CASE SERIES

Alveolar soft part sarcoma in childhood: A report of two cases and review of literature

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Abstract

Background: Alveolar soft part sarcoma (ASPS) is a rare, distinctive soft tissue sarcoma, typically occurring in young people. In children, a substantial percentage of cases occur in the head and neck, often in the orbit or tongue. Although it displays a relatively indolent clinical course, the ultimate prognosis is poor with late metastases.

Aims and Objectives: Review of literature to give an insight into the current knowledge about this enigmatic tumor, in terms of genetic and diagnostic aspects.

Materials and Methods: Clinical, radiological, and morphological features of two cases, an 8-year-old female with tongue lesion and a 14-year-old female with orbital lesion are described. Immunohistochemistry (IHC) with a panel of antibodies was performed.

Results: Clinical presentation and microscopic features were remarkable in two young females, one in the tongue and another in the orbit and similar to other case reports. The use of TFE3 for IHC established the diagnosis.

Conclusion: Alveolar soft-part sarcoma remains an enigma clinically. ASPS should be considered in the differential diagnosis of pediatric head and neck masses with a solid morphology.

Keywords
Alveolar soft part sarcoma, orbit, tongue, Transcription factor E3

Introduction

Alveolar soft part sarcoma (ASPS) is a rare sarcoma of soft tissue, usually occurring in young people. Even though it exhibits an indolent clinical course, the eventual prognosis is poor with late metastases. The most common site involved is extremities, but we present two cases in the head and neck region in adolescent females, in a period of 10-year, in our setup of a predominantly rural population, a challenge to the clinicians and pathologists alike.

Case Reports

Case 1 [Figure 1]

An 8-year-old female presented with discomfort in swallowing and inability to put out her tongue. On examination, a sublingual mass was seen and transillumination was inconclusive. At operation, a solid nodular mass was seen infiltrating the tongue, and heavy bleeding was encountered at excision. Clinical diagnosis of a vascular lesion was favored.

Gross specimen received was 3 cm × 2 cm with no capsule. Cut section was solid with no areas of hemorrhage and was fibrous.

Case 2 [Figure 2]

A 14-year-old female child presented with protrusion and inability to open right eye completely since 3 months. On examination, the right eye was pushed upwards and medially. Movements of the eyeball were restricted all round. The lower eyelid swelling was not fixed to skin or underlying bone and was firm, pushing the globe superiorly and inward. The cornea and pupil were unremarkable. The vision was not impaired in both the eyes. Computed tomography scan revealed a 3 cm × 3 cm well enhancing mass in the inferior part of right orbit adjacent to inferior rectus muscle favoring a diagnosis of cavernous hemangioma.

At operation, a 3 cm × 4 cm well encapsulated smooth surfaced mass was noted and excised surgically from inferior part of orbit in close proximity to inferior rectus muscle. The mass was received fixed in formalin. Grossly, it was globoid, encapsulated lesion. Cut section was solid and gray-brown but no hemorrhage or necrosis.
Microscopically, hematoxylin and eosin stained sections of both cases showed encapsulated lesions with tumor cells arranged in compact groups and cords separated by thin walled sinusoidal vascular channels. Pseudoalveolar pattern was seen in the center. Cells were large, round with distinct cell borders, vesicular nuclei and prominent nucleoli, and abundant eosinophilic granular cytoplasm. Occasional mitoses were seen. “Apple bite” nuclei were evident in Case 1.

Infiltration into adjacent tongue musculature was seen in the intraoral Case 1, and vascular invasion was seen at the margins of lesion in the orbital Case 2.

Periodic acid-Schiff (PAS) positive and diastase resistance granules were seen only focally in one section in Case 1. No crystals were seen. Reticulin stain accentuated the alveolar septae. Recovery was turbulent and patient needed transfusions. The patient was lost to follow-up. PAS stain did not reveal any granules or crystals in Case 2. The patient is alive without metastases since 2 years.

Immunohistochemical (IHC) staining with a panel of antibodies cytokeratin (CK), smooth muscle antigen (SMA), vimentin, desmin, leukocyte common antigen, S100, CD99, melanoma, were negative in both the cases. Staining for TFE3 showed positive nuclear immunoreactivity. Appropriate positive and negative controls were used.

