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How I Treat Alveolar Soft Part Sarcoma? The Therapeutic Journey from Nihilism to Cautious Optimism...

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Introduction

Alveolar soft part sarcoma (ASPS) is a very rare subtype, constituting less than 0.5% of malignant Soft tissue sarcoma.[1] It is an orphan disease affecting adolescents and young adults, predominantly females.[2] The rarity of the disease, with its indolent but relentless natural history and enigmatic line of differentiation, makes its diagnosis a challenge. Despite being a chemoresistant disease, it is known for prolonged survival even in a few metastatic patients with spontaneous disease stabilization and indolent disease behavior. Targeted therapy with antiangiogenic agents and immunotherapy is the way forward for this rare disease. In this review, we aim to give an overview of the approach to diagnosis and management of this orphan disease in 2022 in the Indian setting, which is widely applicable in other low-middle income countries (LMIC) as well.

Case history

A 25-years-old lady, a housewife, presented to our outpatient department (OPD) with a 2-year history of discomfort in her right thigh. Six months after the onset of symptoms, she felt a vague mass in the lateral aspect of the proximal right thigh with a doubtful gradual increase in the size of the swelling. There was no associated pain, fever, or weight loss. In view of the COVID pandemic, she reassured herself and had delayed any evaluation of this symptom. Now in view of increased anxiety and insistence of family, she has come to our OPD for evaluation.

How do I Evaluate her to Reach a Diagnosis?

The diagnostic evaluation will be **C.R.P**

- **C**linical evaluation: history and physical examination
- **R**adiological evaluation
- **P**athological evaluation

Clinical Evaluation

History and examination reveal an indolent, slow-growing, painless soft tissue mass of 3×3 cm in the lateral aspect of right thigh, with no constitutional symptoms and no local compressive symptoms. In view of the above clinical presentation, one may misinterpret it to be a benign disease such as hemangioma.

Radiological evaluation

X-ray of the right thigh [antero-posterior/lateral views]: soft tissue mass in the right thigh, with no bony erosion and no calcification.

MRI: Radiological evaluation is to be completed before planning a biopsy.[3–5]

- Flow voids due to intra and peri-tumoral vessels.
- Hyperintense to muscle in T1 images
- Moderate to intense contrast enhancement.

Pathological Evaluation

Core needle biopsy of the lesion classically shows[2]:

- Pseudo-alveolar pattern [which gives it the name]
- Intracytoplasmic rod-shaped crystals [PAS/diastase resistant]
- Intravascular extension
- Immunohistochemistry: TFE-3 and Cathepsin-K are highly sensitive, though not specific for ASPS. It is consistently negative for cytokeratin, epithelial membrane antigen (EMA), human melanoma black (HMB-45), synaptophysin, and chromogranin.

[*When the clinicopathological features of ASPS were initially described in 1952,*[1] *Christopherson noted that "the most striking feature of the alveolar soft-part sarcoma is the basic uniformity throughout a given tumor and the similarity of one tumor to another.*"]

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The highly characteristic histopathology leads us to the diagnosis of ASPS.

Molecular studies

ASTS is a translocation-associated STS, with unbalanced non-reciprocal t(X,17) leading to ASPSCR1-TFE3 fusion gene on der (17) and ASPSCR1-TFE3 chimeric transcript, which is seen in almost all cases. In pathologically challenging cases, RT-PCR for the fusion transcript or FISH for TFE3 rearrangement will be helpful in making a definitive diagnosis.[6,7]

Learning Point

The low incidence, lack of unique clinical features, indolent behavior with the small primary in metastatic disease and atypical sites [adults most common in thigh/gluteal region and in children in head and neck] may lead to misdiagnosis.

A systematic clinical + radiological + pathological evaluation leads us to a definite diagnosis of ASPS.

Now the Definitive Diagnosis of ASPS is Made. How do we Stage the Patient?

The natural history of ASPS is unique with an extremely indolent behavior with late metastasis becoming symptomatic months to years after diagnosis. The most common sites of metastasis are lungs, bone, and brain. Brain metastasis in ASPS is more than in other soft tissue sarcomas.[8]

a) NCCT chest: multiple bilateral lung metastases.
b) MRI Brain: normal.
c) PET-CT: not recommended as initial staging in NCCN/ESMO guidelines.

