



# Alveolar Soft Part Sarcoma: Case Report of a Rare Tumor and Review of Literature

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## Abstract

Alveolar soft part sarcoma (ASPS) is a rare neoplasm occurring most frequently in the soft tissues of both children and adults, which has a tendency for an indolent course and late metastasis. It is characterized by an unbalanced translocation, der(17)t(X:17)(p11;p25), producing a fusion protein which has recently been shown to play a role in promoting cell proliferation and angiogenesis and may provide a potential target for molecular therapy. We present a case of ASPS and discuss the histology, diagnostic considerations, cytogenetics, treatment, and prognosis.

KEYWORDS: Alveolar soft part sarcoma; Soft tissue; Translocation; Immunotherapy

## ABBREVIATIONS:

**ASPS:** Alveolar soft part sarcoma, **PEComa:** Perivascular epithelial cell neoplasm, **TFE3:** transcription factor E3, **IHC:** Immunohistochemistry

## INTRODUCTION

Alveolar soft part sarcoma (ASPS) is a rare tumor that was initially described as a distinctive clinical entity by Christopherson et al. in 1952. [1,2]. It represents 0.2% to 0.9% of all soft tissue sarcomas and tends to occur between ages 15 to 35 years and is rare in patients younger than 5 years and older than 50 years. [3, 4] ASPS is more common in females than it is in males with a 2:1 ratio. This ratio is seen more in the first 3 decades of life but shows a slightly male predominance thereafter [1,3].

ASPS is characterized by an unbalanced translocation: der(17)t(X:17)(p11;p25). This translocation results in the fusion of a gene of unknown function, ASPL, on chromosome 17 to the TFE3 gene on the X chromosome. [5] Because females have an extra X-chromosome, their likelihood of developing an X-autosome translocation is theoretically double that of males [1]. Bu et al. demonstrated a statistical association between the increased risks of ASPS in females, i.e., female predominance, and their possession of an extra X-chromosome and ASPS t(X;17) translocation fusion gene not subject to X-inactivation. [6]

Most often, ASPSPs present as painless masses, which may be

highly vascular on imaging studies. [5] In adults, ASPS tends to involve the deep soft tissues in the thigh or buttock. In children and infants, ASPS has a predilection for the head and neck region, with the tongue and orbit being the most common sites. Other organs reported include the urinary bladder, breast, larynx, and the uterine cervix. Bone involvement, although rare, can occur. The most commonly involved sites are the fibula, tibia, and ileum. [3] Despite a relatively indolent clinical course, the prognosis is poor and is often characterized by late metastases. Intravascular tumor extension is seen in most cases [5]. Alveolar soft part sarcoma has a high incidence of metastatic disease, which may precede the detection of the primary tumor. [3, 7, 8] Patients who present with large tumors are most likely to have metastasis at the time of diagnosis. [3]

## CASE PRESENTATION

A 26-year-old man presented with a painless large right calf mass. Patient reported he noticed a growing mass for at least a year, but recently rapidly increasing in size so he decided to seek medical attention. Patient reported history of well controlled diabetes mellitus type-1, otherwise no significant medical history or family history of malignancy. Plain film radiography demonstrated non-specific pattern with a permeative and destructive deep soft tissue lesion affecting the right calf area. Delayed image arteriogram showed characteristics of a highly vascular soft tissue mass. CT images of the mass showed areas of hyperdensity at the periphery, with a central area of low attenuation suggestive of possible necrosis. Non-enhanced T1-weighted sequences of the right calf area revealed a large 7 x 5 cm soft tissue mass. On the gadolinium-enhanced images, heterogeneous enhancement of the lesion was identified. Radiology imaging studies were suggestive of sarcoma with vascular features.

A tissue biopsy of the mass was performed. Microscopic examination revealed a malignant tumor with nested and organoid growth pattern forming alveolar-like architecture. The tumor was mostly uniform in size and shape, with only occasional variation separated by delicate sinusoidal vascular channels lined by a flattened, single layer of endothelial cells.

