



## Case Report

# A case of multiple synchronously diagnosed brain metastases from alveolar soft part sarcoma without concurrent lung involvement

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## ABSTRACT

**Background:** Alveolar soft part sarcoma (ASPS) is a rare soft-tissue sarcoma with a propensity for early hematogenous dissemination to the lungs and frequent brain metastasis. The development of lung metastasis almost invariably precedes intracranial involvement. There are no previously reported cases in which a patient was synchronously diagnosed with ASPS and multiple brain metastasis without lung involvement.

**Case Description:** A 29-year-old gentleman was found to have three intracranial lesions following the onset of generalized seizures. Staging studies identified a soft-tissue mass in the left thigh and an adjacent femoral lesion. Biopsy of the soft-tissue mass was consistent with ASPS. The patient then underwent neoadjuvant stereotactic radiotherapy to all three brain lesions, followed by *en bloc* resection of the dominant lesion. The patient was then started on a programmed death-ligand 1 (PD-L1) inhibitor. Subsequent surgical resection of the primary lesion and femur metastasis demonstrates a histopathologic complete response of the bony metastasis and partial response of the primary lesion. At present, the patient has received 14 cycles of atezolizumab without recurrence of the primary or bony lesions and the irradiated intracranial disease has remained stable without recurrence of the resected dominant lesion.

**Conclusion:** While intracranial involvement is relatively common in ASPS, a case with multiple, synchronously diagnosed brain metastasis without concurrent lung metastasis has not been described. The presented case discusses the safety and efficacy of aggressive management of intracranial disease in the setting of atezolizumab. Prospective evaluation of the efficacy of checkpoint inhibitors and the prognostic value of PD-L1 expression in ASPS with brain metastasis are necessary.

**Keywords:** Abscopal effect, Brain metastasis, Checkpoint inhibitor, Immunotherapy, Sarcoma, Stereotactic radiotherapy

## INTRODUCTION

Alveolar soft part sarcoma (ASPS) accounts for roughly 1% of all soft-tissue sarcomas (STSs). ASPS typically presents as a slow-growing mass in the lower extremity. Detection of the nonreciprocal translocation t (X; 17) (p11.2; q25) between chromosome 17q25 and Xp11 resulting in the chimeric ASPSCR1-transcription factor E3 (TFE3) fusion gene is diagnostic. The standard of care includes wide margin, function-sparing, excision of the primary lesion, often

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with adjuvant radiation therapy (RT) in the form of external beam RT or brachytherapy.<sup>[17]</sup>

ASPS has a propensity for early, often synchronous, hematogenous dissemination to the lungs and is diagnosed in 63% of cases.<sup>[15]</sup> Five-year survival with Stage IV ASPS is approximately 20%, with a median overall survival of 40 months.<sup>[15]</sup> Intracranial involvement is almost invariably preceded by lung metastasis and often diagnosed within 24–36 months of ASPS diagnosis.<sup>[15,18]</sup> Management of brain metastasis includes either RT alone or surgical resection when possible with adjuvant RT.<sup>[15,20]</sup> Given the high rates of metastasis, current guidelines for ASPS staging include both cranial and lung imaging.<sup>[18]</sup>

The role of systemic therapy for metastatic ASPS is poorly understood.<sup>[17]</sup> Metastatic disease was traditionally treated with anthracycline-based chemotherapy, such as doxorubicin, though the response rate was poor.<sup>[15]</sup> Conducting a randomized clinical trial in advanced ASPS is challenging given its rarity and in the few that have occurred, patients with symptomatic brain metastasis were excluded from the study.<sup>[12]</sup> Given the high rate of programmed death-ligand 1 (PD-L1) expression in ASPS, atezolizumab alone or pembrolizumab with concurrent axitinib is being studied in clinical trials.<sup>[2,22]</sup>

The presented case describes the clinical and surgical management of a patient with synchronous brain metastases from ASPS without definitive evidence of concurrent lung metastasis, which is exceptionally rare, with similarities to only one prior case.<sup>[5]</sup> In addition, we discuss the implications of immune checkpoint inhibitor (ICI), atezolizumab, in patients with metastatic ASPS, which led to a partial response (PR) of the primary lesion, complete response (CR) of bony metastasis, and stable intracranial disease at 15 months follow-up.