Discussion

The literature about this tumor is remarkably large, but the majority are simple case reports except for two large studies.\(^1,2\) The interest and the frustration when encountering this neoplasm, and inability to follow a relatively large number of cases has led to this review and sharing of our cases.

ASPS, a rare tumor accounts for <1% of all soft tissue sarcomas. A 3:1 female preponderance and a tendency for the right side in young adults is described.\(^3\)

ASPS unlike most other sarcomas has an odd sex distribution with an intriguing female predominance.\(^4\)

In ASPS, a nonreciprocal der(17)t(X;17) translocation with the corresponding fusion gene located in chromosome 17 has been found. An extra X-chromosome in females doubles the chances of developing an X; autosome translocation than in males, and this is a likely explanation for high proportion of females.\(^5\)

Nearly 50% of the cases at presentation were in the lower extremity,\(^2\) and less frequently in head and neck of adolescents and young adults.\(^6\)

In children, a significant number of cases occur in the head and neck, often in the orbit or tongue. Many ASPS present as painless masses, which on imaging studies are highly vascular.\(^3\) Both our cases were in young females, one in orbit and other in the tongue. In Case 1 because of bleeding at surgery and in Case 2 on imaging studies both were suspected to be vascular tumors.

The Armed Forces Institute of Pathology, from 1970 to 2003, had only 266 cases of ASPS in all anatomical locations. Only 5% of these (13/266) cases were in a lingual location.\(^1\)

Fourteen cases of lingual ASPS in eight males and six females (ages 3-21 years) (size 8-50 mm) were examined. All were intramuscular, circumscribed, and multinodular. Mostly solid (non-alveolar) growth pattern was seen in tumors from all but the older patients. Vascular invasion was common. The number of crystals ranged from none, extremely rare to nearly in all tumor cells.\(^6\)

A female preponderance is noted in literature even in lingual ASPS, in line with other anatomical locations but a slight male predominance was noted in this series.\(^6\)

In pediatric population between 0 and 18 years, of 41 cases in oral cavity (in a literature search and 2 cases of the authors), 26 in females and 14 in males, the median age was 8.4 years and sex was not mentioned in one case. The most often intraoral

Figure 1: Case 1: (a) Alveolar pattern of tumor cells. (b) “Apple-bite” nuclei (H and E stain). (c) Periodic acid-Schiff positive granules in cytoplasm. (d) Infiltration into tongue (H and E)

Figure 2: Case 2: (a) Inability to open left eye completely in the patient, computed tomography scan showed a well enhancing mass in inferior part of right orbit, grossly a circumscribed lesion. (b) Solid alveolar pattern with prominent nucleoli (H and E). (c) Immunohistochemistry showed nuclear positivity for TFE3. (d) Vascular invasion (H and E)
location was the tongue in 32/37 cases (90.2%), followed by the mandibular angle, the buccal mucosa and infratemporal fossa. Among the lingual cases, in 8 and 7 of the cases, the dorsal surface and the base of the tongue were affected, respectively, but precise location was not available in 17 cases. Base of the tongue was the location in Case 1 of oral cavity and hence was clinically opined to be a ranula.

The most common site for pediatric ASPS is in the head and neck region, but orbital involvement is rare, forming a small proportion of orbital tumors.

Thirty-four cases have been reported in the orbit on review of the literature till 2012. 13 of the tumors in young patients occurred in the first decade, with the average age being 19 years with a slight female preponderance. Proptosis was seen in most patients, and the other symptoms were chemosis, lid swelling, palpable mass, pain, loss of vision, restricted motility, diplopia, and tearing.

Poor prognostic factors include increasing age, tumors larger than 5 cm and metastatic disease at initial presentation. The tumor can metastasize late in the progress of the disease (median 6 years) with 38% of metastases appearing 10 years after the diagnosis. Metastasis usually occurs in the lung, brain or skeletal bone.

The “pattern” of classical alveolar architecture associated with abundant sinusoidal vessels is relied on to diagnose ASPS. Diagnostic difficulties are encountered when this pattern is absent; in small true-cut biopsies or at an unusual site.

Variants of ASPS are surprisingly absent and hence it is remarkable among soft-tissue neoplasms. The term “pseudoalveolar pattern” is used when there is prominent cellular dyscohesion in the organoid nests of uniform, polygonal tumor cells, separated by fibrovascular septa with capillary-sized vascular channels.

Our cases had predominantly solid pattern in keeping with the age of the patients, and hence a need for the differential diagnosis from other tumors arises.

