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Case Report

Alveolar soft part sarcoma with neural differentiation and aberrant TLE1 expression: A case report

Maydhaavi Gupta[1]*, Ashalatha Neeravari[1], Nirmala Chandran[1], Dayananda S Biligi[1]

[1]*Dept. of Pathology, Bangalore Medical College and Research Institute, Bangalore, Karnataka, India*

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ABSTRACT

Alveolar soft part sarcoma (ASPS) is a rare soft tissue tumor of uncertain histogenesis. It occurs most commonly in deep soft tissues of the lower extremities. Relevant histomorphology and diffuse and strong immunoreactivity of TFE3 has been included in essential diagnostic criteria by WHO Soft tissue and Bone tumors, 5th edition.

A 35 years female presented with recurrent painless posterior right thigh mass which progressed to a size of 15x15cm in 6 months. MRI of the swelling showed T1 isointense and T2 hetrointense lesion with multiple flow voids and few non enhancing areas suggestive of necrosis. Fine needle aspiration cytology showed tight clusters of round to oval tumor cells with moderate cytoplasm. Sections from the cell block revealed tumor cells arranged in an organoid pattern. Individual cells showed a round to oval nucleus with powdery chromatin and abundant eosinophilic to clear cytoplasm. Diagnosis of undifferentiated sarcoma was made. Histopathological examination of the excised lesion showed round to oval shaped cells arranged in nests and alveolar pattern. Individual cells showed mild degree of atypia with a vesicular nucleus, moderate eosinophilic cytoplasm and distinct cell borders. Increased mitoses, prominent vascularity, extensive areas of necrosis and hemorrhage were seen. Immunohistochemistry (IHC) for TFE3, TLE1, synaptophysin and BCL2 was positive and it was negative for pan cytokeratin and S100. Periodic acid-Schiff stain for intracytoplasmic crystalline structures was negative. Based on the histomorphology and IHC, diagnosis of ASPS was made showing neural differentiation and abberent TLE1 expression. Further studies were suggested for confirmation of the diagnosis.

Accurate diagnosis of ASPS requires trained pathologists and molecular testing to lead the treatment accordingly. This case is presented owing to its overlapping histomorphological and immunohistochemical findings.

1. Introduction

Alveolar soft part sarcoma (ASPS) is a rare tumor comprising <1% of all soft tissue sarcomas.They are classified under tumor of uncertain differentiation in the WHO classification of soft tissue tumors 2022.[1] They typically affect people between the ages of 15 and 35, with a male to female ratio of 1:2. These tumors most commonly present as slow growing, painless masses in the extremities. The tongue and orbit are the most frequently affected areas in children and newborns with ASPS, which tends to favour the head and neck region.[2] MRI shows characteristic vascular pattern and moderate to intense postcontrast enhancement. They are characterized by a specific translocation, der(17)t(X;17) (p11.2; q25), resulting in ASPSCR1-TFE3 gene fusion.[3] Metastasis usually occurs

* *Corresponding author*.
E-mail address: maydhaavigupta@gmail.com (M. Gupta).

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late in the course of the disease (>10 years of diagnosis) and involves the lungs, bones, lymph nodes and brain. ASPS shows nuclear immunoreactivity for transcription factor E3(TFE3).[4]

2. Case Report

A 35 years female presented with a recurrent painless posterior right thigh mass with previous history of a similar swelling at the same site one year back which was completely excised. The mass progressed to a size of 15x15cm in six months. Ultrasound scan showed likely neoplastic lesion in the inter and intra muscular plane of hamstrings. MRI showed a relatively well-defined lobulated T1 isointense and T2 heterointense lesion measuring 9.5x6.5x8.3cm, with multiple flow voids suggestive of vessels traversing the lesion, noted in the inter and intramuscular plane of postero-medial aspect of mid 1/3rd of right thigh. It was compressing, displacing and infiltrating the surrounding structures. On post- contrast study, the lesion showed a heterogenous enhancement with few non enhancing areas within suggestive of necrosis. No evidence of underlying bone erosion was noted. Radiology imaging studies were suggestive of malignant soft tissue sarcoma. (Figure 1 A-C).