## CASE DESCRIPTION

A 29-year-old gentleman with no significant medical history presented following a generalized tonic-clonic seizure. His physical examination and vital signs were unremarkable except for a grossly evident left lateral thigh mass. MRI brain showed three contrast-enhancing lesions: 14 × 6 mm right posterior temporal lesion, 7 × 5 mm posteromedial right thalamic lesion, and 3 mm subcortical posterior right frontal lobe lesion [Figures 1a-c]. Imaging of the left femur revealed a 7.1 × 3.9 × 4.1 cm mass in the vastus lateralis and an adjacent femoral metastasis. Biopsy of the soft-tissue mass was consistent with ASPS. Following soft-tissue biopsy, PET scan showed pathologic radiotracer uptake in the left femur without radiotracer uptake in the lungs [Figures 2a and b].

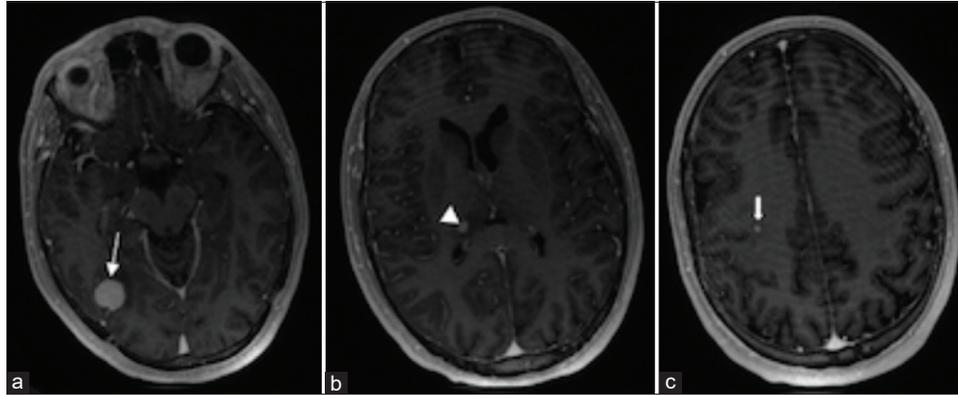
In <1 month from initial diagnosis, the dominant posterior temporal lesion grew from 14 mm to 22 mm in axial diameter.

After interdisciplinary discussion, the patient agreed to neoadjuvant stereotactic radiotherapy (SRT) (24 Gy in three fractions)<sup>[11]</sup> to all three brain lesions, followed immediately by *en bloc* resection of the dominant right posterior temporal lesion. TFE3 immunostaining and ASPL-TFE3 chimeric transcript detection of the brain tumor confirmed metastatic ASPS.<sup>[23]</sup> The specimen was strongly positive for PD-L1 (tumor proportion score [TPS] 90%). Based on emerging data for PD-L1 ICI in ASPS, atezolizumab was initiated.<sup>[2,4,7]</sup>

