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**Case Report**

# Epithelioid angiosarcoma arising from Schwannoma: report of a rare case and potential of circulating tumor DNA as a useful biomarker

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## ABSTRACT

Epithelioid angiosarcoma arising from Schwannoma (EASS) is an exceptionally rare and aggressive malignant neoplasm with a poor prognosis. To date, only 22 cases have been reported in the literature, and its risk factors, etiology, and pathogenesis remain poorly understood. There is no established consensus for optimal management or surveillance strategies. These tumors may present as an asymptomatic or symptomatic mass, with most diagnoses being unexpected. Given the rarity and therapeutic challenges of EASS, we present a 58-year-old man diagnosed with EASS, highlighting the potential role of next generation sequencing (NGS) in identifying therapeutic targets and the use of circulating tumor DNA (ctDNA) as a potential tumor burden biomarker. Tumor-informed ctDNA was elevated to 30.49 at the time of diagnosis and increased to 213.90 after presence of metastasis. This case is the first documented instance of a SMARCB1 mutation in EASS, suggesting a potential therapeutic target. Further research is needed to better understand the etiology, pathogenesis, and optimal management strategies for EASS, including the role of targeted therapies based on NGS findings and the utility of ctDNA as a monitoring tool. Overall, the rarity and aggressive nature of EASS, a comprehensive metastatic workup, including cross-sectional imaging, is crucial for staging and management.

**Keywords:** Epithelioid angiosarcoma, Circulating tumor DNA, Next generation sequencing, SMARCB1

## INTRODUCTION

Angiosarcoma is an endothelial tumor that arises in the soft tissue and accounts for 2 to 4 % of soft tissue sarcomas. It is extraordinarily rare for angiosarcomas to arise from schwannomas, a benign peripheral nerve sheath tumor. Only 22 cases have been reported in literature.[1,2] The prognosis of epithelioid angiosarcoma arising from Schwannoma (EASS) is very poor with no definite management and surveillance guidelines due to the rarity of the disease. The average age of patients diagnosed with EASS is 53, ranging from 17 to 74 years old with a male to female ratio of 2:1.[1] The etiology of this transformation has not been elucidated, but several researchers have highlighted the involvement of chronic vasculostasis, edema, and immune response for the transformation process.[1-5]

In this report, we present a 58-year-old male patient with an angiosarcoma arising from a schwannoma found in the left upper medial back and highlighting the use of ctDNA on evaluating prognosis.

## CASE REPORT

Patient is a 58-year-old gentleman with past medical history significant for lipomas who presented with discomfort and pain from the two lipomatous lesions on his back. The palpable lesions were located on posterior left back, one within the subcutaneous plane and another overlying the left shoulder blade, deep to the musculature.

The deeper mass was tender to palpation. Patient denied recent unintentional weight loss, night sweats, or fevers.

Ultrasound of the chest and back was obtained showing a subcutaneous lesion measuring 4.0×3.9×0.4 cm with similar echogenicity surrounding subcutaneous fat suggesting a lipoma. The deeper, superomedial lesion on the left shoulder measured 4.3×1.8×2.9 cm (Figure 1A).

Patient also underwent magnetic resonance imaging (MRI) to better define this lesion. MRI in T1 phase shows an ovoid mass deep to the paraspinal muscles at the level of the 6th rib with avid heterogenous peripheral predominant enhancement suspicious for a nerve sheath tumor (Figure 1B) and MRI in STIR sequence further shows the well-defined borders of the tumor (Figure 1C).

