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Case Report

Clavicular and meningeal alveolar soft part sarcoma: An unusual case and literature review

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ABSTRACT

Introduction: Alveolar soft part sarcoma (ASPS) commonly arises in the soft tissue of the lower extremities. Primary bone involvement is rare.

Methods/Results: We report a 23-year-old male who presented with pathologic fracture of the clavicle, and diagnosis of clavicular ASPS. Workup demonstrated a lumbar meningeal mass, also involving the vertebral bodies.

Conclusions: Few cases of primary bone ASPS have been identified. Most common primary bone involvement includes the fibula, ilium and tibia. Likewise, meningeal involvement is quite rare. In summary, primary bone ASPS is rare and may involve the clavicle. Meningeal involvement is likewise rare, and presumably represents metastatic spread.

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1. Introduction

First described by Christopherson et al in 1952,¹ alveolar soft part sarcoma (or ASPS) is a rare malignant neoplasm most commonly found in the soft tissue. ASPS accounts for less than 1% of all soft tissue malignancies, and generally occurs between 15 and 35 years of age.¹ ASPS primarily arises from the deep soft tissue of the extremities, trunk, retroperitoneum, head and neck.² In children and infants, ASPS has an unusual tendency to involve the tongue and orbit.^{3,4} ASPS rarely occurs in other locations, such as the female genital tract,⁵ mediastinum,⁶ lung,^{7,8} gastrointestinal tract,⁹ and bone.¹⁰ Primary bone involvement is rare, and

characteristically involves the fibula, ilium and tibia. Grossly, tumors are often gray-white and fleshy. Histologically, large, epithelioid cells with abundant eosinophilic cytoplasm are arranged in a characteristic nesting or pseudoalveolar pattern. Recent evidence has found that ASPS represents a translocation sarcoma, with cytogenetic studies demonstrating chromosome 17 nonreciprocal translocation [der(17)t(X;17)(p11.2;q25)], involving the TFE3 gene, in almost all cases.¹¹

ASPS has a relatively slow growth, but frequently metastasizes and has a poor long-term prognosis. Survival rates decrease substantially with time, from 77% survival at 2 years to only 15% survival at 20 years.¹² Patients presenting with localized disease have a greater disease-free survival (71% at 5

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years), in comparison to those presenting with metastasis (20% at 5 years).² Common sites of metastases include the lung, brain and bone.^{2,12} Interestingly, as compared to other sarcomas, ASPS has a predilection for brain metastases (three-fold increase in frequency as compared to uterine, gastrointestinal or nasopharyngeal sarcomas).^{13,14} While meningeal involvement is quite rare, it is presumed to represent metastatic involvement in nearly all cases.

Here, we report, to our knowledge, the first case of clavicular ASPS, which presented as a pathologic fracture of the clavicle in an otherwise healthy young man. After workup and staging, a meningeal/parameningeal ASPS was also identified, likely a site of metastasis. This case, which was initially misdiagnosed as hemangioendothelioma, highlights some of the pitfalls in the diagnosis of ASPS, and the possible unusual sites of presentation.

2. Case report

A 23-year-old Hispanic male presented to an outside hospital with a pathologic fracture of the clavicle. The patient's past

medical history was non-contributory, surgical repair was performed and a biopsy was sent for routine pathology. A pathologic diagnosis of hemangioendothelioma was given (interpretation performed at an outside hospital). Two months later, the patient experienced back spasms and numbness in his right leg. Workup including chest and abdominal CT revealed a clavicular tumor and a meningeal based mass of the lumbar spine. The lytic lesion on the clavicle was centered in the bone, now measuring 4.5 cm and with 2.0 cm soft tissue extension (Fig. 1A,B). The vertebral lesion involved the meningeal/parameningeal space and L1 vertebral body, measuring approximately 6.0–7.0 cm and with significant impingement of the lumbar spinal cord (Fig. 1C). A follow-up MRI demonstrated the mass was at the level of T10 to L3 and confirmed the right meningeal/parameningeal mass with osteolytic destruction of the T12-L1 levels (Fig. 1D).

