soft-part sarcoma: A review of the pathology and histogenesis. Ultrastructural Pathology. 1998; **22**:275-292

[47] Ordóñez NG, Ro JY, Mackay B. Alveolar soft part sarcoma. An ultrastructural and immunocytochemical investigation of its histogenesis. Cancer. 1989;**63**:1721-1736

[48] Casanova M, Ferrari A, Bisogno G, Cecchetto G, Basso E, De Bernardi B, et al. Alveolar soft part sarcoma in children and adolescents: A report from the soft-tissue sarcoma Italian cooperative group. Annals of Oncology. 2000;**11**:1445-1449

[49] Evans HL. Alveolar soft-part sarcoma. A study of 13 typical examples and one with a histologically atypical component. Cancer. 1985;**55**:912-917

[50] Mittinen M. Modern Soft Tissue Pathology. 2nd ed. Lavoisier. Cambridge University Press; 2016. Available from: https://www.lavoisier.fr/livre/medecine/modern-soft-tissue-pathology-2nd-ed/descriptif_3454990 [Accessed: December 2, 2017]

[51] Ladanyi M, Antonescu CR, Drobnjak M, Baren A, Lui MY, Golde DW, et al. The precrystalline cytoplasmic granules of alveolar soft part sarcoma contain monocarboxylate transporter 1 and CD147. The American Journal of Pathology. 2002;**160**:1215-1221

[52] Schoolmeester JK, Dao LN, Sukov WR, Wang L, Park KJ, Murali R, et al. TFE3 translocation-associated perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: Morphology, immunophenotype, differential diagnosis. The American Journal of Surgical Pathology. 2015;**39**:394-404

[53] Chen X, Yang Y, Gan W, Xu L, Ye Q, Guo H. Newly designed break-apart and ASPL-TFE3 dual-fusion FISH assay are useful in diagnosing Xp11.2 translocation renal cell carcinoma and ASPL-TFE3 renal cell carcinoma. Medicine (Baltimore). 2015;**94**(19). DOI: 10.1097/MD.0000000000000873

[54] Tsuji K, Ishikawa Y, Imamura T. Technique for differentiating alveolar soft part sarcoma from other tumors in paraffin-embedded tissue: Comparison of immunohistochemistry for TFE3 and CD147 and of reverse transcription polymerase chain reaction for ASPSCR1-TFE3 fusion transcript. Human Pathology. 2012;**43**:356-363

[55] Riethdorf S, Reimers N, Assmann V, Kornfeld J-W, Terracciano L, Sauter G, et al. High incidence of EMMPRIN expression in human tumors. International Journal of Cancer. 2006;**119**:1800-1810

[56] Martignoni G, Gobbo S, Camparo P, et al. Differential expression of cathepsin K in neoplasms harboring TFE3 gene fusions. Modern Pathology. 2011;**24**:1313-1319

[57] Jaber OI, Kirby PA. Alveolar soft part sarcoma. Archives of Pathology & Laboratory Medicine. 2015;**139**:1459-1462

[58] Cykowski MD, Hicks J, Sandberg DI, Olar A, Bridge JA, Greipp PT, et al. Brain metastasis of crystal-deficient, CD68-positive alveolar soft part sarcoma: Ultrastructural features and differential

diagnosis. Ultrastructural Pathology. 2015;**39**:69-77

[59] Goldberg JM, Fisher DE, Demetri GD, et al. Biologic activity of autologous, granulocyte-macrophage colony-stimulating factor secreting alveolar soft-part sarcoma and clear cell sarcoma vaccines. Clinical Cancer Research. 2015;**21**:3178-3186

[60] Cullinane C, Thorner PS, Greenberg ML, Kwan Y, Kumar M, Squire J. Molecular genetic, cytogenetic, and immunohistochemical characterization of alveolar soft-part sarcoma: Implications for cell of origin. Cancer. 1992;**70**:2444-2450

[61] Joyama S, Ueda T, Shimizu K, Kudawara I, Mano M, Funai H, et al. Chromosome rearrangement at 17q25 and xp11.2 in alveolar soft-part sarcoma: A case report and review of the literature. Cancer. 1999;**86**:1246-1250

[62] Uppal S, Aviv H, Patterson F, Cohen S, Benevenia J, Aisner S, et al. Alveolar soft part sarcoma--reciprocal translocation between chromosome 17q25 and Xp11. Report of a case with metastases at presentation and review of the literature. Acta Orthopaedica Belgica. 2003;**69**:182-187

[63] AulmannS,LongerichT,SchirmacherP, Mechtersheimer G, Penzel R. Detection of the ASPSCR1-TFE3 gene fusion in paraffin-embedded alveolar soft part sarcomas. Histopathology. 2007;**50**:881-886