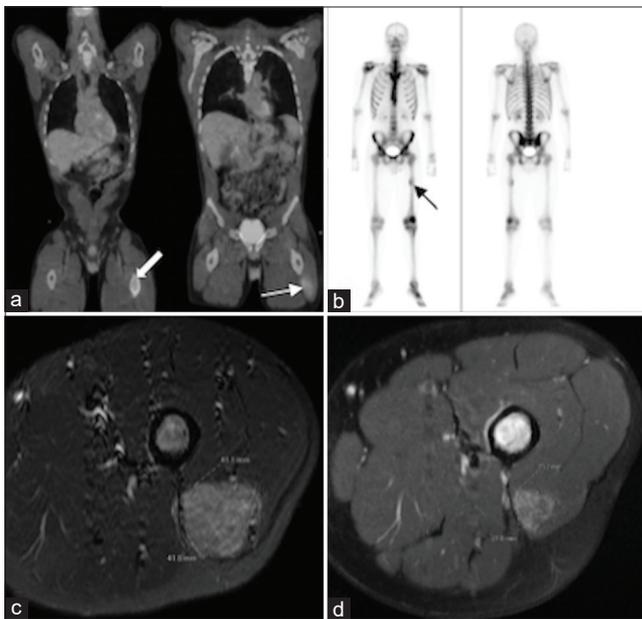
Atezolizumab was started 2 weeks after surgery (1200 mg dose every 21-day cycle). After 4 cycles, PET imaging showed continued radiotracer uptake in the left vastus lateralis and femur. MRI brain at that time showed no evidence of recurrence in the postoperative bed, a PR and reduced T2-FLAIR signal of the thalamic lesion and stable appearance of the posterior frontal lobe lesion (RECIST 1.1). Following 7 cycles, repeat MRI femur showed a PR of the primary lesion from 4.2 × 4.1 cm to 2.3 × 2.1 cm (RECIST 1.1) [Figures 2c and d]. Approximately 5 weeks following the MRI femur, the patient underwent resection of the primary and adjacent metastatic femoral lesions, which although unappreciable on examination, had remained hypermetabolic on PET imaging [Figure 2b]. Pathology noted 75% necrosis/fibrosis in the primary lesion and CR of the femoral metastasis. At present, 15 months following initial diagnosis, the patient has received 14 cycles. Review of CT chest, MRI brain, and CT femur shows no recurrence of the left lower extremity disease or the dominant right posterior temporal lesion [Figure 3a]. A faint linear enhancing focus remains at the posterior aspect of the right thalamus [Figure 3b] and the posterior right frontal lobe lesion has decreased in size from 4 mm to 3 mm [Figure 3c], with unchanged peritumoral edema. No new appreciable lesions were noted [Figures 3a-c].

## DISCUSSION

The presented report describes the first definitive case of ASPS synchronously diagnosed with multiple brain metastases and no concurrent lung metastasis. In a retrospective review of 70 patients with ASPS, 48 patients (65%) were diagnosed with Stage IV disease.<sup>[15]</sup> Among these patients, 14 were found to have multiple metastatic sites, of which the lung was involved in all 14 cases and always preceded the diagnosis of brain metastases in the nine patients who developed intracranial lesions.<sup>[15]</sup> Several cases have described brain metastasis without concurrent lung metastasis, however, intracranial involvement occurred metachronously.<sup>[19,21,23]</sup> To the best of our knowledge, one reported case of ASPS metastatic to the brain without concurrent lung metastasis shares characteristics with the patient described in this report, although important details are lacking.<sup>[5]</sup> In this previous case, a 25-year-old male was diagnosed with a single occipital brain lesion.<sup>[5]</sup> He underwent surgical resection and



**Figure 1:** Pre- and posttreatment T1 gadolinium-enhanced MRI brain. A pretreatment T1-gadolinium enhanced MRI brain. Contrast-enhancing lesions are shown in the right temporal lobe (a – arrow), thalamus (b – arrowhead), and frontal lobe (c – block arrow).



**Figure 2:** Pretreatment PET scan and MRI femur. There are hypermetabolic lesions of the left femur (block/black arrow) and vastus lateralis (arrow) (a and b). No radiotracer uptake is noted within the lungs (a). MRI femur depicted a 4.2 cm × 4.1 cm vastus lateralis lesion (c) which, following 7 atezolizumab cycles, regressed to 2.3 cm × 2.1 cm (d).