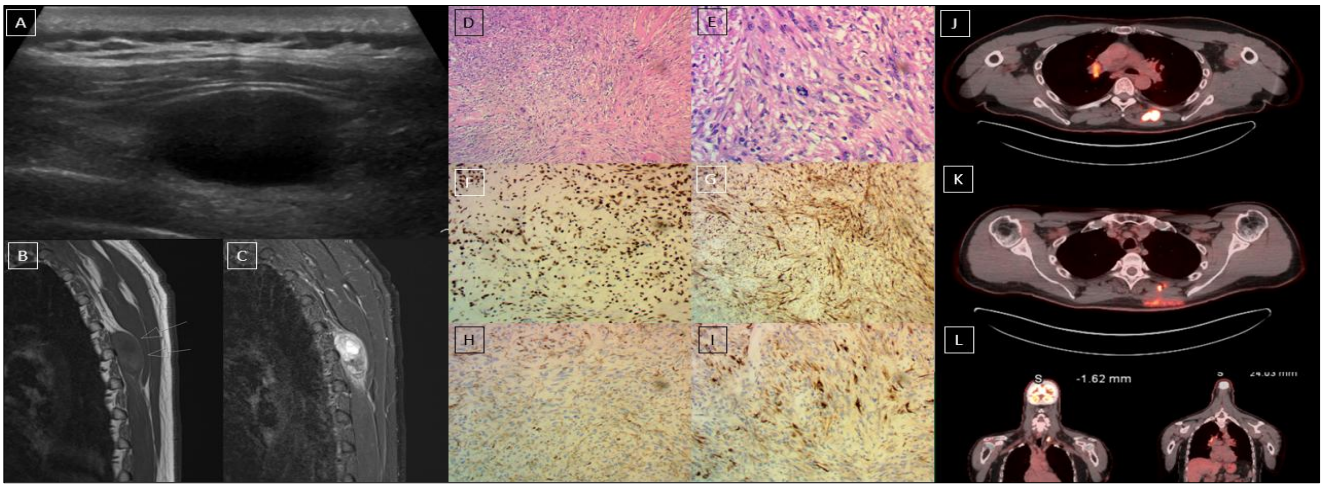


**Figure 1: (A) Ultrasound of a hypoechoic, avascular lesion measuring 4.3×1.8×2.9 cm in the superomedial left shoulder deep to the musculature, (B) MRI T1 phase of the ovoid mass deep to the paraspinal muscles with slight hyperintensity with a tapered tail of enhancement extending into the adjacent soft tissue, (C) MRI in STIR sequence, (D) H and E stain of the ovoid lesion demonstrating multilayering of irregular endothelial shaped cells with nuclear atypia, increased mitosis and sheet like growth with poor demarcation consistent with epithelioid angiosarcoma in the left upper portion of the image. The right lower portion of the image portrays spindle and oval nuclei of cells consistent with schwannomas, (E) 100x of H and E slide focusing on an area of epithelioid angiosarcoma with atypical mitosis in the center of the image, (F) immunohistochemistry of SOX10, (G) immunohistochemistry of S100 (markers for neurocrest origin) in the lesion consistent with Schwannoma, (H) presence of CD31,( I) and patchy areas of CK in area of epithelioid angiosarcoma, and (J-L) PET-CT showing another area of subcutaneous soft tissue activity at the lower level of the left scapula and multiple areas of nodal activity including the left supraclavicular nodes, bilateral hilar nodes.**

Patient underwent excision of both masses. The gross specimen of the suspicious lesion was smooth, white, and firm containing dry and particulate matter similar to a dry sebaceous cyst. Final pathology revealed that the superficial mass was a lipoma whereas the deep mass was a high grade epithelioid angiosarcoma, arising in a schwannoma and extending to peripheral resection margins. Hematoxylin and eosin stain (H and E stain) of the lesion shows spindle and oval nuclei without nuclear atypical consistent with Schwann cells and multilayering of irregular endothelial shaped cells with nuclear atypia, increased mitosis and sheet like growth with poor demarcation consistent with epithelioid angiosarcoma (Figure 1D and E). Immunohistochemistry of the mass with S100 and SOX10 (SRY-related HMG box) are positive, marking the presence Schwann cells (Figure 1F and G) Positive immunohistochemistry of cluster of differentiation 31 (CD 31) or platelet endothelial adhesion molecule) and CK (cytokeratin) shows presence of endothelial cells (Figure 1H and I). The lesion's immunohistochemistry was negative for mucicarmine, transducin-like enhancer of split 1 (TLE1), epithelial membrane antigen (EMA), Desmin, and SMA (Smooth muscle actin) thus ruling out mucinous neoplasms, synovial sarcoma, neoplasms arising from epithelial, fibrogenic and myofibroblast lineage. ctDNA burden at this time was 30.49.

Patient then underwent positron emission tomography–computed tomography (PET-CT) which showed accumulation of activity extending from the level of the fifth rib to the ninth rib, subcutaneous soft tissue activity at the lower level of the left scapula, multiple areas of nodal activity at the left supraclavicular nodes, and bilateral hilar nodes (Figure 1J-L). Fine needle aspiration of the left supraclavicular lymph nodes revealed atypical epithelioid cells with occasional giant cell forms in a background of lymphocytes although interpretation is limited by paucicellularity. Repeat PET-CT show progression of left posterior chest wall soft tissue/muscular mass with extensive involvement compared to previous study, several new skeletal metastases including manubrial

sternum, mid thoracic area, right pelvis near acetabular area, L5 vertebra, S2 and involvement of ribs, persistent nodal metastasis within chest. Patient had completed paclitaxel with minimal response thus he was switched to Pembrolizumab and palliative external beam radiation of 30 centrigray (cGy) over 10 fractions.