Fine needle aspiration (FNA) and cell block of the mass were performed. Smears from the FNA showed tight clusters of round to oval tumor cells with moderate cytoplasm. Sections from the cell block revealed tumor cells arranged in an organoid pattern. Individual cells showed a round to oval nucleus with powdery chromatin and abundant eosinophilic to clear cytoplasm. (Figure 2 A-B). Diagnosis of undifferentiated sarcoma was given with possibility of synovial sarcoma to be considered. Following this, the patient underwent wide local excision of the mass and specimen was sent for histopathological examination. Grossly, the mass showed a large, ill defined, homogeneous grey white tumor measuring 10x10x8cm, with areas of necrosis and hemorrhage (Figure 3).

Histopathological examination showed round to oval tumor cells arranged in nests and alveolar pattern. Individual tumor cells showed mild degree of atypia and had a vesicular nucleus, moderate eosinophilic to clear cytoplasm and distinct cell borders. (Figure 4 A-B). Mitosis of 10/high power field was noted. Prominent vascularity with hemangiopericytoma like pattern and extensive areas of necrosis and hemorrhage were also seen. Lymphovascular invasion was noted at places. No evidence of perineural invasion was seen. All surgical margins were free of the tumor.

Immunohistochemistry (IHC) for TLE1, BCl2 and pan cytokeratin were done to rule out synovial sarcoma. TLE1 showed diffuse nuclear staining, BCL2 showed positive nuclear and cytoplasmic staining and pancytokeratin was negative. IHC for synaptophysin and S100 were also performed. Synaptophysin showed positive cytoplasmic staining and S100 was negative. Lastly, IHC for TFE3 was done which showed positive nuclear staining. (Figure 5 A-F). Periodic acid-Schiff stain for intracytoplasmic crystalline structures was negative. (Figure 6)

Six monthly follow up showed no signs of recurrence or metastasis.

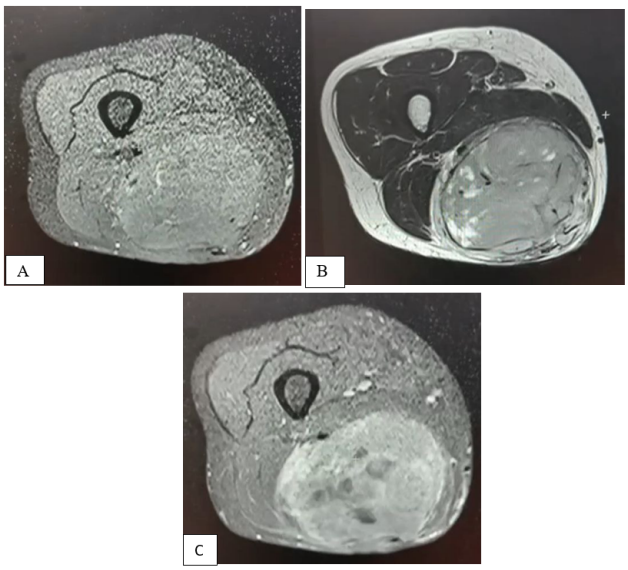

Figure 1: A): MRI of the swelling showing T1 isointense and **B)**: T2 hetrointense lesion with multiple flow voids in the inter and intramuscular plane. **C)**: On post- contrast study, heterogenous enhancement with few non enhancing areas seen within suggestive of necrosis

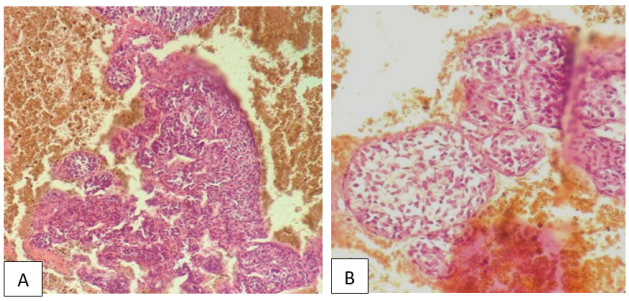

Figure 2: A): Cell block H&E, 10X magnification and **B)**: Cell block H&E, 40X magnification showing tumor cells arranged in an organoid pattern. Individual cells showed a round to oval nucleus with powdery chromatin and abundant eosinophilic to clear cytoplasm

3. Discussion

ASPS is a rare soft tissue tumor with uncertain histogenesis. It often affects young adults and is characterized by slow growing painless tumor in the deep soft tissue of extremities.

