

Effective treatment of advanced alveolar soft part sarcoma with sunitinib

A case report

Chenyang Ye, MM^b, Ji Wang, MD^{c,d}, Wenshan Li, MM^a, Mingjing Yuan, MD^a, Ying Chai, BS^{a,*}

Abstract

Rationale: Alveolar soft part sarcoma (ASPS) is a very rare soft tissue sarcoma. ASPS often occurs in deep soft tissues of the lower extremities, and develops into metastatic diseases. Chemotherapy is considered to be ineffective in patients with ASPS, which constitutes a very important clinical challenge. The strategy for ASPS treatment still requires clarification in order to improve survival outcome. Patients concerns: A 19-year-old female patient presented with a 5-year history of painless lump in the left knee and 4-day cough. Her previous medical history was unremarkable. Menstruation and family history were also normal in this patient, whose physical examination and laboratory test results showed no abnormalities.

Diagnosis: ASPS was confirmed by clinical manifestations, radiological data and pathological diagnosis of the biopsy of left knee.

Interventions and outcomes: This patient received circulating tumor DNA detection and only a mutation of the SMARCA4 gene was detected. The patient received sunitinib treatment (37.5 mg once daily) for 15 months and showed partial regression of lung metastatic lesions and stabilization of brain metastases. She achieved 15 months of progression free survival.

Conclusions: Sunitinib is effective for the treatment of advanced ASPS with lung and brain metastases. The current patient had long-term progression free survival under sunitinib administration.

Abbreviations: ASPS = alveolar soft part sarcoma, CT = computed tomography, ctDNA = circulating tumor DNA, FDG-PET = 18F-fluoro-deoxyglucose-positron emission tomography, H&E = hematoxylin and eosin, MRI = magnetic resonance imaging, RTK = receptor tyrosine kinase, TKI = tyrosine kinase inhibitor.

Keywords: alveolar soft part sarcoma, metastasis, progression free survival, sunitinib

1. Introduction

Alveolar soft part sarcoma (ASPS) is a very rare malignancy, with a reported yearly incidence of 0.5 per 100,000 individuals; ASPS has a controversial histogenesis, mainly occurring in deep soft tissues of the extremities in young patients.^[1] To some extent, the clinical behavior of ASPS is indolent with slow progression, but it is devastating once developed into an extensive metastatic

disease, commonly involving the lungs, bone, liver, soft tissue, and brain.^[2] Metastasized ASPS is incurable, and the affected patients show unfavorable prognosis despite prolonged overall survival. Chemotherapeutic treatment has been proven to be inefficient in patients with ASPS. Therefore, the clinical treatment of ASPS remains very challenging. This is a case report of a patient with advanced ASPS showing response to the multi-targeted receptor tyrosine kinase (RTK) inhibitor sunitinib, with partial regression of lung metastases and stabilization of brain metastases.

Editor: N/A.

Chenyang Ye and Ji Wang These authors contributed equally to this work.

The authors have no conflicts of interest to disclose.

^a Department of Thoracic Surgery, Second Affiliated Hospital, ^b Cancer Institute (Key Laboratory of Cancer Prevention & Intervention, National Ministry of Education; Provincial Key Laboratory of Molecular Biology in Medical Sciences), Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou, ^c Department of Surgical Oncology, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, ^d Biomedical Research Center and Key Laboratory of Biotherapy of Zhejiang Province, Hangzhou, Zhejiang, China.

* Correspondence: Ying Chai, Department of Thoracic Surgery, Second Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang University, Hangzhou 310009, China (e-mail: chaiy@zju.edu.cn).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2018) 97:51(e13584)

Received: 16 August 2018 / Accepted: 16 November 2018

<http://dx.doi.org/10.1097/MD.0000000000013584>

2. Case report

Standard care is performed, so ethical approval is not applicable in this study. Written informed consent was obtained from the patient.