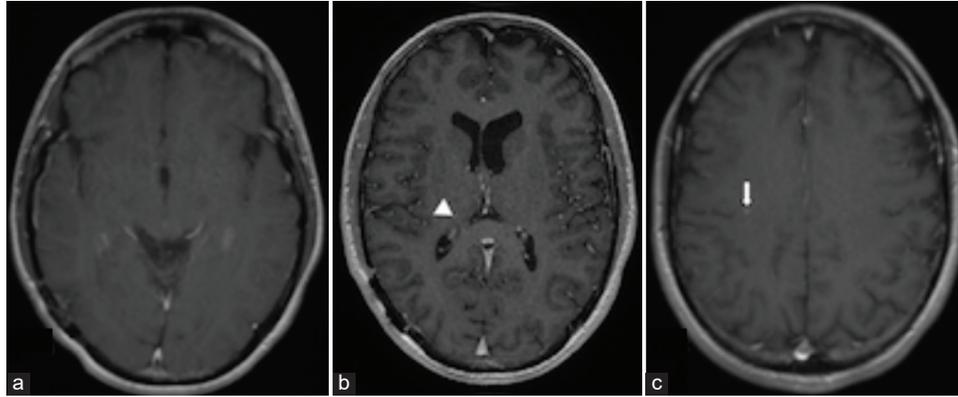
postoperative radiation to the lesion, which lead to a CR.<sup>[5]</sup> Surgical pathology suggested clear-cell renal cell carcinoma, although a primary renal tumor was not identified.<sup>[5]</sup> Surprisingly, 5 years later, he presented with a mass of the left adductor muscles, which was resected and histologically confirmed to be ASPS.<sup>[5]</sup> The intracranial specimen was reevaluated and felt to be consistent with ASPS.<sup>[5]</sup> He was started on an unspecified chemotherapy and subsequently lost to follow up.<sup>[5]</sup>

Important deviations from the presented case include the fact that lung involvement was evaluated with

chest X-ray only, which has a lower sensitivity for metastases than CT chest, the current standard of care in ASPS.<sup>[18]</sup> Furthermore, confirmation of the tumor specimen with immunohistochemical and genetic analysis was not described. Finally, the brain lesion preceded diagnosis of a systemic lesion by 5 years, which is not a synchronous diagnosis and is unexpectedly long survival for untreated metastatic ASPS. Thus, the patient in the presented report seems to be the first with a definitive diagnosis of ASPS with synchronous brain metastases and no concurrent lung involvement using modern diagnostic techniques. In addition, it represents the first case of multiple synchronously diagnosed brain metastases without concurrent lung involvement.

The response to ICI is currently being determined by multiple clinical trials. A Phase II trial evaluating the efficacy of atezolizumab in the treatment of metastatic ASPS is currently active, however, patients with symptomatic intracranial disease are excluded (NCT03141684).<sup>[2]</sup> The decision was made to start the presented patient on atezolizumab given the previously described success in metastatic ASPS without brain metastasis. However, it is important to consider STS subtype and the role of %TPS PD-L1 expression of an individual's tumor to determine the likelihood of an adequate response.

In some STS subtypes, PD-L1 expression is associated with higher tumor stage, deep-seated sarcoma, distant metastasis, higher histologic grade, tumor differentiation, and tumor necrosis.<sup>[6]</sup> In others, PD-L1 expression confounds clinicopathological parameter correlations and clinical outcomes.<sup>[3]</sup> Antibody specificity, affinity, and/or epitopes may contribute to correlative differences in PD-L1 expression and clinical outcomes.<sup>[8]</sup> Variability in previous reports of PD-L1 expression includes differing values for defining PD-L1 positivity, various anti-PD-L1 immunohistochemistry assays, and preoperative treatment protocols that influence PD-L1 expression.<sup>[9,13,14]</sup>



**Figure 3:** Eleven-month posttreatment T1 gadolinium-enhanced MRI brain. An eleven-month postoperatively MRI. The temporal lesion has not recurred (a) with near complete response of the thalamic lesion (b – arrowhead) and stable frontal lesion (c – block arrow).

