The untold story of primary alveolar soft part sarcoma of the fibula: A rare case report with review of the literature

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Received - 05 February 2020 Initial Review - 29 February 2020 Accepted - 11 April 2020

ABSTRACT

Alveolar soft part sarcoma (ASPS) is a rare soft-tissue tumor occurring in skeletal muscles or musculofascial planes with an incidence of 0.5–1%. In adults, the lower extremity is most commonly involved, whereas in children, the involvement of the head-and-neck region is more common. Metastasis to the brain, bone, and lungs is common; however, primary bone involvement is extremely rare. We report the case of a 25-year-old male who presented with a painless slowly progressive swelling in the left lower limb for 1 year with no history of trauma. The case was diagnosed as primary ASPS of the fibula after ruling out the involvement of soft tissue and other organs. To the best of our knowledge, only 11 cases of primary ASPS of bone have been reported so far.

Key words: *Alveolar soft part sarcoma, Bone, Fibula*

Alveolar soft part sarcoma (ASPS) is an unusual malignant soft-tissue tumor that was named and first described by Christopherson *et al*., in 1952 [1]. It accounts for 0.5–1% of all the soft-tissue sarcomas. Muscle and soft tissue of the trunk and extremity are the most common sites of involvement [2]. Pediatric ASPS occurs usually in the head-and-neck region; however, lower extremity involvement may occur in adults [3]. The most common sites for metastasis are the lungs, brain, and bone [4]. The primary involvement of the bone is extremely uncommon. The first case of the bone as primary was reported by Furey *et al*. [5], in 1969, followed by Park *et al*. [4] who reported six primary ASPS of bone in 1999. The primary ASPS of the bone is extremely rare and should be considered in the differentials of a bony lytic lesion in a young adult with the alveolar architecture of tumor cells.

CASE REPORT

A 25-year-old man presented to our hospital with a complaint of slowly progressive swelling in the left lower leg for 1 year. There was no history of trauma or any other systemic disease. General examination and vitals of the patient were within normal limits. On local examination, swelling measured 4 × 3 cm in size, located on the lateral aspect of the lower leg above the lateral malleolus with a firm to hard consistency and ill-defined margins. The local temperature of the overlying skin was normal.

Routine hematological and biochemical investigations were within normal limits. Digital X-ray revealed a lytic lesion in the lower third of the left fibula (Fig. 1). Segmental resection of the fibula was done and the sample was sent for histopathology.

Gross examination of the sample received displayed a soft friable mass occupying the marrow cavity of the fibula and destroying the adjacent cortex. No soft-tissue extension was identified. Histopathological examination showed tumor cells arranged in an alveolar pattern interspersed by thin vascular septa. The tumor cells were round to polygonal, displayed vesicular nuclei, prominent nucleoli, and clear to granular cytoplasm (Fig. 2). Based on the characteristic histological findings, the differentials considered were alveolar rhabdomyosarcoma, clear cell sarcoma, and granular cell tumor.

Immunohistochemistry (IHC) was applied with a panel of myogenin, MyoD1, desmin, HMB45, and S100 all of which were negative, thus ruling out the differentials considered. This prompted us to consider metastatic renal cell carcinoma, metastatic paraganglioma, and ASPS based on the characteristic alveolar pattern. IHC was applied for pancytokeratin, EMA, PAX 8, CD 10, CD56, synaptophysin, chromogranin, and TFE3. TFE3 showed strong nuclear positivity thus confirming the diagnosis of ASPS (Fig. 3) while all other markers were negative. A thorough clinical and radiological examination was done to confirm the primary site.

Based on the clinical, radiological, and histopathological examination, a final diagnosis of ASPS of the fibula was made. The patient underwent above-knee amputation followed by chemotherapy. The post-operative period was uneventful until 4 months post-surgery after which the patient was lost to follow-up.

DISCUSSION

ASPS is a rare, distinctive soft-tissue sarcoma characterized by ASPSCR1-TFE3 fusion gene [1]. Only a few cases of ASPS have been reported in the literature since the cancer was first described in 1951 by Smetana and Scott [6] as a malignant tumor of non-chromaffin paraganglia. They chose this term because the tumors resembled non-physiologically active paraganglia. Christopherson *et al*. [1] gave it the descriptive name "alveolar soft part sarcoma" in 1952 and defined it histologically by the presence of cells arranged in nests ("alveoli") separated by connective tissue containing sinusoids lined by flattened endothelium [1].