In October 2016, a 19-year-old Han female presented to the Second Affiliated Hospital, Zhejiang University School of Medicine, with a 5-year history of palpable and painless mass in the left knee and cough for 4 days. Her previous medical history was unremarkable. Menstruation and family history were also normal in this patient, whose physical examination and laboratory test results showed no abnormalities. Enhanced magnetic resonance imaging (MRI) revealed a 54.5 mm × 33.8 mm × 77.3 mm soft tissue mass on the trailing edge of the left knee (Fig. 1). Then, chest computed tomography (CT) scan showed multiple masses in bilateral lungs, indicating metastatic tumors (Fig. 1). Subsequent 18F-fluoro-deoxyglucose-positron emission tomography (FDG-PET) revealed a significantly hypermetabolic round mass in the left knee as well as round

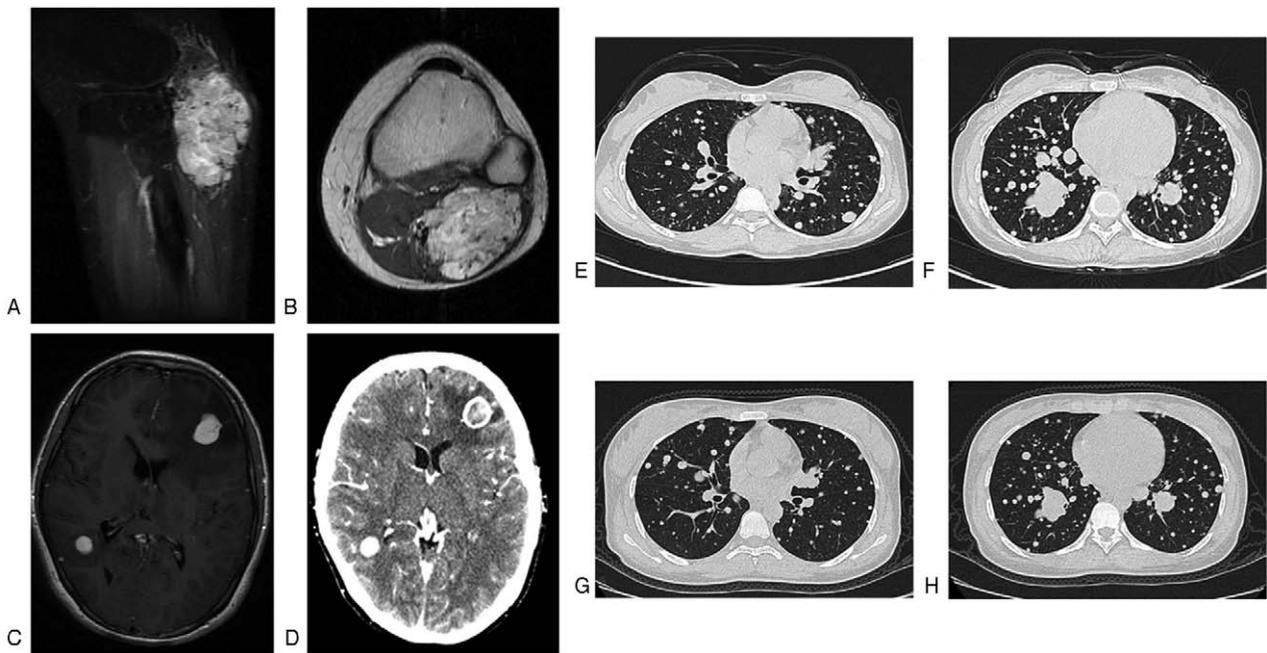


Figure 1. Magnetic resonance imaging (A–D) of left lower extremity and brain metastases, and chest computed tomography (E–H) of lung metastases. (A) Sagittal image showing an irregularly round mass on the trailing edge of the left knee. (B) Axial image of the mass. (C) October 2016 image showing metastatic lesions in the brain. (D) April 2017 image indicating that the brain metastasis remained stable. (E, F) October 2016 image showing multiple bilateral lung lesions. (G, H) April 2017 image showing size reduction of some lesions in bilateral lungs.

masses distributing in bilateral lungs diffusely with mild to high metabolism. Brain enhanced MRI indicated multiple metastatic lesions (Fig. 1). Thus, diagnosis of malignant soft tissue tumor in the left knee with metastasis to the lung and brain was considered. A core biopsy of the soft tissue mass in the left knee was performed, and hematoxylin and eosin (H&E) and immunohistochemistry analysis indicated the diagnosis of ASPS (Fig. 2). Immunohistochemistry indicated strong nuclear positivity to TFE3 in cells.

