

CASE REPORT**EXPLORING THE THERAPEUTIC POTENTIAL OF SUNITINIB IN THE MANAGEMENT OF METASTATIC ALVEOLAR SOFT PART SARCOMA: A COMPREHENSIVE CASE REPORT**

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Alveolar soft part sarcoma is a rare subtype of sarcoma. It comprises around 0.5% of all soft tissue sarcomas. It is a disease of the young, mainly affecting people less than 25 years of age. Its incidence is much higher in females than in males. We report the case of a 22-year-old female patient. She is a known case of metastatic retroperitoneal alveolar soft part sarcoma with lung metastasis. She was initially evaluated outside our institute for complaints of abdominal pain and a large left retroperitoneal mass, measuring 17×9×13.5 cm, extending to the left pelvis. She had a locally unresectable disease. CT scan of the Chest revealed bilateral sub-centimeter pulmonary nodules, approximately 8.6 mm in diameter. She later came to us for further management. She had complaints of abdominal pain and discomfort. Following a thorough discussion, she was counselled about the diagnosis of metastatic disease, and it was explained that the treatment would be palliative in intent. She was started on treatment with Sunitinib 37.5 mg once a day. She was also assessed for genetic syndromes. Her genetic test was negative. She has been tolerating the treatment well. This tumour is very rare, and data are scarce regarding its presentation and management. There is no consensus on the treatment of this disease yet, and it follows an indolent course with an increased risk of distant metastases. Targeted treatment, including novel small tyrosine kinase inhibitors in patients with metastatic disease, has shown some promising results regarding response to these therapeutically resilient soft tissue sarcomas along with improved survival.

Keywords: Alveolar soft part sarcoma; Palliative intent; Targeted treatment

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INTRODUCTION

Alveolar soft part sarcoma (ASPS) was first described in 1952 as one of the subtypes of soft tissue sarcoma. It affects 0.5–1% of the population.¹ In some instances, it may be associated with exposure to prior radiation and genetic syndromes such as Li Fraumeni and Retinoblastoma.² It is mainly a disease of the younger population, aged 15–35 years of age. In children, it is more commonly found in the head and neck, and extremities while in adolescents and adults, it is seen involving the chest, abdomen, and soft tissues of the extremities.³ Clinically, it presents as a soft, slowly growing tumour with no symptoms. Since it has an indolent growth, patients may present in the clinic with distant metastasis at the time of initial presentation. Lungs (42%) are the most common site of distant metastasis followed by bones (19%), the brain (15%), and the lymph nodes (7%).⁴ Early ASPS is usually treated via radical surgery. We have limited options for the treatment of advanced

disease as it has a decreased response rate to radiotherapy and chemotherapy.

CASE REPORT

A 22 years old female patient, a passive smoker with no previously known comorbid, presented to the medical oncology clinic in August 2022. In June-July 2022 the patient had developed complaints of lower left abdominal pain along with a large firm abdominal mass 17×9×13.5 cm, extending to the left pelvis. She was being treated outside our institute. Her Computerized Tomography (CT) scan abdomen was done in August 2022 which revealed a mass in the left retroperitoneum 17×19×13.5 cm extending down to the left pelvis causing displacement of the left iliopsoas muscle laterally and left ureteric compression resulting in mild left-sided hydronephrosis. She underwent exploratory laparotomy and biopsy in August 2022. The surgeons saw that the tumour was involving the major pelvic vessels and it was deemed unresectable and a biopsy was taken. The biopsy was submitted to our institute

for further evaluation. Multiple tan, white irregular pieces from the pelvic region were submitted. Microscopically the tumour was composed of sheets and aggregates of large neoplastic cells (Figure-1). Individual cells exhibited abundant eosinophilic to clear cytoplasm with distinct cell boundaries (Figure-2). The cytoplasm appeared finely granular. Nuclei were vesicular, moderately pleomorphic with occasional nucleoli. Tumour fragments appeared richly vascularized by capillary-sized blood vessels. In some areas, tumour cells were arranged in packets with surrounding capillaries. PASD stain shows diastase-resistant granules and crystals within the cytoplasm of these cells (Figure-3). Immunohistochemical stains performed showed Cytokeratin AE1/AE3 Negative, S-100 Negative, Synaptophysin Negative, Chromogranin Negative, and TFE-3 positive (Figure-4). A diagnosis of alveolar soft part sarcoma was made.

