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CASE REPORTS

Alveolar Soft Part Sarcoma of the Oro-Maxillofacial Region in the Pediatric Age Group: Immunohistochemical and Ultrastructural Diagnosis of Two Cases

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Abstract
Alveolar soft part sarcoma (ASPS) is infrequent in children. While head and neck locations, including the orbit and tongue, are described, only six cases of sinonasal ASPS are reported in the literature. We report two cases of pediatric oro-maxillofacial ASPS. The first case presented as a sinonasal mass in a 13-year-old girl, while the second was a tongue lesion in a 4-year-old female. Histologic examination, TFE3 immunopositivity, and ultrastructural findings of rhomboid crystalline inclusions helped confirm the diagnosis. The diagnosis of ASPS is challenging in children and in uncommon sites like the head and neck. Patients should be routinely followed up for detection of residual or recurrent disease, particularly in cases with positive resection margins.

Keywords Alveolar soft part sarcoma · Pediatric · Head and neck · Sinonasal · Immunohistochemistry · Electron microscopy

Introduction

Alveolar soft part sarcoma (ASPS) is a rare mesenchymal neoplasm that accounts for less than 1% of all sarcomas [1, 2]. It primarily affects the deep soft tissues of the extremities and trunk. Less than 10% of cases are described in the head and neck region, mostly as isolated case reports or small series [2]. ASPS presents in young adults with a median age range of 25 years [2]. Unusual in the pediatric population, these tumors often cause a diagnostic quandary and may be misdiagnosed as morphologically similar tumors, especially at unusual sites. While ASPS is well-documented in the orbit and tongue in children, sinonasal ASPS is extremely unusual. Only six cases of sinonasal ASPS are recorded in the literature to date [3, 4]. We present two cases of pediatric ASPS occurring in head and neck: one affecting the sinonasal region and the other in the tongue.

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Case Reports

Case 1 A 13-year-old female presented with left-sided nasal obstruction, headache, and epistaxis of 6 months duration. She underwent left lateral rhinotomy and excision of a nasal cavity mass (Fig. 1a, b). Her symptoms recurred a month later prompting a referral to our center. Examination revealed a polypoid growth in the left nasal cavity. Endoscopic examination showed an irregular, non-pulsatile, pink, polypoid mass in the nasal cavity above the maxillary ostium as well as fibrous scarring of the nasal cavity roof. Contrast enhanced MRI showed a lesion involving the anterior and posterior ethmoid sinuses and cribriform plate. Whole body PET imaging revealed mild FDG avidity at the same site in the ethmoids, raising suspicion of residual disease. The patient underwent endoscopic revision surgery whereby the residual, vascular-appearing tumor in the anterior ethmoids was completely excised along with unhealthy-appearing mucosa from the medial maxillary wall, septum, and sphenoethmoidal recess. The patient subsequently received