Circulating tumor DNA (ctDNA) revealed no clinically significant mutations. Only a mutation of the SMARCA4 gene was detected. Based on the patient's multiple bilateral pulmonary lesions and brain metastasis, with chemotherapy known to be inefficient in ASPS, surgical resection, chemotherapy and radiotherapy were not feasible. After informed consent, the patient was treated orally with sunitinib (37.5 mg/day), a multi-targeted receptor tyrosine kinase inhibitor (TKI). Slight rash and diarrhea were observed several times during this treatment.

However, no significant adverse events (grade 3 or higher) were observed.^[3]

Follow-up by chest CT after 6 months of therapy revealed that the bilateral lung mass had shrunk. The patient therefore continued sunitinib treatment. Repeated chest CT revealed partial regression of lung metastases, while brain enhanced CT showed intracranial lesions were stable (Fig. 1). There was no significant change in left knee mass before and after treatment. The patient is currently administered maintenance sunitinib and has been progression free for 15 months.

3. Discussion

ASPS is a rare soft tissue sarcoma, which accounts for less than 1% of all soft tissue malignancies.^[4] Although ASPS mostly grow slowly, it is greatly inclined to metastasize, typically to the lungs, bone, liver, soft tissue, and brain.^[2] Normally, ASPS is characterized by the unbalanced recurrent translocation t (X;

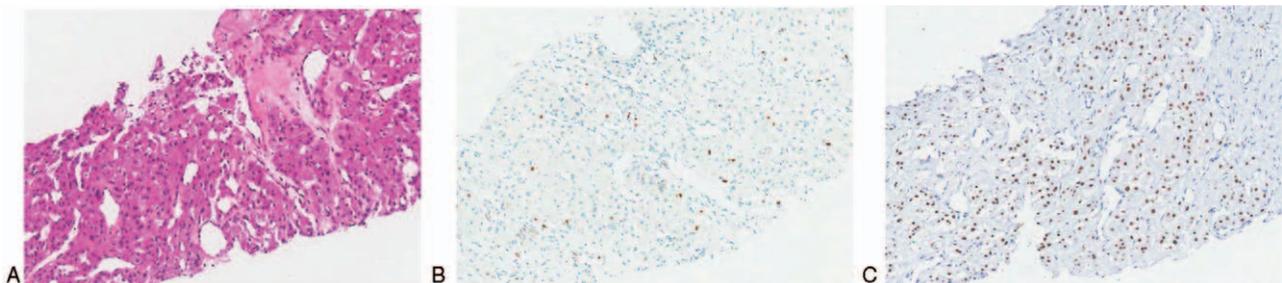


Figure 2. Pathological assessment revealing the primary lesion in the left lower extremity to be alveolar soft part sarcoma. (A) Hematoxylin and eosin (H&E) staining (magnification $\times 100$). (B) A very low Ki-67 index was obtained (magnification $\times 100$). (C) Strong nuclear positivity to TFE3 was detected in cells (magnification $\times 100$).

17) (p11; q25), which leads to the ASPACR1-TFE3 fusion protein, resulting in the activation of MET and the downstream signaling.^[5] Fluorescence in situ hybridization for TFE3 gene rearrangement and IHC for nuclear TFE3 positivity are the pathognomonic characteristics of ASPS. In the current case, the tumor cells showed strong and diffuse nuclear positivity for TFE3, in accordance with the diagnosis.

Circulating DNA is degraded DNA fragments in the blood, and originates from primary tumors, circulating tumor cells, or micrometastasis.^[6] Despite challenges regarding the specificity and sensitivity of current detection techniques, ctDNA is considered a real-time biomarker for cancer screening and monitoring, and especially valuable in situations where solid cancer samples are insufficient or too invasive to be obtained. Since ASPS usually has already developed into metastatic disease at presentation, non-invasive diagnosis is advantageous for the affected patients. Currently, no research has reported ctDNA application in ASPS cases. We performed ctDNA detection by using a primary lesion sample to identify any potential meaningful variations. Only a variation of the SMARCA4 gene was detected. Previous reports have revealed SMARCA4 mutations in lung cancer, medulloblastoma and pancreatic cancer.^[7] Mutations of the SMARCA4 gene seem to be mutually exclusive with the activation of the MYC-gene, suggesting that the SMARCA4 and MYC proteins are functionally correlated.^[7] However, the relationship between SMARCA4 variation and ASPS tumorigenesis remains unknown and requires further investigation.