The role of ICI with concurrent radiation for STS is being evaluated by the NEXIS trial (NCT03116529), though patients with symptomatic or uncontrolled brain metastases are excluded.<sup>[10]</sup> In the setting of SRT and atezolizumab in this case, a possible abscopal response of the primary and femoral metastatic lesion was observed following irradiation of the intracranial lesions. However, the response was unable to be corroborated by laboratory testing, as tumor tissue, blood and CSF samples were not readily available for analysis. In addition, the intracranial specimen demonstrated high PD-L1 expression (TPS 90%). The CR of the bony metastasis and PR of the primary lesion suggest that with high PD-L1 expression, ICI is a viable option for systemic treatment. Concurrent SRT and ICI may result in radiation-induced increased PD-L1 expression and increase the likelihood of an abscopal response.<sup>[13]</sup> Future studies are necessary to assess PD-L1 %TPS as a predictive biomarker and subsequent suitability for PD-L1 ICI.<sup>[6,9]</sup>

In addition to a concurrent ICI and SRT strategy, the authors also employed a relatively new treatment paradigm involving neoadjuvant SRT followed by surgical resection of the dominant lesion. As described first by Asher *et al.*, potential benefits of neoadjuvant radiation are 3-fold: (1) a better-defined treatment target thus diminishing the volume of healthy parenchyma exposed to radiation and decreasing risk for radiation necrosis, (2) the sterilization of tumor cells preoperatively may decrease the risk of intraoperative dissemination and leptomeningeal seeding, and (3) an increase in tumor antigen exposure, which may further enhance ICI response.<sup>[1,16]</sup> Previous reports have suggested that ICI, particularly with concurrent radiation, may have increased risk of radiation necrosis, thus a neoadjuvant radiation strategy may assist in mitigating this risk, as the need for resection cavity margin expansion to include surround healthy parenchyma is avoided.<sup>[1,16]</sup> In addition to the above, the presented patient demonstrated rapid

progression of the dominant lesion from 14 mm to 22 mm in <1 month, thus it was determined that additional local control with surgical resection would be beneficial. After a 15-month follow-up period, no radiographic evidence of radiation necrosis or intraoperative dissemination/leptomeningeal involvement is present; in fact, intracranial control has been excellent and there is no evidence of recurrence at the site of resection.