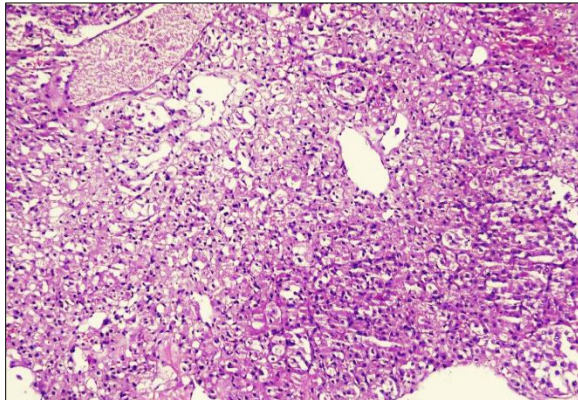


Figure-1: H&E stain, Magnification 4X: Sheets of large polygonal cells with an organoid pattern of growth.

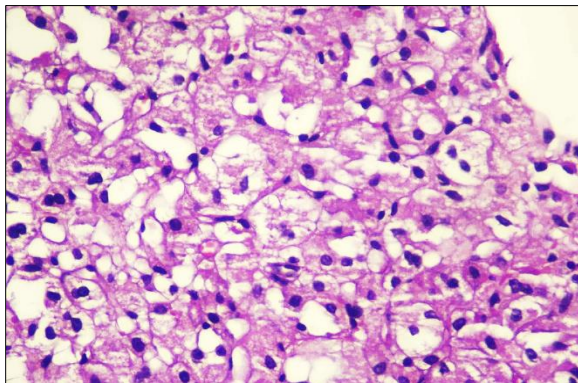


Figure-2: H&E stain, Magnification 40X: Large polygonal cells with well-defined cell borders, eosinophilic to clear, granular cytoplasm and rounded central nucleus.

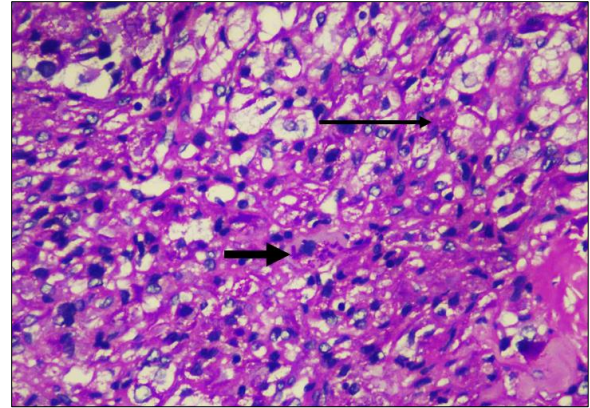


Figure-3: PASD stain, Magnification 40X: PASD stain exhibit PAS positive, diastase-resistant granules (Long arrow) and rod-like crystal (Short arrow).