The ultimate prognosis of ASPS is poor and is often characterized by late metastases. Advanced ASPS with distant metastasis are usually not sensitive to traditional radiotherapy or chemotherapy alone. However, metastases excision with or without radiotherapy may achieve better local control.^[2] Targeted therapy is recently recognized as a promising method for advanced ASPS. Gene sequencing has demonstrated an array of potentially therapeutically targetable in ASPS. To this day, PDGFR, EGFR, c-MET and RET have been identified overexpression in ASPS.^[8,9]

ASPS are usually rich in blood vessels and have a distinctive angiogenic phenotype marked by a peculiar tumor-associated vasculature. Besides, some studies have described preclinical in vivo models which demonstrated the feasibility of using an antiangiogenic approach in the treatment of ASPS. Therefore, anti-VEGF drugs is regarded as a promising way to achieve better results for advanced ASPS. Cediranib, a potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases, new trial from England; adult doses have already been established. Since various therapeutically targetable have been identified overexpression in ASPS. Multiple target therapy has also received more attention. Sunitinib is an oral, small-molecule, multi-targeted receptor TKI, which inhibits the kinase activity and signaling of PDGFR, KIT, RET, VEGFR1/2, FMS-like tyrosine kinase 3, macrophage colony-stimulating factor, and platelet-derived growth factor,^[10] thereby exhibiting antitumor and antiangiogenic roles in the processes of tumor growth, metastasis and angiogenesis. Sunitinib was approved for the treatment of advanced renal cell carcinoma and imatinib-refractory gastrointestinal stromal tumors.^[11] It was reported to have promising clinical efficacy in ASPS, constituting a new

strategy for ASPS therapy.^[8,12] The current case achieved 15 months of progression-free survival under sunitinib therapy, revealing promising antitumor effects on ASPS.

In summary, sunitinib was shown to be effective in an ASPS patient with lung and brain metastases. The diagnosis and monitoring of ASPS should be facilitated by improving ctDNA detection methods. To date, the patient is still alive, and has been progression free for 15 months. This study indicates that multi-targeted receptor tyrosine kinase inhibitors could constitute an effective choice for the treatment of ASPS, even in case of brain metastasis and multiple bilateral lung metastatic lesions.

Acknowledgments

Thank you.

Author contributions

Conceptualization: Chenyang Ye, Ji Wang, Ying Chai.

Data curation: Chenyang Ye, Ji Wang, Wenshan Li, Mingjing Yuan.

Formal analysis: Chenyang Ye, Ji Wang, Wenshan Li, Mingjing Yuan, Ying Chai.

Writing – original draft: Chenyang Ye, Ji Wang.

Writing – review & editing: Wenshan Li, Mingjing Yuan, Ying Chai.

References

- [1] Portera CA Jr, Ho V, Patel SR, 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.
- [2] Ogose A, Yazawa Y, Ueda T, et al. Alveolar soft part sarcoma in Japan: multi-institutional study of 57 patients from the Japanese Musculoskeletal Oncology Group. *Oncology* 2003;65:7–13.
- [3] Common Terminology Criteria for Adverse Events v4.0. Cancer Therapy Evaluation Program. 2010. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed on June 14, 2010
- [4] Zarrin-Khameh N, Kaye KS. Alveolar soft part sarcoma. *Arch Pathol Lab Med* 2007;131:488–91.
- [5] Ladanyi M, Lui MY, Antonescu CR, et al. The der(17)t(X;17)(p11; q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. *Oncogene* 2001;20:48–57.
- [6] Aravanis AM, Lee M, Klausner RD. Next-generation sequencing of circulating tumor DNA for early cancer detection. *Cell* 2017;168:571–4.
- [7] Medina PP, Romero OA, Kohno T, et al. Frequent BRG1/SMARCA4-inactivating mutations in human lung cancer cell lines. *Hum Mutat* 2008;29:617–22.
- [8] Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol* 2011;22:1682–90.
- [9] Stockwin LH, Vistica DT, Kenney S, et al. Gene expression profiling of alveolar soft-part sarcoma (ASPS). *BMC Cancer* 2009;9:22.
- [10] Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res* 2003;9:327–37.
- [11] Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884–96.
- [12] Stacchiotti S, Tamborini E, Marrari A, et al. Response to sunitinib malate in advanced alveolar soft part sarcoma. *Clin Cancer Res* 2009;15:1096–104.