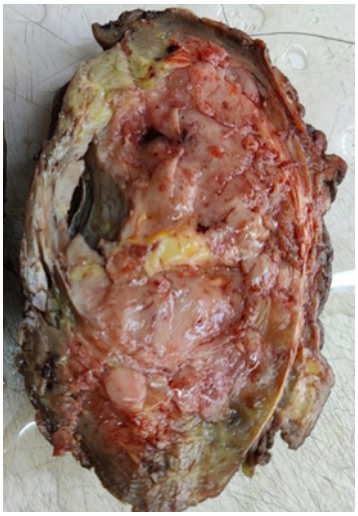

Figure 3: Gross appearance of tumor

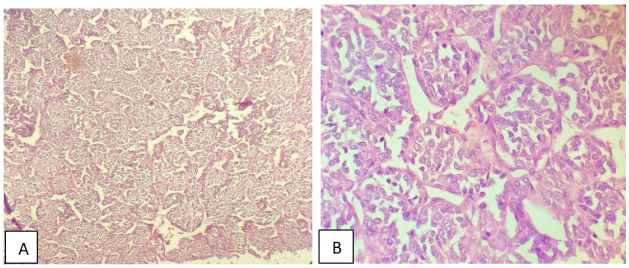

Figure 4: A, B): H and E, 10X and 40X magnification showing round to oval tumor cells arranged in nests and alveolar pattern. Individual tumor cells have mild degree of atypia, vesicular nucleus, moderate eosinophilic to clear cytoplasm and distinct cell borders

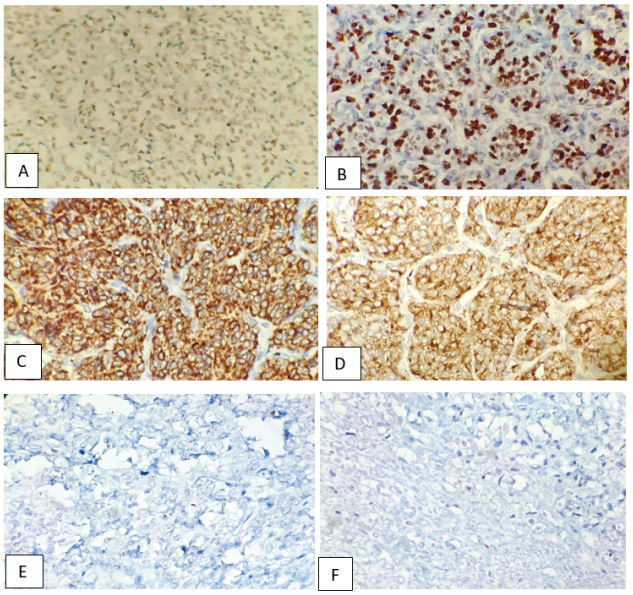

Figure 5: A): TFE3 Positive, 40X magnification; **B):** TLE1 Positive, 40X magnification; **C):** BCL2 Positive, 40X magnification; **D):**. Synaptophysin Positive, 40X magnification; **E):** S100 Negative, 40X magnification; **F):** Pancytokeratin Negative, 40X magnification

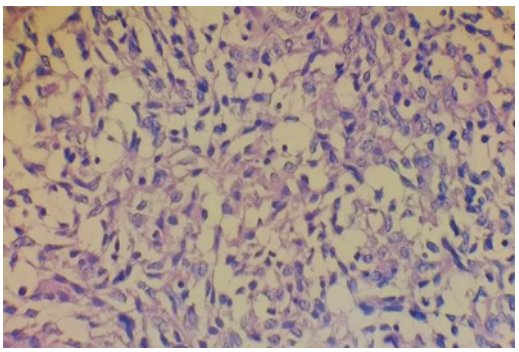

Figure 6: PAS stain, negative for intracytoplasmic crystalline structures (40X magnification)

The most common sites of metastasis include lung, bone and brain. Unlike most sarcomas, metastasis to the lymph nodes is uncommon.[3]

Grossly, the tumor is ill defined with a rubbery, soft consistency and a tan to grey yellow cut surface. Large tumors may show areas of necrosis and hemorrhage.[3] ASPS has a unique and recognisable nested or organoid pattern under the microscope. Delicate sinusoidal vascular channels, lined by a single layer of flattened endothelial cells, divide the nests. Detachment of the central cells results in the typical alveolar pattern. Individual tumor cells are large and have round, regular, eccentrically placed nuclei with vesicular chromatin and a prominent central nucleolus and granular cytoplasm. The intracytoplasmic, periodic acid-Schiff (PAS) positive, diastase-resistant needle like crystals are a common trait of ASPS.[5]

Cytogenetically, ASPS is defined by a specific alteration, der(17)t(X;17) (p11; q25). This unbalanced translocation results in the fusion of the TFE3 gene at Xp11 to the ASPSCR1 (also known as ASPL) at 17q25.3.[6] This results in the activation of MET signalling pathway which promotes angiogenesis and cell proliferation.[5] Fluorescence in situ hybridization (FISH) is a highly sensitive and specific test for TFE3 rearrangements.