We have reached a final diagnosis of metastatic ASPS.

Learning Point

ASPS is unique among STS, to have a small primary with an indolent behavior with late metastasis in the lungs. It is one of the few STS, with a high risk of brain metastasis.

How do we Treat Patients with ASPS?

Goals of Treatment

- Minimize local recurrence.
- Minimize perioperative morbidity and mortality.
- Maximize functionality and QOL.
- Maximize overall survival.

The overview of the management plan of ASPS is depicted in the ►**Fig. 1**.

Localized Disease

Localized disease is treated with wide local excision followed by adjuvant radiotherapy if there is evidence of microscopic or macroscopic residual disease or if the margin status is questionable.[9]

Metastatic Disease

Is there a role for surgical excision of primary in metastatic disease with resectable primary?

In the pre-targeted-therapy era, if complete resection was feasible, with limited postoperative morbidity then surgery of the primary, followed by systematic treatment was adopted, the rationale being the indolent disease biology. SEER retrospective data of 25 patients with 58% having a metastatic disease with primary resections, showed an improvement in the overall survival. The role remains questionable and controversial in the present targeted therapy era.[9]

- **Metastatic Disease, Limited Disease Burden:**

Patients with the limited disease who are asymptomatic may be observed with close follow-up, considering the indolent behavior. Brain metastasis [symptomatic/asymptomatic] should be treated with CNS-directed therapy.

- **Metastatic Disease with Heavy disease burden/ Symptomatic/Rapidly progressive Disease:**

ASPS is a relatively chemo-resistant disease. Hence, in both adjuvant and metastatic settings, chemotherapy is not offered.[2,10]

First-line therapy includes targeted therapy with anti-angiogenic [VEGF] agents pazopanib and sunitinib and immunotherapy with immune checkpoint inhibitors and combinations of both.

In view of the rarity of the disease, evidence for treatment options comes from small retrospective case series and recent prospective studies. So, it is difficult to draw definite conclusions. The best treatment happens to be a lot of educated guesses.

Recommended Treatment Agents for Metastatic Disease

NCCN recommendation 2021 [Evidence blocks of therapy is shown in ►**Table 1**].

1. Pazopanib
2. Sunitinib
3. Pembrolizumab

Targeted Antiangiogenic Agents against VEGF

Rationale

ASPS is a translocation associated STS, with the ASPSCR1-TFE3 fusion as a hallmark. This fusion transcript leads to MET overexpression and increased angiogenesis in this highly vascular tumor. Hence antiangiogenic targeted therapy holds promise in this disease.

Approved agents: pazopanib, sunitinib
Investigational agents:

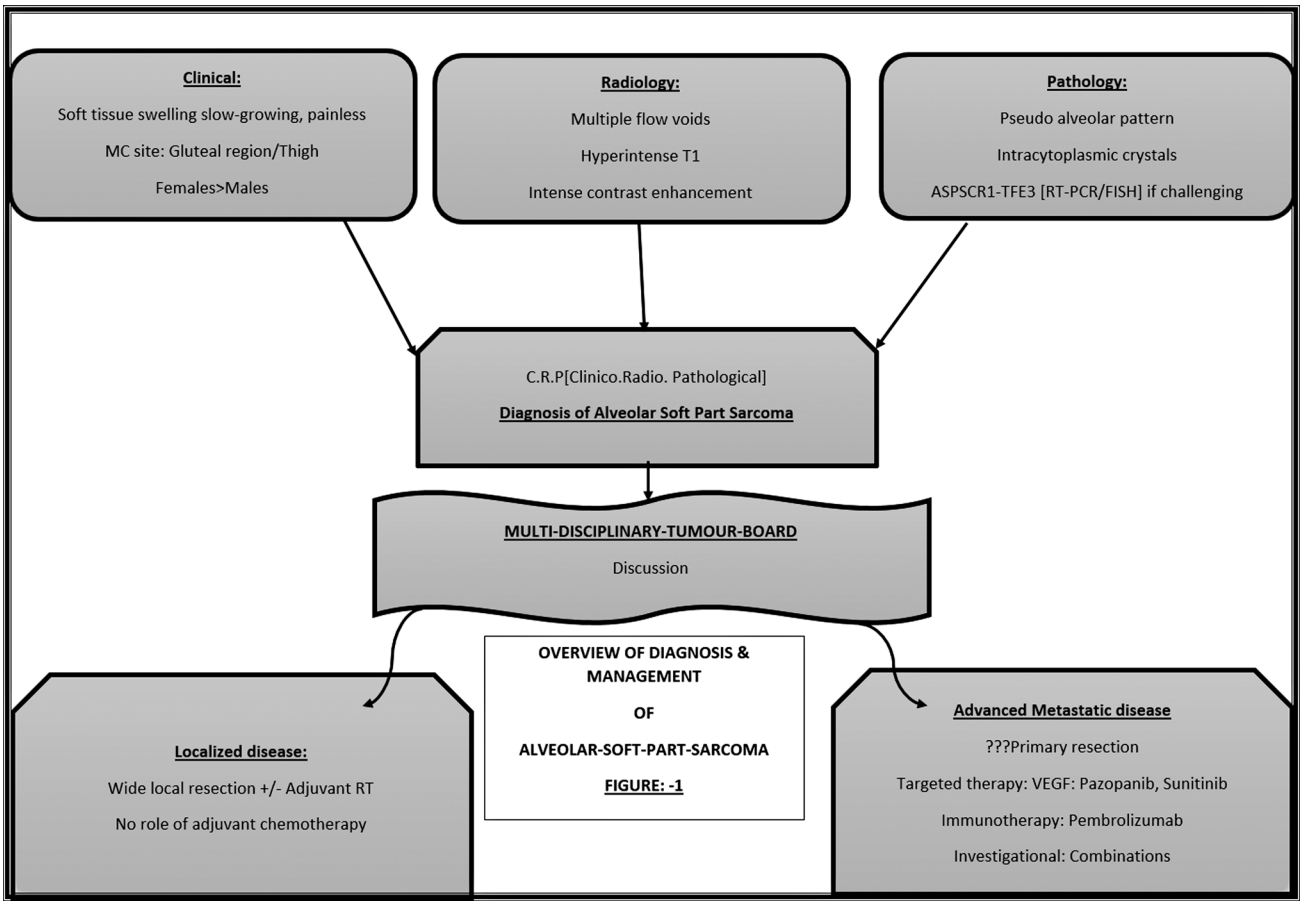

Fig. 1 Overview of management.

Table 1 NCCN 2021 evidence blocks

Sunitinib					
	3/5	3/5	2/5	3/5	2/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability
Pazopanib					
	3/5	3/5	2/5	3/5	2/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability
Pembrolizumab					
	3/5	3/5	2/5	2/5	1/5
	Efficacy	Safety	Quality of evidence	Consistency of evidence	Affordability

Table 2 Systemic treatment with targeted therapy in ASPS

Sunitinib			
Author	**Year**	**Number of patients**	**Outcomes**
Stacchiotti[11]	2011	9	5PR/3SD/1PD Median TTP: 17months
Li[12]	2016	14	4PR/10SD Median PFS:41months
Jagodzinska[13]	2017	15	6PR/8SD/1PD MedianPFS:19months Median OS:56months
Pazopanib			
Year	**Author**	**Number of patients**	**Outcomes**
Stacchiotti[14]	2018	30	1CR/7PR/17SD/4PD/1NE Median PFS:13.6months
Kim[15]	2019	6	ORR:17% Median PFS:5.5 months
Cediranib			
Kummar[16]	2013	43	ORR:35%
Judson[17]	2014	6	2PR/4SD
Judson [RCT, Ph2] CASPS[18]	2019	32/16	3PR/14SD Median PFS:10.8months
Dasatinib			
Schurtze[19]	2017	12	Median PFS:11months 5yr OS:30%
Crizotinib			
Schoffski[20]	2018	45	1PR/35SD 1year PFS:38%
Tivantinib			
Wagner[21]	2012	27	21SD/5PD/1NE Median PFS:5.5 months
Combination of targeted therapy			
Flores[22]	2018	69 [11 targetted/ 15chemo/ 6observation]	2PR/6SD/3PD Median TTP: - Targetted:12months Chemo:7months Observation:4months
J.Bajpai[23]	2019	54[6 with sunitinib/pazopanib]	2CR/2PR Median PFS:23 months

Anti-VEGF: cediranib, anlotinib
Anti-MET: crizotinib
The following table gives a broad overview of systemic targeted therapy in ASPS. [Selection of studies with at least 5 patients] ►**Table 2**.