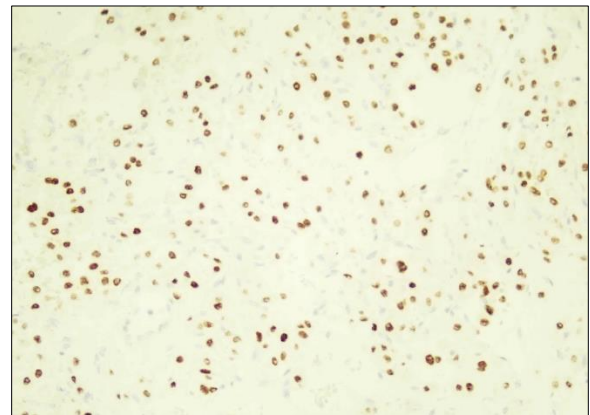


Figure-4: TFE3 immunostaining: nuclear staining with TFE3 immunostaining in the tumour cells

She was also advised to get CT Chest with contrast done. She then presented to our clinic for further management. Her CT Chest revealed bilateral multiple sub cm lung deposits, with a right upper lobe deposit measuring 8.6 mm and a left lung deposit measuring 8 mm. She was advised to get further baseline workup done including CBC, creatinine, liver function, Hepatitis B and C, urine analysis, Echo and TSH. She was advised to get genetic testing done. Her genetic test was negative. Her Bone scan and MRI Brain with contrast were also unremarkable.

She was explained about her stage of disease and that the intent of her treatment would be palliative in nature. After all her initial workup came back fine. She was started on treatment with Oral tyrosine kinase inhibitor, Sunitinib 37.5 mg once a day in September 2022 after explaining all the toxicities and taking detailed informed consent. Almost 1 month after starting treatment she complained of generalized weakness, oral mucositis,

and loose motions. The symptoms were mostly grade I and stabilized with supportive treatment. She also said that her complexion had lightened, and the abdominal mass felt softer on examination. Two months after her treatment started, we checked her TSH (Thyroid Stimulating Hormone). It was elevated and we got endocrinology input after further workup since it was subclinical hypothyroidism. She was started on Oral Thyroxine 50 Ug once a day with regular follow-ups with an endocrinologist and her sunitinib was continued.

In December 2022 her routine workup was done, and she had an absolute neutrophil count (ANC) of 1138, so her treatment was held till her counts recovered she was also advised to get CT

Chest, Abdomen, and pelvis done. Her CT scan done in December 2022 showed that the lung deposits were the same, 0.9×0.6 cm in the left lung and right upper segment measuring 0.8×0.6 cm. The large retroperitoneal mass had also not decreased, it was stable in size, 17.2×9.3×13.3 cm. Scans again showed left-sided mild hydronephrosis. She was asymptomatic and her creatinine was fine. She then continued the same medication.

She has been taking the same medication with minimal side effects for the last 5 months. Plan to continue it for now and then get a CT scan and bone scan done after 3 months and earlier if clinically indicated