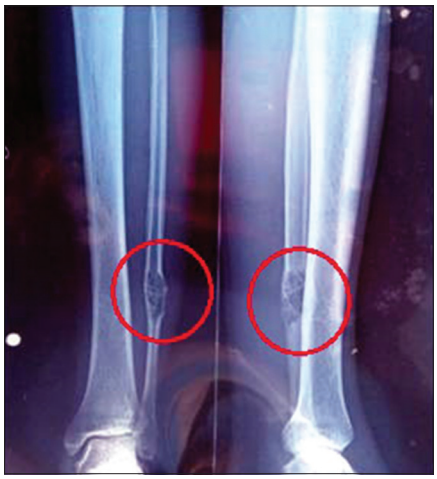

Figure 1: Digital X-ray showing a diaphyseal lytic lesion in the left fibula

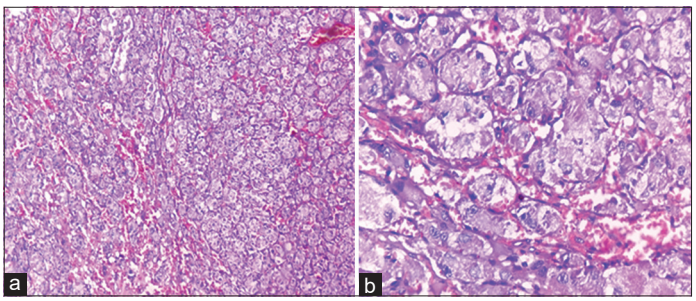

Figure 2: Photomicrograph showing (a) tumor arranged in alveolar pattern separated by fibrovascular septa (H and E ×100); (b) round to polygonal cells with central nucleus, prominent nucleoli, and granular cytoplasm (H and E ×400)

This lesion typically occurs in young adults with a female predilection. ASPS typically presents as a painless, slow-growing mass that is asymptomatic in most cases. As they are extremely vascular, occasionally present as a pulsatile mass with an associated bruit [7]. In adults, it typically involves the deep soft tissue of extremities, trunk, and retroperitoneum, whereas in children, the predominant site of the involvement is the head-and-neck region. The common sites of metastasis are the lung, brain, and bone [2]. In the present case, the primary involvement of fibula was noted. Only two cases with primary involvement of fibula have been reported till date, by Park *et al*. [4], in 1999.

Radiological features of primary bone manifestations of ASPS have been described by Park *et al*. [4]; a common feature being bone destruction with ill-defined tumor margins. ASPS appears to be hypervascular on angiography and computed tomography scan, with a dense tumor stain and tortuous, dilated draining veins. Magnetic resonance imaging characteristically exhibits the high signal intensity of tumor on both T1- and T2-weighted images [7].

Grossly, tumor size usually ranges from 3 to 8 cm, but cases of ASPS up to 20 cm have also been reported. The cut surface is pale gray or yellowish in color with a soft consistency. Areas of necrosis and hemorrhage are common in larger lesions [7]. The microscopic feature is characterized by nests of tumor cells separated by thin-walled vascular channels. The tumor cells are uniform in size, round to polygonal, with distinct cell borders. The nucleus is bland looking, centrally located with prominent nucleoli and abundant eosinophilic granular cytoplasm. Occasional tumor cells display cytoplasmic clearing mimicking renal cell carcinoma [8] (Fig. 4).

In 80% of the cases, cytoplasm displays periodic acid schiff (PAS)-positive diastase-resistant rhomboid or rod-shaped crystalline structures. However, almost all the cases exhibit PAS-positive cytoplasmic granules, which represent the precursor of the crystals[2]. Depending on the young age, clinical presentation, and specific

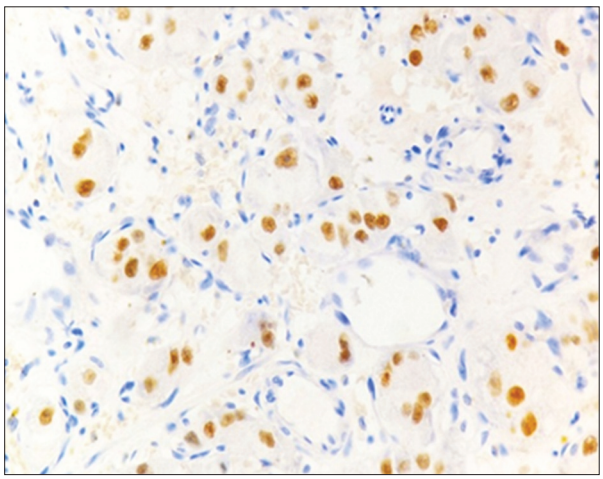

Figure 3: Photomicrograph showing strong nuclear TFE3 positivity (H and E ×400)