The notable preponderance of solid, “non-alveolar” growth pattern seen in their study of lingual ASPS was because of young patient age, the usually small size and short prebiopsy duration, particularly in children. Often in older patients, in other anatomical locations, and in tumors of longer duration, i.e., larger tumors, a dyscohesive pattern emerged. The somewhat immature cells form solid cell clusters and then become dyscohesive as time progresses and the patient becomes older. The preponderance of solid ASPS observed in this study may be a reflection of referral bias, as more classic tumors may not be referred for a consultation.

A characteristic focally concave “apple bite” morphology of the nuclei in cells was a finding that could be helpful in the diagnosis. This is not a specific criteria but has not been described in lingual ASPS. The “apple bite” nuclear morphology was well appreciated in the Case 1. It had a predominantly solid, nonalveolar growth pattern with occasional clusters showing dyscohesive features.

A characteristic finding is the presence of PAS-positive, diastase-resistant crystalline structures, which may be rhomboid, rod-like or spiked, in individual, sheaf-like or stacked configurations. These crystals are not conspicuous in all cases, and multiple sections may have to be carefully searched to identify them.

These crystals serve as a diagnostic clue and are found in up to 80% of cases. They consist of aggregates of the monocarboxylate transporter protein 1 (MCT1) and its cellular chaperone CD147. They are usually seen intermingled with electron-dense granules consisting of finely filamentous material, which are termed “precryalline” by some authors. 15 tumor tissue blocks were sampled and after meticulous search, they found only 2 cells that harbored the typical crystals. In their case, ASPS did not exhibit typical large crystals; PAS staining showed numerous, striking, round granules, thus matching the designation of a crystal-deficient ASPS. In Case 1, only few PAS positive diastase-resistant granules were seen after staining multiple sections, but no crystals were identified. In Case 2, no granules or crystals were seen.

The diagnosis of ASPS is commonly based on characteristic histology and distinctive PAS positive crystals; however, the crystals may not always be observed, rendering the diagnosis difficult. We did not find the crystals despite a thorough search after staining.

While IHC can be helpful, the diagnosis should be mainly on morphology and supported by diastase-resistant, PAS-positive cytoplasmic crystals or granules or by demonstration of inclusions by electron microscopy.

Nuclear expression of TFE3 is considered to be a sensitive and specific marker for ASPS. It is representative of the ASPS locus-TFE3 fusion protein because of the fusion of the TFE3 gene on chromosome Xp11 to the ASPS locus gene on chromosome 17q25, which is characteristic of ASPS. TFE3 is universally expressed in normal tissues, at very low levels but strong nuclear expression is entirely in tumors known to contain the TFE3 gene fusions, such as ASPSs and rare pediatric renal carcinomas. Cytoplasmic staining (possibly non-specific) seen the TFE3 gene fusions, such as ASPSs and rare pediatric renal carcinomas. Cytoplasmic staining (possibly non-specific) seen in various tumors is of no diagnostic value.

Karyotyping will confirm the translocation between chromosomes 17q25 and Xp11.2. This translocation with the associated TFE3 gene is also seen in renal cell carcinoma. The reason as to why certain patients develop renal cell carcinoma and others ASPS is unclear.

In a review of 47 cases of ASPS that were either treated or were referred from other parts of India, TFE3 IHC staining was performed on 22 ASPSs and on 21 other tumors. The tumors were located in various sites and were positive for TFE3 (91%), desmin (16%), myoglobin (17%), and smooth muscle actin (11%). TFE3 was also positive in tumor controls that comprised paragangliomas (3/4), translocation-related renal cell carcinoma (1/1), adrenocortical carcinoma (1/3), and granular cell tumor (1/3). This knowledge of TFE3 expression in other tumors is important. Both our cases were negative for desmin, myoglobin, SMA, CK and melanoma markers.
The histologic features of ASPS are mimicked by other tumors such as granular cell tumor, paraganglioma, clear cell sarcoma, and metastatic renal cell carcinoma. The discernment of ASPS from these tumors is necessary as the management protocol differs markedly for each tumor type. In both our cases, IHC for TFE3 was performed and strong nuclear positivity was demonstrated to confirm the diagnosis.