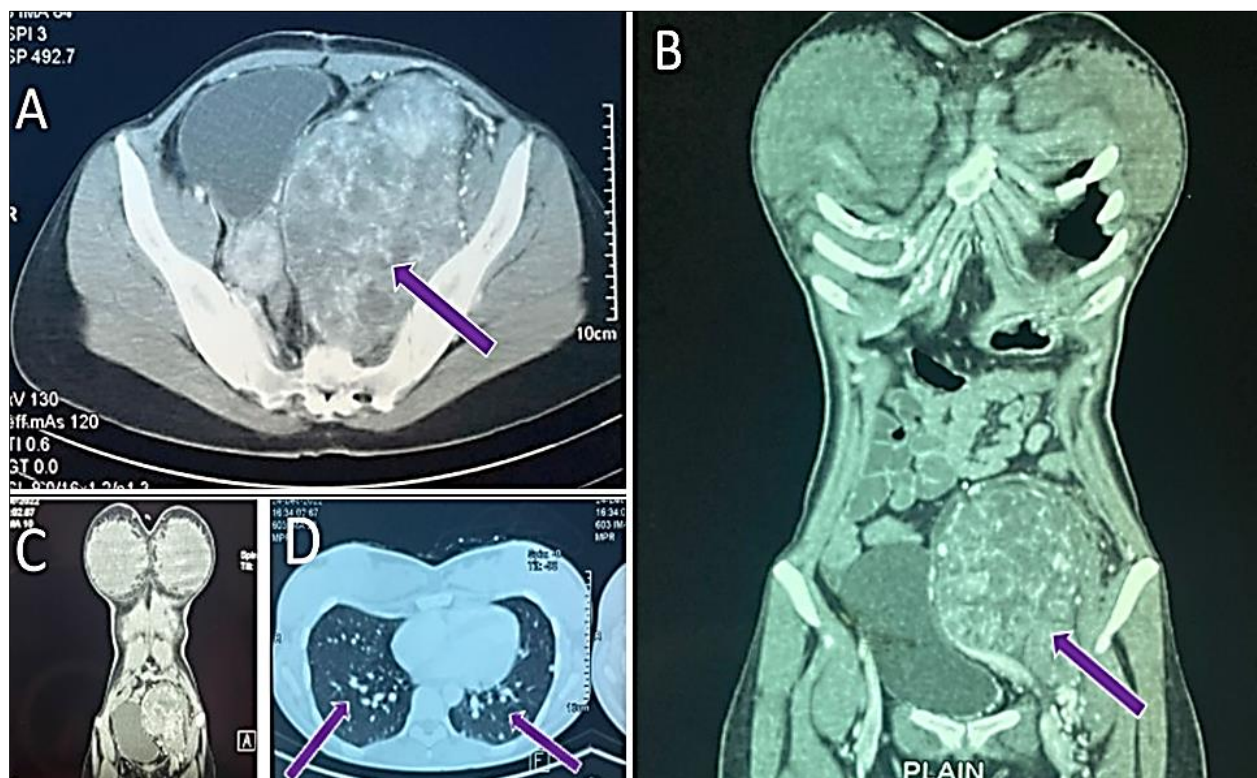


Figure-5: Heterogeneously enhancing large soft tissue mass in the left hemi pelvis predominantly in the retroperitoneum with a mass effect and displacing the uterus and urinary bladder towards the right side. (A) It is abutting the iliac bone however there is no definite erosion and extending into the sciatic notch. It is inseparable from the neurovascular bundle. (B). Multiple bilateral sub cm lung nodules are suggestive of metastasis. (D)

DISCUSSION

Alveolar soft part sarcoma (ASPS) is a rare and aggressive malignant tumour with a high propensity for distant metastasis. It is a slowly growing tumour with no distinct clinical features which might delay the workup and diagnosis. About 33% of patients present with de novo brain and lung metastasis.⁴ The histopathological diagnosis remains the gold standard

for diagnosis. The polygonal tumour cells are divided by thick fibrous septa, forming equal-sized lobules. The tumour cells have eosinophilic cytoplasm, which contains diamond-shaped or needle-like PAS crystals. Moreover, most ASPSs are positive for nuclear TFE3 expression.⁴ Transcription factor E3 (TFE3) is located at the short arm of X chromosome 11.22. It behaves like an oncogene, once triggered it gets translocated

to the nucleus, resulting in increased cell survival and growth.

Alveolar soft part sarcoma is caused by an unbalanced translocation, namely der (17) t (X:17) (p11; p25), which fuses the TFE3 gene at Xp11 to the ASPL gene at 17q25, creating the ASPL-TFE3 fusion protein.⁵ The transcripts expressed by the fusion protein induce aberrant cellular proliferation along with the secretion of angiogenesis-promoting factors. These contribute to the increased vascularity and increased propensity of ASPS to metastasize.⁶ Because females have an extra X chromosome, they have an increased chance of developing this translocation.⁷ Clinically, ASPS presents as a slow-growing, soft, non-ulcerated mass. Imaging including Ultrasound, CT scan, or MRI scan usually shows a hyper vascular tumour.⁸ PET CT Scan may also be done for the initial staging of the disease.⁹ Since there is a high propensity for these tumours to metastasize to the brain and bones. MRI brain and bone scan can be considered with the initial workup and especially if the patient is symptomatic.¹⁰