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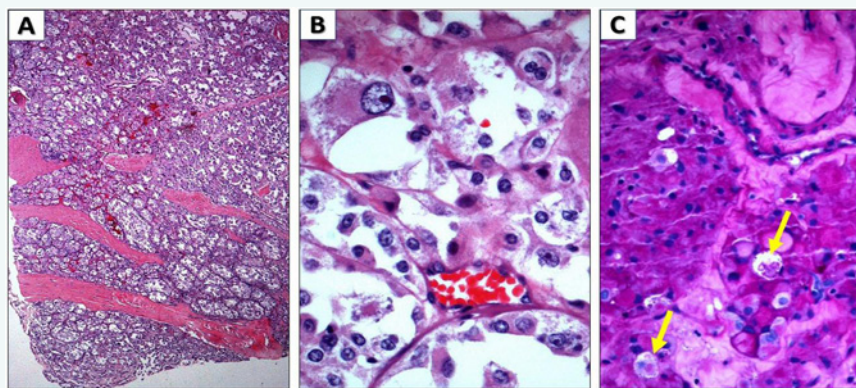
The tumor cells were mostly round, with regular, eccentrically placed nuclei with vesicular chromatin, dense eosinophilic cytoplasm and a prominent central nucleolus; multinucleation was occasionally noted. Degree of atypia was mild to moderate with mitotic activity 4/10 HPF, and rare foci of necrosis (**Figure 1A-B**). Presence of intracytoplasmic, periodic acid-Schiff (PAS), diastase-resistant crystals was noted which is a characteristic feature of ASPS (**Figure 1C**)

Immunohistochemistry (IHC) studies were utilized for definitive diagnosis. The tumor cells were positive for CD-68, Desmin, Myo D-1 and positive nuclear staining for TFE3, while negative for Myogenin and S-100 (**Figure 2A-B-C**). Tumor cells were strongly positive for Vimentin and negative for epithelial, lymphoid, and melanocytic markers. Molecular testing was performed, and the tumor showed an unbalanced translocation t(X:17). Surveillance imaging for metastasis showed no evidence of metastasis except for two small left lung lesions measuring 1.5 and 1.8 cm. Ultrasound guided fine needle aspiration of one of

the lung masses revealed features similar to the calf tumor. The histomorphology together with the IHC profile and molecular studies were diagnostic of alveolar soft-part sarcoma of the deep soft tissue of the calf with lung metastasis.

A multidisciplinary tumor board recommended complete excision of the calf mass, surgical removal of the two lung masses followed by post-operative external beam radiation therapy to the calf region. The excised calf mass revealed a well-circumscribed white-tan focally hemorrhagic tumor with border pushing into the surrounding skeletal muscles measuring 6.7 x 6.5 x 5.4 cm. All surgical margins were free of the tumor, but vascular invasion was noted in the surrounding areas outside the tumor mass. The histomorphology and IHC profile of the excised calf mass and the two lung masses were similar to the original biopsy findings. Post-operative external beam radiation therapy to the calf region was initiated.

Patient was followed up for 18 months with no evidence of recurrence or metastasis, then he started to develop neurological

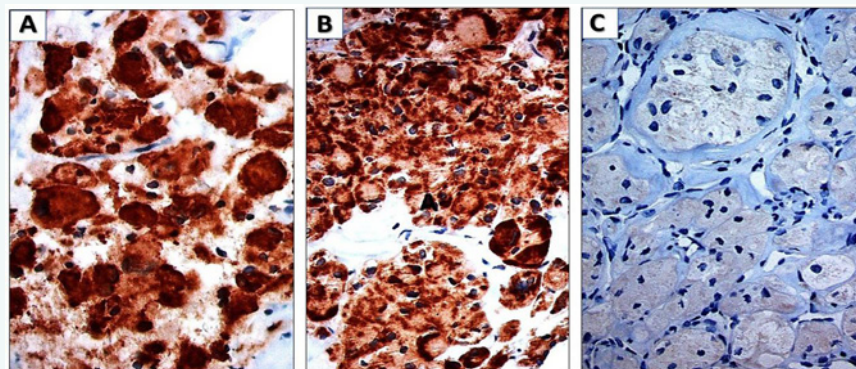


**Figure 1** Histomorphology of the excised alveolar soft part sarcoma (ASPS).

1A: Nested and organoid growth pattern making alveolar-like architecture (H&E stain X20).