Regarding IHC, antibody that recognises the carboxyl terminal region of the TFE3 gene preserved in the fusion protein is consistently positive with strong nuclear staining. Protease cathepsin K, muscle-specific actin and desmin are also frequently positive in ASPS. TFE3 is quite sensitive but not very specific because it also shows positivity in other tumours such as granular cell tumors, subset of perivascular endothelial cell tumors (PEComa), subset of epithelioid hemangioendotheliomas and renal cell carcinomas (RCC).[7]

In our case, the microscopy findings of necrosis, a branching vascular pattern, thin fibrovascular septa separating groups of hyperchromatic tumour cells and increased mitoses along with diffuse and strong nuclear Transducin-like enhancer of split 1(TLE1) positivity favoured the differential diagnosis of poorly differentiated synovial sarcoma[1,6] However, TLE1 is a highly sensitive but not specific marker for synovial sarcoma. A study done by Ali Z et al. evaluated the frequency and intensity of TLE1 staining in synovial sarcomas and other soft tissue lesions including ASPS. Both the cases of ASPS showed 1+ positivity (5-25% of cells positive) with TLE1. They concluded that the 'gold standard' for diagnosing synovial sarcoma should continue to be morphology and IHC along with genetic evidence of fusion genes linked to the disease.[8]

The organoid pattern of arrangement of the tumor cells and cytoplasmic staining for synaptophysin made us consider the diagnosis paraganglioma. Paragangliomas are tumors of neural crest derived endocrine cells or organs known as paraganglia. They arise in several anatomic locations in the body along the parasympathetic and sympathetic chains most commonly in abdomen, chest and head and neck regions.[9]Paragangliomas arising in extremities is very unlikely. A study was done by Kasajima A et al. on the review of literature regarding the rate of synaptophysin and chromogranin A expression in the various entities of non-epithelial neoplasms (NENs). Two cases of ASPS showed synaptophysin positivity and one case showed chromogranin positivity. They concluded that the underlying genetic mechanisms that cause production of synaptophysin or chromogranin A in non-neuroendocrine neoplasms are still unclear. They suggested that synaptophysin or synaptophysin-like proteins may be produced in cells of some NENs.[10]

While granular cell tumours and ASPS usually have different histological features, there are rare instances where there is a noticeable morphologic overlap. Unlike ASPS, granular cell tumours are positive for S100, SOX10, inhibin and nestin and lack fine intercellular vascularity.[11] PEComa may have similar morphological features as ASPS and may show TFE3 positivity and cytoplasmic eosinophilic granules that are positive for PAS. However, PEComa is positive for MART-1 and HMB-45 while ASPS is negative.[12]Metastatic tumors that can mimic ASPS with similar cytologic features include clear cell RCC, hepatocellular carcinoma, adrenocortical carcinoma and melanoma.[7]

The overall survival rate for ASPS is 82% at 2 years and 56% at 5 years. Negative prognostic factors include is largely dependent on the initial presentation metastatic disease at the time of diagnosis, tumor size>10cm and older age.[1,13] The preferred course of treatment for localised illness is radical resection. Conventional chemotherapy and radiation therapy are typically ineffective against metastatic ASPS.[5,7] In a study done by Liu Z et al., the combination of antiangiogenic agents and PD-1 inhibitor showed promising efficacy and acceptable toxicity in patients with ASPS.[14] ASPSCR1-TFE3 fusion protein induces a strong overexpression of MET receptor tyrosine kinase. This results in strong autophosphorylation and activation of the downstream kinase cascade. Hence, MET inhibitors can slow down cell proliferation and they have been showing promising early results with ongoing clinical trials.[15]

4. Conclusion

Diagnosis of ASPS requires experienced pathologists, IHC and molecular testing. This case is presented owing to its overlapping histomorphological and immunohistochemical findings.

5. Source of Funding

None.

6. Conflicts of Interest

The authors declare no conflicts of interest.

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Author's biography

Maydhaavi Gupta, Post Graduate https://orcid.org/0009-0002-1282-0877

Ashalatha Neeravari, Professor

Nirmala Chandran, Professor

Dayananda S Biligi, Professor

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