Complete surgical excision of the disease is the primary treatment in case of localized disease followed by adjuvant radiation therapy if margins are involved to decrease the risk of recurrence. There is no data regarding adjuvant chemotherapy or any targeted treatment yet.¹⁰ The prognosis for locally advanced, unresectable, or metastatic disease is poor, and these patients are usually treated with palliative intent. The five-year overall survival is around 20 percent. And the median survival is around 40 months, but that may improve with the ongoing advancements and developments in treatment.¹¹

Some patients with de novo metastatic or unresectable disease can be managed conservatively with surveillance as it is a very slow-growing tumour. Except for patients with CNS disease, as it needs immediate treatment, if not addressed it may result in a rapid decline in quality of life and other neurological complications.

For other symptomatic patients, single-agent immunotherapy can be considered for treatment. Atezolizumab, a monoclonal antibody that inhibits PDL-1 is effective and well tolerated. In a single-arm phase II study, ML39345, 49 adult and paediatric metastatic ASPS patients were included. Atezolizumab gave an objective response rate of 24%, all of which were partial responses. Pembrolizumab is an immunotherapy agent, a PD-1 inhibitor, which can be used, studies have also shown partial response with this drug.¹² For patients with the heavy-burden disease, pembrolizumab plus axitinib can be considered. It gives an objective response of 55% as evaluated in a phase II study.¹³ If the patient cannot tolerate the combination or has cost

constraints as our patient had. They can also be treated with single-agent Tyrosine kinase inhibitors (TKIs). Pazopanib gives a response rate of 17–28 percent.¹⁴

Sunitinib has shown benefits in both observational studies and clinical trials. Moreover, sunitinib has shown promise in prolonging progression-free survival and overall survival in ASPS patients. A study published in 2017 by Paulina Jagodzińska-Mucha on 15 patients showed that patients treated with metastatic ASPS with Sunitinib had a median progression free survival (PFS) of 19 months with median (OS) of 56 months.¹⁵ Another Chinese study published in 2016 by Ting Li showed a median PFS of 41 months in 14 patients.¹⁶ Indeed the studies on sunitinib in metastatic ASPS show some promise, although the data is based on a small number of patients. The fact that sunitinib demonstrated activity in limiting the disease spread and improving PFS is encouraging. Moreover, the observation that the average 5-year survival of localized disease was 60% 3 decades ago is now similar for metastatic ASPS also suggests improvements in treatment.¹⁷ The beneficial response to sunitinib in ASPS is further advocated by its manageable safety profile. Although some patients may experience adverse effects such as fatigue, hypertension, and hand-foot syndrome, these can typically be effectively managed or diminished with appropriate monitoring and supportive care.

Another case report discussed the combination of camrelizumab, another PD-1 inhibitor, and apatinib, which also resulted in a high response rate, PFS, and disease control.⁴ Most of the data regarding treatment are from phase II studies and case reports, large, randomized control trials are needed to evaluate the potential benefit of these targeted treatments.

Ongoing trials including collaborative efforts amongst researchers, clinicians and patients will continue to lead us towards advancements for more effective future management of this indolent disease.

CONCLUSION

ASPS is a rare disease, mainly affecting the younger population. It is an aggressive malignancy associated with poor prognosis, though it follows an indolent course. It has a high propensity for lung, bony, and cranial metastasis. We have discussed a case of a young female patient who had upfront metastatic disease and is being treated with Sunitinib, TKI. She is tolerating the treatment well and her latest scans showed stable disease. There is no consensus on the optimal treatment regimen for metastatic unresectable ASPS. Immunotherapy and targeted treatment including tyrosine kinase inhibitors have shown some

benefit, mostly in phase II studies and case series and reports. Till more advanced research is done and relevant newer advancements are brought into the current practice, these case reports help in making tailor-made decisions for patients with advanced ASPs.