A month later and in order to resolve his spinal cord compression, the patient underwent a posterior L1-2 laminectomy, partial resection of the meningeal/parameningeal tumor, a partial L1 vertebrectomy, and spinal fusion from T9 to L3 levels. The specimen consisted of several friable white-tan pieces of tissue. Hematoxylin and Eosin (H&E) stained

Fig. 1 – Radiographic appearance of clavicle and meningeal/parameningeal ASPS. (A,B) Axial CT images of the left clavicle demonstrate a destructive lytic lesion with associated soft tissue mass. (C) Axial image from a CT of the lumbar spine demonstrates the destructive soft tissue mass about the L1 vertebral body that involves the spinal canal. (D) Sagittal MRI of the lumbar spine demonstrates a destructive soft tissue mass about the L1 vertebral body involving the epidural space and spinal canal. Red arrow heads indicate the approximate edges of tumor; yellow arrow heads indicate spinal cord compression; white asterisk indicates spinal cord.

histologic sections showed an organoid arrangement of tumor cells separated by thin-walled sinusoidal spaces (Fig. 2A,B). Nests of cells had central loss of cellular cohesion, giving rise to an alveolar pattern. Mitotic figures were inconspicuous; necrosis was focally seen. PAS-D (periodic acid–Schiff positive with diastase) staining highlighted characteristic intracytoplasmic, membrane bound, needle-shaped crystalline inclusions (Fig. 2C). Immunohistochemical stains were performed, and were negative for endothelial markers (including CD 31, Factor 8, and CD 34), epithelial markers (epithelial membrane antigen (EMA) and Pan-Keratin), and S100. With these histological features, a diagnosis of ASPS was rendered, most likely a metastasis given the unusual location.

Subsequently, a year after his initial diagnosis, the patient underwent resection of his clavicular tumor. The resection specimen consisted of one fragment of clavicle with soft tissue attached measuring 10.0 × 4.0 × 3.5 cm. The tumor measured 4.0 cm in greatest dimension and was centered in the medullary space of the bone. On cross-section, the tumor was fleshy tan with foci of hemorrhage and necrosis. Hematoxylin and Eosin (H&E) stained histologic sections showed an organoid arrangement of tumor cells with similar appearance to the meningeal lesion (Fig. 2D,E). Some areas of the tumor demonstrated a diffuse infiltrative growth pattern into the soft tissue. The tumor cells were round to oval with hyperchromatic vesicular nuclei, prominent nucleoli and eosinophilic granular cytoplasm. Rare mitoses were observed.

PAS-D staining again highlighted characteristic intracytoplasmic inclusions (Fig. 2F). Immunohistochemical stains were performed, and were negative for endothelial and epithelial markers. Similar to the meningeal mass, a diagnosis of ASPS was made. The medullary based nature of the tumor was consistent with a primary bone ASPS.

2.1. Clinical follow-up

During the patient's workup, chest CT was also notable for innumerable pulmonary metastases in both lung fields that measured from 2.0 mm to 5.0 cm (Fig. 3A). The patient's condition continued to worsen, with intermittent hemoptysis. Two years after his initial diagnosis the patient developed headaches and focal neurologic deficits, a brain MRI identified cerebral metastases causing a 2.0 mm shift with hemorrhage and edema (Fig. 3B). In addition, the patient developed progressive nasal congestion and a CT scan revealed a left sinonasal mass. As well, the patient presented with a new right acetabular fracture, likely related to bony metastasis. Unfortunately, the patient was subsequently lost to follow-up.

3. Discussion

The pathologic diagnosis of ASPS is based on histologic features, including the well-characterized pseudoalveolar pattern of cells, nests of relatively uniform cells with large round or polygonal shapes and fibrils that define and separate these nests of cells. Typically, prominent, periodic acid–Schiff (PAS) positive, diastase-resistant crystals and granules are seen.^{15,16} Initial studies of these cytoplasmic granules reported protein and polysaccharide complexes.¹⁶ Further experimentation has found an accumulation of MCT1-CD147 complexes, as CD147 has two potential TFE3 binding sites (the transcription factor which was translocated), this overproduction could be related to the novel genetic sequence of ASPS; however, further transactivation assays need to be performed.¹⁷ Electron microscopy has shown a lattice pattern

Fig. 2 – Histological appearance of clavicle and meningeal/parameningeal ASPS. (A–C) Histologic appearance of the clavicular mass, demonstrates alveolar nests of tumor cells separated by thin fibrous septae, with adjacent involved bone tissue. Large epithelioid cells have abundant cytoplasmic granules and eosinophilic deposits with irregular nuclei. (A,B) H&E staining, presented at 100× and 200×. (C) PAS-D staining, presented at 400×. (D–F) Histologic appearance of the meningeal mass in the right L1 vertebral body illustrates the characteristic well-defined pseudoalveolar structures. (D,E) H&E staining at 40× and 200×. (F) PAS-D staining, presented at 40× Red arrowheads indicate representative cells with PAS-D intracytoplasmic crystals.

Fig. 3 – Pulmonary and brain metastases. (A) Axial CT image of metastatic alveolar soft part sarcoma involves innumerable bilateral pulmonary metastases. (B) Axial T1 MRI image of the brain demonstrates an enhancing mass in the left frontoparietal lobe.

of fibers and determined that many inclusions are bound to one membrane.¹⁸

Immunohistochemistry is generally not helpful in confirming the diagnosis of ASPS. Vimentin is generally positive, and variable immunoreactivity for muscle markers has been reported (including muscle-specific actin, desmin, myosin, and MyoD1).¹⁹ This has led to debate on the myogenic origin of ASPS,^{20,21} however subsequent studies have refuted this hypothesis.^{19,22,23} Generally, epithelial, melanocytic, neural, glial, and neuroendocrine markers are negative.^{24,25} S100 and neuron-specific enolase are rarely positive.