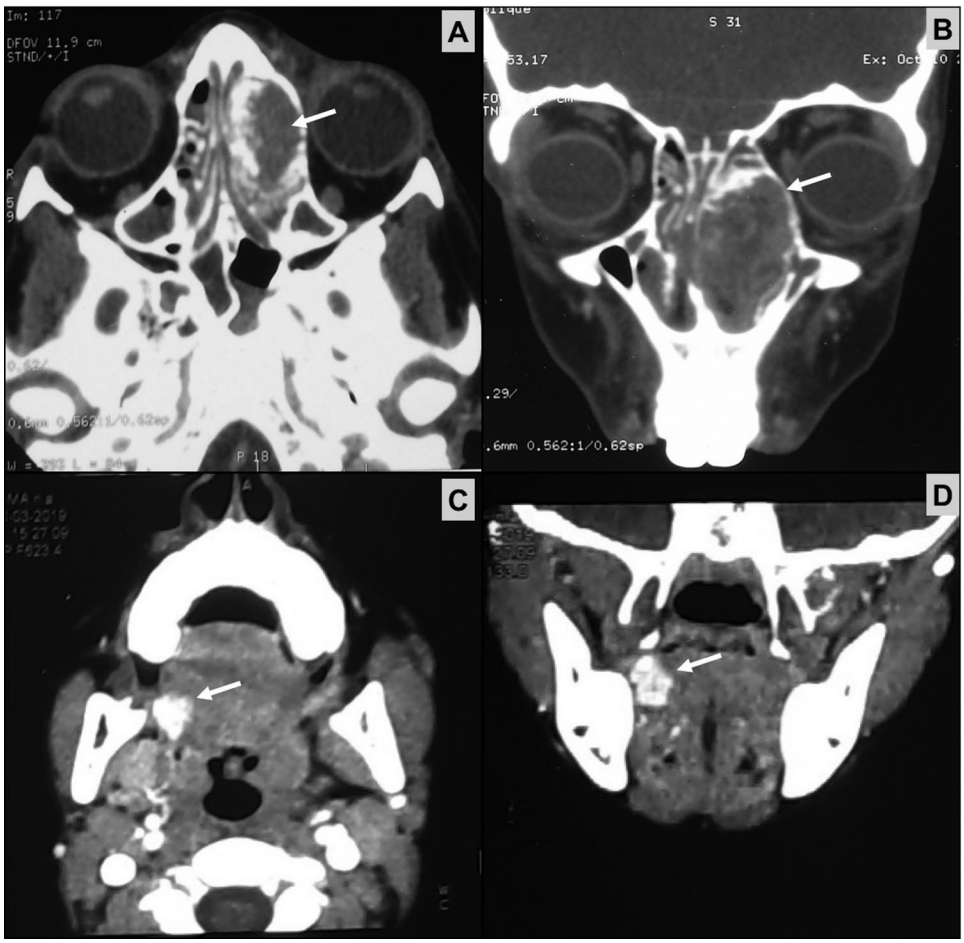

Fig. 1 Axial (**a**) and coronal (**b**) CECT nose and paranasal sinus images of patient 1 depicting a heterogeneously enhancing mass lesion (arrows) in the left nasal cavity and ethmoid sinus. The mass causes expansion of the bony walls and demonstrates foci of hyperostosis in left ethmoid sinus and an intact skull base. **c** Axial and **d** coronal CECT oral cavity images of Case 2 depict an intensely enhancing mass on the posterior aspect of the right lateral border of the tongue

chemotherapy and radiotherapy by the sandwich method and is disease-free at 15 months.

Case 2 A 4-year-old female presented with a swelling of the tongue of 2 months duration (Fig. 1c, d). An excisional biopsy had been previously performed elsewhere with a diagnosis of granular cell tumor (GCT). The swelling reappeared a month later. On imaging, an intensely enhancing lesion was present at the right lateral border of the tongue that involved the genioglossus and hyoglossus muscles. It measured 1.2 × 0.8 centimeters. Re-excision of the growth with wide margins was performed. Owing to the rapid recurrence of the tumor following initial excision, the child received radiotherapy (34 Gy) and is disease-free at 13 months.

Histopathological Examination

Both cases showed similar histopathologic features of nests and lobules of large, polygonal cells separated by slender, fibrous septae containing thin-walled blood vessels (Fig. 2a–g). An alveolar pattern was observed with discohesion of tumor cells at the center of the nests. The cells contained abundant, clear to granular eosinophilic cytoplasm and moderately pleomorphic vesicular nuclei with conspicuous nucleoli. Mitotic figures were infrequent. Foci of necrosis were present, and the tumor infiltrated the adjacent bone in Case 1. In Case 2, the overlying mucosa was ulcerated and vascular invasion was present. With periodic acid-Schiff (PAS) staining, intracytoplasmic PAS-positive, diastase-resistant granules were identified. Immunohistochemical stains demonstrated nuclear immunopositivity for TFE3 and nuclear and cytoplasmic negativity for S100, favouring a diagnosis of ASPS in both cases. Ultrastructural examination revealed rhomboid crystalline inclusions within the tumor cells which confirmed the diagnosis (Fig. 2h, i).

Discussion

ASPS is a rare sarcoma that arises in skeletal muscle or fascial planes and shows a strong predilection for the thighs, gluteal region, and trunk [2]. Anecdotal cases have been reported in the head and neck, where 41% occur in the orbit and 25% in the tongue. Tumors affecting the sinonasal