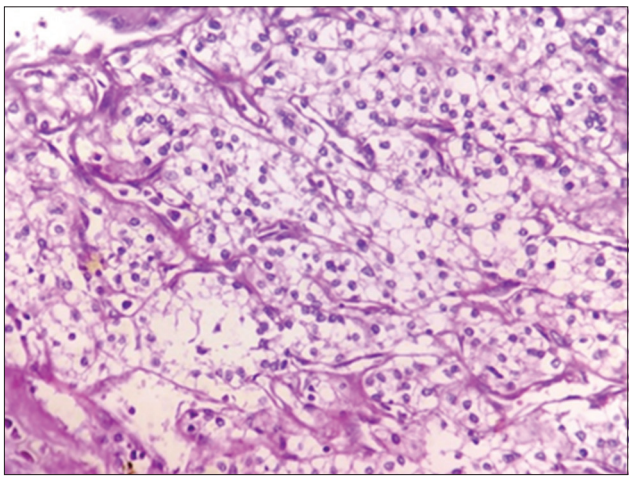

Figure 4: Photomicrograph showing cytoplasmic clearing in the tumor cells (H and E ×400)

morphology of the tumor in our case, differentials considered were alveolar rhabdomyosarcoma, clear cell sarcoma, and granular cell tumor. Negativity for myogenin, desmin, HMB45, and S100 prompted us to consider metastatic paraganglioma, metastatic renal cell carcinoma, and ASPS. A second IHC panel for the above differentials was applied which showed strong nuclear positivity of TFE3, thus confirming the diagnosis of ASPS. The most characteristic finding in ASPS is the consistent expression of strong nuclear positivity of TFE3, reflecting the ASPSCR1-TFE3 fusion gene that has been identified by cytogenetic analysis [8]. Recent studies have shown that the crystals are immunoreactive to a protein MCT1 (monocarboxylate transporter) and to CD 147 [8]. The differential diagnosis of ASPS includes neoplasms with a characteristic alveolar or nested pattern such as alveolar rhabdomyosarcoma, clear cell sarcoma, granular cell tumor, metastatic renal clear cell carcinoma, and metastatic paraganglioma.

Alveolar rhabdomyosarcoma and ASPS share similar clinical features being common in young adults, involving the extremities. The former demonstrates myogenin and Myo-D1 positivity. Clear cell sarcoma represents malignant melanoma of soft parts, common in young adults, differentiated by HMB 45 and Melan-A positivity. Granular cell tumor displays positivity for S100 and is rare in soft tissues. Renal cell carcinoma shows similar cytoarchitectural features as ASPS accompanied by a tubular pattern of growth and lacks the cytoplasmic crystals of ASPS. Paragangliomas show a strong expression of neuroendocrine markers such as synaptophysin and chromogranin. It is reported that ASPS has an indolent course with characteristic slow growth and is associated with a poor overall outcome and a 5-year survival rate of only 20% in unresectable cases with metastasis [8]. Early metastasis is a characteristic feature of this tumor and metastasis to the lung or brain is often the first manifestation. Factors that influence prognosis are age at presentation, tumor size, and the presence of metastasis at the time of diagnosis [8]. Local recurrence rates have been reported to range from 11 to 50% [7].

Surgical excision remains the mainstay of therapy. Any definite role of adjuvant chemotherapy and radiotherapy has not been reported [8]. Recently, in view of the specific chromosomal translocation present in ASPS, systemic cancer therapeutics have focused on the use of molecular targeted therapies in addition to or as an alternative for non-specific cytotoxic agents [7].

CONCLUSION

To the best of our knowledge, only 11 cases of primary ASPS of bone have been reported. The identification of ASPS is important due to its poor prognosis and occurrence of distant metastases. It must be included in the differential diagnosis of bony lytic lesion of young adults with alveolar architecture on histopathology. Characteristic morphology and specific molecular genetic abnormality help in its diagnosis. Based on its specific chromosomal translocation, molecular targeted therapy is currently under evaluation.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Singh V, Bhargava M, Kumar V, Misra V. The untold story of primary alveolar soft part sarcoma of the fibula: A rare case report with review of the literature. Indian J Case Reports. 2020;6(4):209-211.

Doi: 10.32677/IJCR.2020.v06.i04.020