## CONCLUSION

The presented case provides a unique presentation of ASPS with multiple, synchronous brain metastases without evidence of lung metastasis. Aggressive local management of brain metastases with surgery and SRT, in addition to ongoing ICI followed by surgical resection of the primary lesion, has thus far led to disease control. This report supports aggressive local therapy including surgery and SRT for symptomatic brain metastases from ASPS. Patients with similar presentations may warrant consideration for clinical trials given the rarity of metastatic ASPS and the potential for good outcomes with aggressive, early treatment of brain metastases. Additional studies are necessary to clarify optimal management strategies for patients with ASPS brain metastases.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Asher AL, Burri SH, Wiggins WF, Kelly RP, Boltes MO, Mehrlich M, *et al.* A new treatment paradigm: Neoadjuvant radiosurgery before surgical resection of brain metastases with analysis of local tumor recurrence. *Int J Radiat Oncol Biol Phys* 2014;88:899-906.
2. Chen AP. Testing Atezolizumab in People with Advanced Alveolar Soft Part Sarcoma; 2020.
3. D'Angelo SP, Shoushtari AN, Agaram NP, Kuk D, Qin LX, Carvajal RD, *et al.* Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol* 2015;46:357-65.
4. 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;5:100.
5. Howard BA, Rubenstein JD, Lewis AJ. Case report 371: Alveolar soft parts sarcoma (brain and thigh). *Skeletal Radiol* 1986;15:468-72.
6. Kim JR, Moon YJ, Kwon KS, Bae JS, Wagle S, Kim KM, *et al.* Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. *PLoS One* 2013;8:e82870.
7. Lewin J, Davidson S, Anderson ND, Lau BY, Kelly J, Tabori U, *et al.* Response to immune checkpoint inhibition in two patients with alveolar soft-part sarcoma. *Cancer Immunol Res* 2018;6:1001-7.
8. McLaughlin J, Han G, Schalper KA, Carvajal-Hausdorf D, Pelekanou V, Rehman J, *et al.* Quantitative assessment of the heterogeneity of PD-L1 expression in non-small-cell lung cancer. *JAMA Oncol* 2016;2:46-54.
9. Mitsis D, Francescutti V, Skitzki J. Current immunotherapies for sarcoma: Clinical trials and rationale. *Sarcoma* 2016;2016:9757219.
10. Ng VY. Neoadjuvant Durvalumab and Tremelimumab Plus Radiation for High Risk Soft-Tissue Sarcoma (NEXIS); 2020.
11. Palmer JD, Sebastian NT, Chu J, DiCostanzo D, Bell EH, Grecula J, *et al.* Single-isocenter multitarget stereotactic radiosurgery is safe and effective in the treatment of multiple brain metastases. *Adv Radiat Oncol* 2020;5:70-6.
12. Paoluzzi L, Maki RG. Diagnosis, prognosis, and treatment of alveolar soft-part sarcoma: A review. *JAMA Oncol* 2019;5:254-60.
13. Patel KR, Martinez A, Stahl JM, Logan SJ, Perricone AJ, Ferris MJ, *et al.* Increase in PD-L1 expression after pre-operative radiotherapy for soft tissue sarcoma. *Oncoimmunology* 2018;7:e1442168.
14. Patel SP, Kurzrock R. PD-L1 expression as a predictive biomarker in cancer immunotherapy. *Mol Cancer Ther* 2015;14:847-56.
15. Portera CA, Ho V, Patel SR, Hunt KK, Feig BW, Respondek PM, *et al.* Alveolar soft part sarcoma: Clinical course and patterns of metastasis in 70 patients treated at a single institution. *Cancer* 2001;91:585-91.
16. Prabhu RS, Patel KR, Press RH, Soltys SG, Brown PD, Mehta MP, *et al.* Preoperative vs postoperative radiosurgery for resected brain metastases: A review. *Neurosurgery* 2019;84:19-29.
17. Ramu EM, Houdek MT, Isaac CE, Dickie CI, Ferguson PC, Wunder JS. Management of soft-tissue sarcomas; treatment strategies, staging, and outcomes. *SICOT J* 2017;3:20.
18. Rekhi B, Ingle A, Agarwal M, Puri A, Laskar S, Jambhekar NA. Alveolar soft part sarcoma revisited: Clinicopathological review of 47 cases from a tertiary cancer referral centre, including immunohistochemical expression of TFE3 in 22 cases and 21 other tumours. *Pathology* 2012;44:11-7.
19. Salvati M, Cervoni L, Caruso R, Gagliardi FM, Delfini R. Sarcoma metastatic to the brain: A series of 15 cases. *Surg Neurol* 1998;49:441-4.
20. Tao X, Hou Z, Wu Z, Hao S, Liu B. Brain metastatic alveolar soft-part sarcoma: Clinicopathological profiles, management and outcomes. *Oncol Lett* 2017;14:5779-84.
21. Wang CH, Lee N, Lee LS. Successful treatment for solitary brain metastasis from alveolar soft part sarcoma. *J Neurooncol* 1995;25:161-6.
22. 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;20:837-48.
23. Williams A, Bartle G, Sumathi VP, Meis JM, Mangham DC, Grimer RJ, *et al.* Detection of ASPL/TFE3 fusion transcripts and the TFE3 antigen in formalin-fixed, paraffin-embedded tissue in a series of 18 cases of alveolar soft part sarcoma: Useful diagnostic tools in cases with unusual histological features. *Virchows Arch* 2011;458:291-300.

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