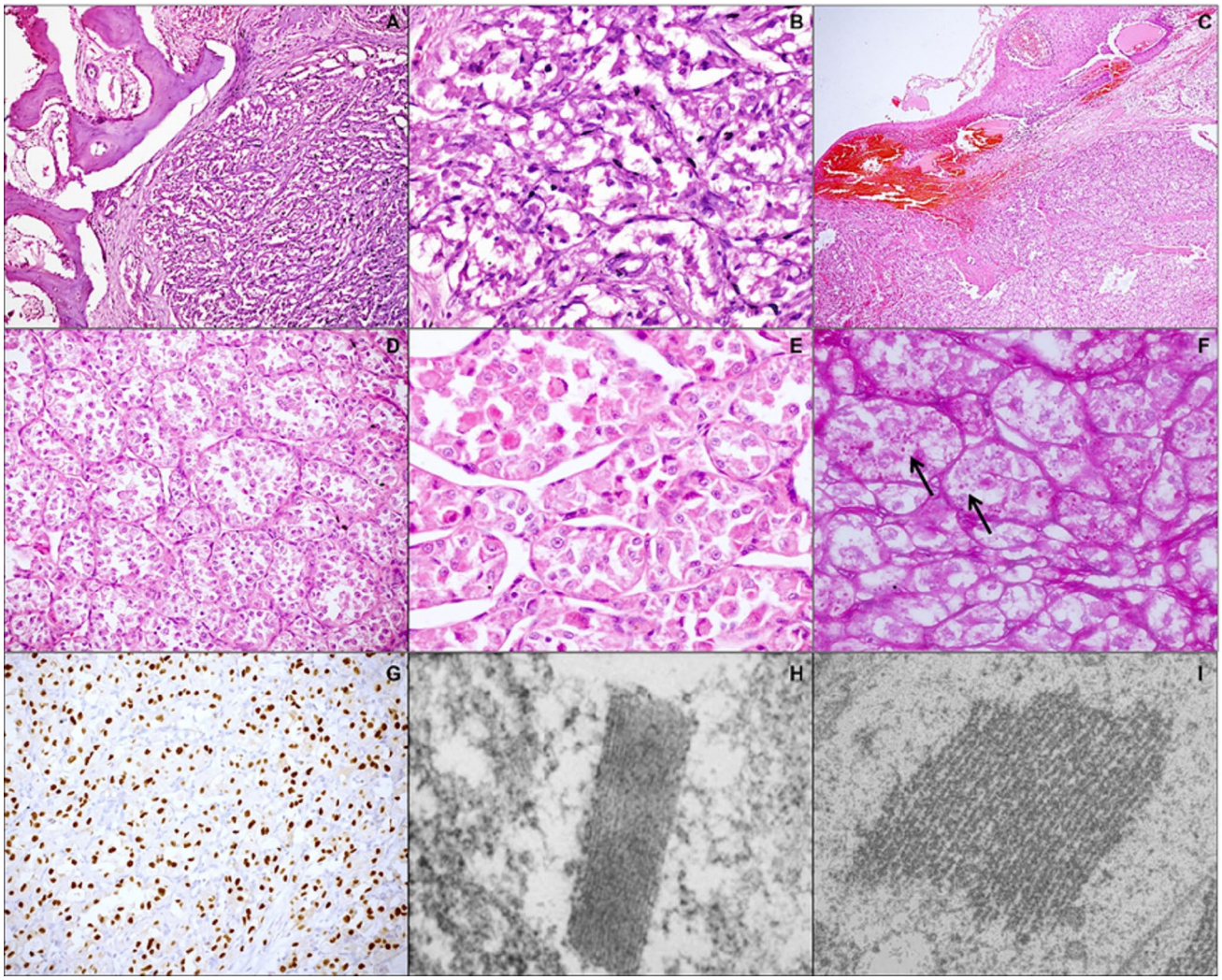

Fig. 2 Photomicrographs from Case 1. **a** Bone destruction is identified; **b** tumor cells are arranged in nests and alveolar pattern and contain abundant clear cytoplasm. **c** Case 2 shows a similar tumor with ulceration of the overlying epithelium. **d** The tumor cells have a striking alveolar pattern and **e** abundant granular, brightly eosinophilic cytoplasm. **f** PAS stain highlights intracytoplasmic granules. **g** tumor cell nuclei are immunopositive for TFE3 and **h** ultrastructural examination shows rhomboid crystalline inclusions with a lattice pattern (**i**)

location are exceedingly rare [1, 5–7]. ASPS has a strong predilection for adolescents and young adults with a female preponderance [2]. In children, ASPS accounts for 5% of all sarcomas [2]. In two large series of pediatric and adolescent ASPS, the extremities were the most common site, while head and neck locations accounted for 15% of cases [8, 9]. Conversely, in a series of 18 oro-maxillofacial ASPS, 50% affected children, highlighting an increased proportion in the head and neck in the pediatric age group [1]. Due to its presentation as a polypoidal growth with prominent vascularity, childhood ASPS is often clinically misinterpreted as a nasal polyp, benign mesenchymal neoplasm such as haemangioma, lymphangioma, or rhabdomyoma, or a developmental lesion such as a hamartoma or arteriovenous malformation [10]. In such clinical scenarios, suspicion of sarcoma may be low, and histopathologic examination is required to achieve the diagnosis. Further, multidisciplinary case review with sarcoma specialists is recommended for treatment planning and optimal management.