Immunotherapy

Rationale

ASPS is a cold tumor with low TMB and low PDL1 expression. The responses seen with immunotherapy are postulated to be due to neoantigens created by the unique fusion gene in ASPS.

Pembrolizumab

A retrospective series[24] by Roman et al of 50 patients with advanced STS at the Phase1 clinic at MD Anderson included 4 ASPS patients. All 4 ASPS patients showed clinical benefit, and the best response seen in this study of mixed histologies was partial response in 2 ASPS patients. This has led to the approval and recommendation for advanced ASPS.

Atezolizumab

A phase-2 study by Coyne et al,[25] presented at the ASCO 2021 of 43 patients, ORR was 37% (16/43). [CR:1/PR:15/SD:25], with the median time to response of 3.5 months (range, 2.1–14.9 months) and the median duration of response of 16.5 months (range, 4.9–38.1 months).

Combination Regimens

Immune checkpoint inhibitor with antiangiogenic targeted therapy:

Table 3 Therapeutic journey of ASPS from nihilism to cautious optimism

Year	Author	Number	Outcome localized disease	Outcome metastatic disease
1989	Lieberman[28]	91 [69/22]	Median OS = 11 y OS at 2 y-77% OS at 5 y-60% OS at 10 y-38% OS at 20 y-15%	Median OS = 3 y
2018	Flores[22]	69 [31/38]	OS at 5 y-87%	OS at 5 y-61%

VEGF mediates neo-angiogenesis and an immunosuppressive tumor microenvironment. VEGF inhibitors would evade the immunosuppressive microenvironment and thus show synergism with immunotherapy.

Pembrolizumab with axitinib, in a phase-2 study of 36 advanced STS with 12 ASPS, showed overall response rate of 55% and 3 months PFS of 75%. This was independent of the PDL1 status.[26]

Systematic review and meta-analysis of immune checkpoint inhibitors in soft tissue sarcoma[27]:

Sarens et al have published a meta-analysis in 2021, evaluating 900 patients with advanced soft tissue sarcoma including 109 ASPS patients. The ORR by RECIST and Choi criteria was 0.35 [95%CI 0.27–0.44]. Exploratory analysis of ORR showed:

Checkpoint inhibitor monotherapy: 0.31 [0.22–0.42 CI]
Checkpoint inhibitor +TKI: 0.47 [0.26–0.69]
Checkpoint inhibitor+ others: 0.55 [0.28–0.79]

Therapeutic Journey from Nihilism to Cautious Optimism

The progress in systemic therapy with targeted agents has led to improvement in survival as shown in ►**Table 3**. The 5 years overall survival of patients with the localized disease was 60%. Now over three decades later, patients with metastatic disease, treated with targeted therapy have the same survival. This clearly shows the progress in our therapeutic journey.

With many novel agents in the pipeline and pathway-driven basket trials and collaborative prospective clinical trials, the future of management of ASPS looks bright and promising.

Take Home Messages

- ASPS is a rare orphan disease, with an indolent yet relentless clinical course.
- A detailed clinico–radio-pathological evaluation is the key to diagnosis.
- It usually presents as a painless slow-growing vascular soft tissue mass in the lower limb of adolescents and young adults, predominantly females.
- It has characteristic histopathology with Pseudo-alveolar patterns and intracytoplasmic crystals. IHC with TFE3 and Molecular studies for ASPSCR1-TFE3 help in challenging situations.
- Metastatic disease to lung/bone/brain leads to poor prognosis. It is unique among STS to have brain metastasis.
- Localized disease is managed with wide local excision followed by adjuvant radiotherapy if microscopic or macroscopic residual disease.
- It is essentially a chemoresistant disease with an almost negligible role for Adjuvant chemotherapy.
- Metastatic disease is treated with targeted anti-VEGF agents such as pazopanib/sunitinib and immunotherapy such as pembrolizumab or combination.
- With many novel agents in the pipeline and pathway-driven Basket trials with collaborative prospective clinical trials, the future of management of ASPS looks promising. It is truly a therapeutic journey from Nihilism to cautious optimism.

Conflict of Interest
None declared.

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