1B: The tumor cells are mostly round, regular, eccentrically placed nuclei with vesicular chromatin, dense eosinophilic cytoplasm and a prominent central nucleolus (H&E stain X60)

1C: Presence of intracytoplasmic, periodic acid-Schiff (PAS), diastase-resistant crystals, which is a characteristic feature of ASPS (PAS stain X60)



**Figure 2** Immunohistochemistry profile of the excised alveolar soft part sarcoma (ASPS).

1A: Tumor cells positive for desmin

1B: Tumor cells positive for Myo D-1

1C: Tumor cells negative for myoglobin



symptoms and brain MRI revealed multiple brain metastases. He was placed on a clinical trial utilizing immune-based PD1/PDL1 inhibitors “checkpoint inhibitors.” Six months later patient expired due to multiple organ failure.

## DISCUSSION

Alveolar soft-part sarcoma (ASPS) is a rare, translocation-driven sarcoma of the soft tissues. ASPS often affect young adults and is characterized by indolent behavior but early evidence of metastatic spread. The histogenesis of this tumour is still unknown, despite IHC studies, electron microscopy and molecular studies. The associations of TFE3 and facilitation of an immunosuppressive microenvironment provide a rationale for exploring treatments that affect the balance between T-effector cells and T-regulatory cells. [18]

Grossly, alveolar soft part sarcoma is usually a poorly circumscribed mass with a soft and rubbery consistency that has a tan-pale to yellow cut surface, which may be accompanied by areas of hemorrhage or necrosis, especially in large tumors. [3] Microscopically, ASPS has a distinctive and characteristic, nested or organoid growth pattern. The nests tend to be uniform in size and shape, although some variation may be present. The nests are separated by delicate sinusoidal vascular channels lined by a flattened, single layer of endothelial cells. [3, 9] The name “alveolar” was derived from its pseudoalveolar appearance with clustered polygonal cells lacking central cohesion. [1] A characteristic feature of ASPS is the presence of intracytoplasmic, periodic acid–Schiff, diastase-resistant rhomboid- or rod-shaped crystals. [3] ASPS cells typically have round, regular, eccentrically placed nuclei with vesicular chromatin and a prominent central nucleolus; multinucleation may be present in a few cells. [5]

Molecular cytogenetic studies of ASPS have demonstrated the chromosomal rearrangement der(17)t(X;17)(p11;q25) resulting in the ASPL-TFE3 fusion gene, which is highly specific and critical for development of the tumor. [1] The translocation in ASPS is unusual in that it is unbalanced, although two patients with a reciprocal translocation have been described. [5, 10, 11] The ASPSCR1-TFE3 fusion protein acts as an aberrant transcription factor resulting in activation of the MET signaling pathway believed to promote angiogenesis and cell proliferation. [3, 12]

The differential diagnosis for ASPS includes other primary soft tissue neoplasms, such as rhabdomyoma, hibernoma, clear cell sarcoma of soft tissue, perivascular epithelial cell neoplasm (PEComa), paraganglioma, and granular cell tumor. Metastatic tumors with similar cytologic features can mimic ASPS, such as clear cell RCC, hepatocellular carcinoma, adrenocortical carcinoma, and melanoma. [3]. PEComa is positive for TFE3 presenting a diagnostic challenge to differentiate it from ASPS. Histologically, PEComa consists of epithelioid cells with alveolar structure and shows a diffuse strong expression of HMB45 (not seen in ASPS) and TFE3 [20].