Histologically, ASPS is characterized by organoid or nested architecture with thin, richly vascularized fibrous septae. The cell are large, round to polygonal, and contain abundant granular eosinophilic or clear cytoplasm. Vascular invasion, as seen in Case 2, is frequent and does not portend a worse prognosis [11]. Loss of intercellular cohesion towards the center of the nests, often accompanied by necrosis, results in the signature 'alveolar' pattern. However, architectural variation, where cells are arranged in compact sheets and cords resulting in a solid appearance, or morphologically spindled cells are known to occur, particularly

in pediatric patients [11]. This may lead to misdiagnosis as a number of neoplasms with similar morphology are more frequent in the head and neck. For example, Case 2 was diagnosed elsewhere as GCT which resembles ASPS by its large cells with granular eosinophilic cytoplasm and frequent location in the tongue. Further confounding, GCT has been documented to demonstrate diffuse immunopositivity for TFE3, a marker consistently expressed in ASPS [12]. However, the former is usually immunopositive for S100 and SOX10 which are negative in ASPS. Rhabdomyoma is another potential mimicker that occurs in the tongue and similarly has abundant granular eosinophilic cytoplasm. It displays a spectrum of skeletal muscle differentiation and is positive for desmin, MYOD1, and myf4. ASPS may also be positive for desmin and MYOD1; however, it shows cytoplasmic but not nuclear MYOD1 staining as seen in rhabdomyoma [2, 5]. Lipomatous neoplasms such as hibernoma and lipoblastoma demonstrate cytoplasmic vacuoles absent in ASPS, and are positive for S100. Rarely, paragangliomas may mimic ASPS due to their similar "Zellballen" architecture; immunopositivity for neuroendocrine markers, with S100 highlighting sustentacular cells, helps differentiate them from ASPS [5]. These examples demonstrate that overlapping histologic and immunohistochemical features may make a diagnosis of ASPS challenging, particularly on small biopsies and in locations where ASPS is rare. In such situations, other ancillary techniques may be of utility. ASPS cells demonstrate intracytoplasmic PAS-positive diastase-resistant granules comprised of rod-like/rhomboid crystalline inclusions, considerably different from the coarse PAS-positive cytoplasmic granules seen in GCT, and can be highlighted with MCT1 and CD147 immunostains [2].

ASPS is characterized by an unbalanced translocation, der(17)t(X; 17)(p11;q25), that results in fusion of *ASPSCR1* (formerly *ASPL*) and *TFE3*, leading to expression of the ASPSCR1-TFE3 fusion protein [2]. Recently, novel *HNRNPH3-TFE3, DVL2-TFE3*, and *PRCC-TFE3* fusions have also been identified [13]. Identification of *TFE3* fusions may assist in diagnosis. In the absence of facilities for advanced molecular testing, ultrastructural examination may serve as a useful adjunct in diagnosis. ASPS demonstrates pathognomonic rhomboid or rod-shaped crystalline inclusions with a regular lattice pattern, while GCT shows abundant lysosomes. In the present report, ultrastructural examination was used to confirm the diagnosis.

An accurate distinction of ASPS from its many mimickers is imperative, as management and prognosis differ vastly among various pediatric soft tissue tumors. Wide local excision with negative margins is the treatment of choice [14]. Radiotherapy may be administered, particularly in cases with incomplete resection; however, ASPS are relatively resistant to chemotherapy [1]. Recently, targeted therapies against the c-Met receptor, an *ASPSCR1/TFE3* transcription target, and its downstream effectors AKT and ERK, as well as anti-angiogenic drugs targeting the VEGF pathway have shown effective initial response [8, 10]. In adults, response to novel immune checkpoint inhibitors has been documented as well [15]. Prognosis is based on the size and location of the tumor, metastasis at diagnosis, and age of the patient. Pediatric ASPS portends better outcome than adult cases [1, 2, 10]. Regardless of the age of patient, tumors affecting the head and neck require continued follow-up due to the difficulty in achieving complete resection and negative margins in this region. This results in frequent residual disease and recurrence, as seen in both of our cases. Due to its rich vascularity, ASPS has significant potential for metastases, sometimes prior to detection of the primary tumor, but also decades after the initial diagnosis [2].

To conclude, the diagnosis of ASPS can be challenging in children and especially in uncommon sites. In the era of subspecialty-based practice, awareness of this entity among head and neck and pediatric pathologists is essential to achieve the correct diagnosis. An integrated approach combining histomorphologic analysis, immunohistochemistry, ultrastructural examination, and molecular testing aids diagnosis. Patients should be kept under strict follow-up after surgery for detection of residual/recurrent disease and for delayed metastases.

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Compliance with Ethical Standards

Conflict of interest The authors declares that they have no conflict of interest.

Informed Consent Written informed consent was obtained from the parents (legally authorized representatives).

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