The presence of ASPSCR1-TFE3 fusion transcript, nuclear immunoreactivity for TFE3, and immunoreactivity for MCT1 and CD147 are the 3 recent important characteristics. The fusion transcript was detected in 24 and TFE3 immunoreactivity was observed in 22 of 24 ASPSs. In non-ASPS tumors, the fusion transcript was not detected; however, the TFE3 immunoreactivity was observed in 2 of 5 granular cell tumors. This shows that the most sensitive marker of ASPS was the presence of the ASPSCR1-TFE3 fusion transcript which can be applicable for formalin-fixed tissues with superior sensitivity as compared with TFE3 IHC staining. The detection of the ASPSCR1-TFE3 fusion transcript would be the highly effective diagnostic technique in unusual location and morphology.

Real-time polymerase chain reaction to detect the fusion transcript on paraffin-embedded tissue blocks seems to be more sensitive and specific than detection of TFE3 by IHC stain. The recent discovery of the role of the ASPSCR1-TFE3 fusion protein in the MET proto-oncogene signaling pathway promoting angiogenesis and cell proliferation offers a promising targeted molecular therapy.

ASPS and granular cell tumor are typically distinctive on histology, but occasional cases show a significant histologic overlap. Differentiating them is important because granular cell tumor is almost always benign and ASPS is invariably malignant. TFE3 was positive in 91% of granular cell tumors and all ASPS. Together with PAS-D, IHC stains for S-100 protein, inhibin, SOX10, and nestin accurately identify ASPS and granular cell tumor. TFE3 has been reported as a specific marker for ASPS but it is also expressed in granular cell tumors.

In the past five decades, the cell of origin of ASPS has been the subject of debate. Previously, the most widely proposed theories include neural crest origin, paraganglial derivation, skeletal muscle origin, and the angiogenin theory.

The recent discovery of ASPS as part of the family of translocation-associated sarcomas makes for a suggestion that ASPS displays a scrambled phenotype, without a normal counterpart. This is supported by the facts such as the lack of resemblance of ASPS to any known structure, inability to categorize it and our understanding that other tumors, such as perivascular epithelioid cell neoplasms, also possibly lack normal counterparts. Alternatively, ASPS may recapitulate the phenotype of a yet-to-be discovered, extremely rare, normal cell of unknown function.

The high survival rates possibly mirror a combination of small size at the time of diagnosis and younger patient age in lingual and orbital tumors.

ASPSs are characterized by their prominent metastatic potential. The findings of Setsu et al suggest that ASPSs do not actively break through the vascular walls to initiate the metastatic process. They instead suggest that ASPSs almost exclusively follow the recently postulated “invasion-independent mechanism” for entry into circulation, in which cancer cells are shed into vessels, covered by endothelial cells, and are subsequently entrapped at site of metastases. This mechanism may explain some of the unique clinical characteristics of ASPS. As this pathway primarily depends on hypervascularity and sinusoidal remodeling, there is a basis for applying antiangiogenic therapy to ASPS.

The vascular invasion was documented in Case 2 but was difficult to demonstrate in case 1 which was more infiltrative into the adjacent muscle of the tongue.

Long-term follow-up of patients with localized ASPS reveals a relatively indolent clinical course with relatively low rates of local and distant recurrence.

ASPS has a high metastasis rate but relatively good short-term survival.

The treatment of choice for the majority of lingual ASPS is complete surgical excision alone. All patients had a relatively good outcome in their series where all had only surgery, and two patients received adjuvant chemotherapy. The need for additional therapy is largely dependent on clinical evaluation with respect to recurrence as in the case of incomplete surgical excision. If a small primary lingual ASPS can be completely resected and there is no clinical recurrence or metastasis adjuvant therapy may not be needed.

Surgery in the form of either partial or total tumor resection or an orbital exenteration was the mainstay in all reported cases. One patient was enucleated along with the tumor resection and one patient received chemotherapy prior to his exenteration. Radiotherapy alone was not received by any patient.

Both our cases had only surgical management and a long-term follow-up advised. ASPS responds poorly to radiotherapy and conventional chemotherapy, molecularly targeted therapies hold promise for the systemic treatment of this tumor.

Conclusions

Alveolar soft-part sarcoma remains an enigma clinically. ASPS should be deliberated in the differential diagnosis of pediatric head and neck masses with a solid morphology. TFE3 is a useful marker for diagnosis of an ASPS as it mimics other tumors. The natural history of late metastases makes treatment options after surgery to be contemplated upon.

References