In general, ASPSs are negative for epithelial markers, such as cytokeratins and epithelial membrane antigen, negative for specific neuroendocrine markers such as chromogranin A and synaptophysin, and negative for specific melanocytic markers,

such as HMB45 and Melan-A. Non-specific markers such as neuron-specific enolase and vimentin may be present in roughly 30–50% of cases. [5] Alveolar soft part sarcoma is consistently positive for an antibody that detects the carboxyl terminal portion of the transcription factor E3 (TFE3) gene retained in the fusion. [3] Although TFE3 seems to be almost universally expressed in normal tissues, this expression is at very low levels and strong nuclear expression of TFE3 is seen almost exclusively in tumors known to contain the TFE3 gene fusions, such as ASPSs and rare pediatric renal carcinomas. [5] It must be emphasized that only nuclear expression of TFE3 is of diagnostic value, as cytoplasmic staining (possibly non-specific) is seen in various tumors. [5]

The rarity of ASPS makes it difficult to draw definitive conclusions regarding its clinical characteristics, prognostic factors, and appropriate treatment. [1] Prognosis is largely dependent on the initial presentation (localized versus metastatic disease), tumor size, and age. [3] Patients with localized disease at presentation have a 71% 5-year survival rate, compared with 20% for patients with metastatic disease at time of diagnosis. [3, 13] Ogura et al. found the median survival of their 26 patients to be 90 months, with overall 5- and 10-year survival rates of 64% and 48%, respectively. [1] Of note, children have an excellent 5-year survival rate of up to 100%, especially if the tumor arises in the head and neck. More recent data report a 5-year survival rate for children to be 83%. [3, 14, 15]

ASPS shows a high incidence (around 30%) of brain metastases, being at least 3 times higher than that of other soft tissue sarcomas. [1, 16] Although it remains unclear whether this high incidence of brain metastases is attributable to disease-specific biology or a long disease duration, the survival of patients after diagnosis of brain metastases remains poor (median survival 12 months). [1]

Most series have suggested that ASPS is resistant to conventional cytotoxic chemotherapy and support the contention that complete excision of the tumor is the only meaningful treatment for ASPS. Moreover, data regarding the clinical value of radiotherapy for treatment of ASPS are still limited. In the series conducted by Ogura et al., none of the patients responded to, or benefited significantly from, conventional chemotherapies including a combination of gemcitabine and docetaxel. [1] The feasibility of using an antiangiogenic agent for the treatment of ASPS was demonstrated by Vistica et al. using in vivo preclinical models [1, 17]. Recently, it has been reported that several antiangiogenic agents such as bevacizumab and sunitinib malate exert tumor-suppressive effects in ASPS. [1] The recent identification of the role of ASPSCR1-TFE3 in the MET signaling pathway promoting tumor cell proliferation and angiogenesis is considered the cornerstone for targeted molecular therapy in ASPS, namely antiangiogenic drugs and MET kinase inhibitors, with ongoing clinical trials showing promising early results. [3]

Wilky et al, (2019), reported that in addition to possible “targeted therapies” to treat ASPS, there should be enthusiasm for treatment with immune-based therapeutics, particularly a class of “checkpoint inhibitors,” PD1/PDL1 inhibitors. These medications are designed to increase the body’s immune response against the



cancer cells and for some cancer types (melanoma for example) have replaced traditional toxic chemotherapies as a first choice for treatment. For ASPS, early reports from clinical trials of this group suggest that a subset of patients with ASPS respond very well to these immune treatments though more work is needed, and many trials are still ongoing. Immunotherapy was tried in our patient but only initiated at a very advanced stage of the disease, and patient expired 6 months after the start of treatment. [19]

In conclusion, ASPS is relatively indolent but has a high propensity for metastasis. Early diagnosis and complete excision of a small primary tumor is important in the treatment of ASPS. Antiangiogenic strategies, targeted medicine and immunotherapy may become a breakthrough form of management for advanced ASPS.

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