REFERENCES

- Ognjanovic S, Olivier M, Bergemann TL, Hainaut P. Sarcomas in TP53 germline mutation carriers: a review of the IARC TP53 database. *Cancer* 2012;118(5):1387–96.
- Kleinerman RA, Tucker MA, Abramson DH, Seddon JM, Tarone RE, Fraumeni JF Jr. Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. *J Natl Cancer Inst* 2007;99(1):24–31.
- Chang X, Li Y, Xue X, Zhou H, Hou L. The current management of alveolar soft part sarcomas. *Medicine (Baltimore)* 2021;100(31):e26805.
- Xu Z, Zhang Y, Yu YH. Successful treatment of advanced alveolar soft part sarcoma with camrelizumab combined with apatinib: a case report. *Ann Palliat Med* 2021;10(1):785–92.
- Wang B, Wang H, Wei J, Qu L, Meng L, Xin Y, *et al.* Alveolar soft part sarcoma of the right calf: A case report. *Medicine (Baltimore)* 2020;99(5):e18952.
- Fujiwara T, Nakata E, Kunisada T, Ozaki T, Kawai A. Alveolar soft part sarcoma: progress toward improvement in survival? A population-based study. *BMC Cancer* 2022;22(1):891.
- Ogura K, Beppu Y, Chuman H, Yoshida A, Yamamoto N, Sumi M, *et al.* Alveolar soft part sarcoma: a single-center 26-patient case series and review of the literature. *Sarcoma* 2012;2012:907179.
- Sood S, Baheti AD, Shinagare AB, Jagannathan JP, Hornick JL, Ramaiya NH, *et al.* Imaging features of primary and metastatic alveolar soft part sarcoma: single institute experience in 25 patients. *Br J Radiol* 2014;87(1036):20130719.
- Nieweg OE, Pruim J, van Ginkel RJ, Hoekstra HJ, Paans AM, Molenaar WM, *et al.* Fluorine-18-fluorodeoxyglucose PET imaging of soft-tissue sarcoma. *J Nucl Med* 1996;37(2):257–61.
- Lin YK, Wu PK, Chen CF, Chen CM, Tsai SW, Chih-Hsueh Chen P, *et al.* Alveolar soft part sarcoma: Clinical presentation, treatment, and outcome in a series of 13 patients. *J Chin Med Assoc* 2018;81(8):735–41.
- Kummar S, Allen D, Monks A, Polley EC, Hose CD, Ivy SP, *et al.* Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol* 2013;31(18):2296–302.
- Groisberg R, Hong DS, Behrang A, Hess K, Janku F, Piha-Paul S, *et al.* Characteristics and outcomes of patients with advanced sarcoma enrolled in early phase immunotherapy trials. *J Immunother Cancer* 2017;5(1):100.
- Wilky BA, Trucco MM, Subhawong TK, Florou V, Park W, Kwon D, *et al.* Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. *Lancet Oncol* 2019;20(6):837–48.
- Kim M, Kim TM, Keam B, Kim YJ, Paeng JC, Moon KC, *et al.* A Phase II Trial of Pazopanib in Patients with Metastatic Alveolar Soft Part Sarcoma. *Oncologist* 2019;24(1):e20–9.
- Jagodźńska-Mucha P, Świtaj T, Kozak K, Kosela-Paterczyk H, Klimczak A, Ługowska I, *et al.* Long-term results of therapy with sunitinib in metastatic alveolar soft part sarcoma. *Tumori* 2017;103(3):231–5.
- Li T, Wang L, Wang H, Zhang S, Atikan Kawuli, Zhang X, *et al.* A retrospective analysis of 14 consecutive Chinese patients with unresectable or metastatic alveolar soft part sarcoma treated with sunitinib. *Invest New Drugs* 2016;34(6):701–6.
- Philip DS, Bajpai J. How I Treat Alveolar Soft Part Sarcoma? The Therapeutic Journey from Nihilism to Cautious Optimism. *Indian J Med Paediatr Oncol* 2024;45(1):068–73.

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