Cytogenetic analysis of ASPS has identified a nonreciprocal translocation: der(17)t(X; 17)(p11; q25). This unbalanced structure results in the fusion of the transcription factor E3 (TFE3) located at Xp11 with the novel gene at 17q25, creating the novel sequence titled ASPL.¹¹ This transcriptional deregulation is not unique to alveolar soft part sarcomas as it is also

found in pediatric papillary renal cell carcinomas, which is characterized by a balanced translocation.²⁶ It is currently hypothesized that the ASPL-TFE3 protein is responsible for irregular transcription of TFE3, which results in the development of ASPS, because of the pathogenetic loss and/or gains of uncharacterized genes. Support for this theory has been found by ASPL-TFE3 upregulation of the MET receptor tyrosine kinase, which disrupts signaling pathways and leads to phenotypes associated with tumorigenesis.²⁷ In addition, other TFE3 fusion proteins are found to be aberrant transcription factors.^{28,29} To aid cytogenetic diagnosis, an antibody for the C-terminus has been developed and made commercially available; however, care must be used to differentiate between other possible neoplasms including pediatric renal carcinomas and granular cell tumors, which also show strong nuclear staining.²⁶

The differential diagnosis of ASPS involves a wide range of neoplasms that contain a similar alveolar nest-like pattern. This includes renal, adrenal and hepatocellular carcinomas, which have a similar eosinophilic cytoplasm, but are distinguished by cytokeratin markers. Malignant melanomas can be differentiated by PAS-D negativity and positivity for melanocytic markers. Unlike ASPS, paragangliomas show strong expression of neuroendocrine markers and S100 typically is positive in the sustentacular cells. Granular cell tumors are strongly positive for S100, and lack the characteristic vascularity of ASPS. Due to the alveolar architecture and occasional staining for muscle markers, a diagnosis of alveolar rhabdomyosarcoma may be considered, however, the cytology of ASPS is larger and with more abundant cytoplasm than seen in alveolar rhabdomyosarcomas. While both are highly vascularized tumors, the differentiation of ASPS from hemangioendothelioma is not commonly a diagnostic dilemma.

Although metastatic deposits in the bone are commonly found in ASPS patients,^{2,12} primary bone involvement is rare with only nine reported cases thus far. The primary sites to date include the femur, ilium, fibula, tibia and scapula.^{14,30–32} Most bone tumors are found in the long tubular bones and involvement of multiple bones such as the fibula and tibia are also described.^{30,32} Distinguishing between bone metastases and primary neoplasms can be difficult; however, cases with primary bone involvement demonstrate cortical bone destruction with ill-defined margins from the soft tissue mass and an epicenter in the bone. These characteristic findings were present in our case, and so a clavicle based primary tumor is considered most likely. In primary bone tumors, pulmonary and brain metastases commonly occur (5/9 and 3/9 cases, respectively). Few patients survive after five years of initial presentation, although clinical follow-up is not reported in most cases.

Primary meningeal involvement is also rare as currently, only five cases have been documented.^{33–37} Primary spinal meningeal neoplasms are especially infrequent with only one case reported in the meninges and thoracic spinal vertebra.³⁸ An important clinical effect of spinal ASPS includes spinal compression, which was found in the aforementioned case and in our patient. Similar to primary bone involvement, it is difficult to discern primary meningeal ASPS from a metastatic deposit with an unknown primary site. With these factors in mind, the presenting clavicular lesion is most likely the

primary tumor with meningeal/parameningeal metastases. However unlikely, the possibility of a primary meningeal tumor or synchronous tumors cannot be entirely excluded. Given that this patient did not show a separate soft tissue mass on initial extensive work up or subsequent follow-up, we do not believe these represent metastases from an unknown soft tissue primary.

In conclusion, we present the first case of ASPS of the clavicle, also with a meningeal/parameningeal lesion. As ASPS is predominantly found as a soft tissue tumor, this case is exceedingly unusual with bony involvement as the primary neoplasm. Additionally the parameningeal lesion on the vertebrae is a rare metastatic site as previous cases of primary bone ASPS has not found metastatic tumors of the bone. The unfortunate clinical course of this patient was characterized by fast progression of the disease and development of the many clinicopathologic features of ASPS including metastases to the brain, lung and meninges and pathologic fractures.

Conflicts of interest

All authors have none to declare.

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