Next generation sequencing (NGS) via Tempus shows potentially actionable mutation to be a frameshift on SMARCB1, a tumor suppressor involved in chromatin condensation, repair and replication. Despite treatment with Tazemetostat and paclitaxel, ctDNA levels rose to 213.90, concerning for increasing tumor burden. The patient underwent palliative radiation and ultimately expired 182 days after index resection.

## DISCUSSION

Schwannomas are benign, slow growing peripheral nerve sheath tumors that are commonly managed with surgical resection. The lesions rarely reoccur or transform into metastatic tumors, and thus have excellent prognosis. On the contrary, angiosarcomas are aggressive malignant endothelial tumors with poor prognosis. Treatment commonly includes a combination of surgical resection, chemotherapy and radiation. Recurrence and metastasis are frequent. A combination presentation of EASS is an extremely rare entity with a total of 22 cases reported in medical literature.[1,2]

Fifteen patients presented with symptomatic disease including pain, dyspnea, facial palsy, headache, memory loss, gait disturbance, paralysis, swelling, hemothorax, hoarseness, and ptosis. Five patients were asymptomatic. All patients underwent surgery, three patients received radiation, three received adjuvant chemotherapy and one received neoadjuvant chemotherapy.[1] At follow up, ten patients had undetectable disease, three patients presented with metastatic disease, and seven died. Three were lost to follow up.

Due to the rarity of EASS, there are no gold standard methods in diagnosing, treating or surveillance. Work up of the disease has been provider dependent, with the majority of patients undergoing cross sectional imaging and staging. In our study, we have incorporated NGS into our workup to identify potential therapeutic targets. Our patient had a loss of function frame shift mutation in SMARCB1 identified on NGS. SMARCB1 is involved in chromatin remodeling and loss of function of this gene has been implicated in malignant rhabdoid tumor of the kidney, atypical teratoid rhabdoid tumor, renal medullary carcinoma, synovial sarcoma, and sinonasal carcinomas.[6] Biallelic and less common, monoallelic loss of function of SMARCB1, which encodes INI1, has been identified in in up to 83% of reported epithelioid sarcoma cases.[6] In one study, >90% of epithelioid sarcoma cases had loss of function of INI1 by absence of staining on immunohistochemistry. Yet, cases of epithelioid angiosarcoma yielded expression of the INI1.[7] To this day, there are no literature that shows SMARCB1 mutation in epithelioid angiosarcoma. Thus, our report is the first case of EASS with SMARCB1 mutation. This may serve as a potential future therapeutic target for EASS. No reports of gene mutations were identified upon review of available literature of EASS cases.

It is widely known that ctDNA can reflect tumor burden and thus, used as a marker to assess progression of the disease.[8] Moreover, it can be used to monitor response to treatment, as seen in metastatic melanoma, breast cancer, and non-small cell lung cancer.[9-11] ctDNA analysis also shows promise in detecting gene mutations associated with breast cancer thus enabling the selection of targeted therapies for more precise treatment.[12] Baseline ctDNA levels and their dynamics during therapy have been associated with serving as prognostic indicators.[13] This concept of using ctDNA as a tumor marker for prognosis was applied to our patient with EASS. His initial ctDNA level was 30.49. PET imaging showed progression of the disease and his repeat ctDNA increased to 213.90 despite systemic chemotherapy, correlating with the increase in tumor burden. Overall ctDNA is beneficial as it is obtained in a minimally invasive way and is an easily repeatable option for monitoring tumor behavior and response. In rare tumors like EASS, obtaining ctDNA becomes a valuable tool in evaluating the disease's heterogeneity, genomic characteristics, and response to therapy.

## CONCLUSION

EASS are rare tumors that are highly malignant with poor prognosis. In this regard, there are no gold standard in work up, management, and surveillance plan for patients diagnosed with EASS. In this case report, we present a patient with this rare entity with a novel mutation identified in EASS, SMARCB1. We also demonstrate that ctDNA correlates with tumor burden and that it can be used to determine tumor response to therapy in rare diseases without specific tumor markers.

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