[64] Jin L, Majerus J, Oliveira A, Inwards CY, Nascimento AG, Burgart LJ, et al. Detection of fusion gene transcripts in fresh-frozen and formalin-fixed paraffin-embedded tissue sections of soft-tissue sarcomas after laser capture microdissection and rt-PCR. Diagnostic Molecular Pathology. 2003;**12**:224-230

[65] Ishiguro N, Yoshida H. ASPL-TFE3 oncoprotein regulates cell cycle progression and induces cellular senescence by up-regulating p21. Neoplasia. 2016;**18**:626-635

[66] Coppé J-P, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biology. 2008;**6**:2853-2868

[67] Lasry A, Ben-Neriah Y. Senescence-associated inflammatory responses: Aging and cancer perspectives. Trends in Immunology. 2015;**36**:217-228

[68] Gorgoulis VG, Halazonetis TD. Oncogene-induced senescence: The bright and dark side of the response. Current Opinion in Cell Biology. 2010;**22**:816-827

[69] Tsuda M, Davis IJ, Argani P, Shukla N, McGill GG, Nagai M, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Research. 2007;**67**:919-929

[70] Wagner AJ, Goldberg JM, Dubois SG, et al. Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: Results of a multicenter phase 2 trial. Cancer. 2012;**118**:5894-5902

[71] Kobos R, Nagai M, Tsuda M, et al. Combining integrated genomics and functional genomics to dissect the biology of a cancer-associated, aberrant transcription factor, the ASPSCR1-TFE3 fusion oncoprotein. The Journal of Pathology. 2013;**229**:743-754

[72] Lazar AJF, Das P, Tuvin D, et al. Angiogenesis-promoting gene patterns in alveolar soft part sarcoma. Clinical Cancer Research. 2007;**13**:7314-7321

[73] Covell DG, Wallqvist A, Kenney S, Vistica DT. Bioinformatic analysis of patient-derived ASPS gene expressions and ASPL-TFE3 fusion transcript levels identify potential therapeutic targets. PLoS One. 2012;**7**:e48023

[74] Azizi AA, Haberler C, Czech T, Gupper A, Prayer D, Breitschopf H, et al. Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma. The Lancet Oncology. 2006;**7**:521-523

[75] Dynek JN, Chan SM, Liu J, Zha J, Fairbrother WJ, Vucic D. Microphthalmia-associated transcription factor is a critical transcriptional regulator of melanoma inhibitor of apoptosis in melanomas. Cancer Research. 2008;**68**:3124-3132

[76] Beckmann H, Su LK, Kadesch T. TFE3: A helix-loop-helix protein that activates transcription through the immunoglobulin enhancer muE3 motif. Genes & Development. 1990;**4**:167-179

[77] HemesathTJ,SteingrímssonE,McGillG, Hansen MJ, Vaught J, Hodgkinson CA, et al. Microphthalmia, a critical factor in melanocyte development, defines a discrete transcription factor family. Genes & Development. 1994;**8**:2770-2780

[78] Kiuru-Kuhlefelt S, El-Rifai W, Sarlomo-Rikala M, Knuutila S, Miettinen M. DNA copy number changes in alveolar soft part sarcoma: A comparative genomic hybridization study. Modern Pathology. 1998;**11**:227-231

[79] Craver RD, Heinrich SD, Correa H, Kao YS. Trisomy 8 in alveolar soft part sarcoma. Cancer Genetics and Cytogenetics. 1995;**81**:94-96

[80] Chamberlain BK, McClain CM, Gonzalez RS, Coffin CM, Cates JMM. Alveolar soft part sarcoma and granular cell tumor: An immunohistochemical comparison study. Human Pathology. 2014;**45**:1039-1044

[81] Clark J, Lu YJ, Sidhar SK, Parker C, Gill S, Smedley D, et al. Fusion of splicing factor genes PSF and NonO (p54nrb) to the TFE3 gene in papillary renal cell carcinoma. Oncogene. 1997;**15**:2233-2239

[82] Argani P, Ladanyi M. Recent advances in pediatric renal neoplasia. Advances in Anatomic Pathology. 2003;**10**:243-260

[83] Dickson BC, Chung CT-S, Hurlbut DJ, et al. Genetic diversity in alveolar soft part sarcoma: A subset contain variant fusion genes, highlighting broader molecular kinship with other MiT family tumors. Genes, Chromosomes & Cancer. 2021;**59**:1-13

[84] Gong Y, Liu M, Wu Q et al. Alveolar soft part sarcoma of the tongue: A case report and review of the literature. International Journal of Clinical and Experimental Pathology. 2020;**13**(5): 1275-1282. Available from: www.ijcep.com/ISSN:1936-2625/IJCEP0110367

[85] Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: A distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. The American Journal of Pathology. 2001;**159**:179-192