

Lingual alveolar soft part sarcoma responsive to pazopanib

A case report

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Abstract

Rationale: The multi-targeted tyrosine kinase inhibitors such as cediranib, sunitinib and pazopanib have been reported to be effective for alveolar soft part sarcoma (ASPS). The efficacy of pazopanib for the patient with lingual ASPS has yet to be reported.

Patient concerns: A 23-year old man presented with articulation disorder and swelling of the tongue. Diagnosis of lingual ASPS was made after incisional biopsy and complete excision of the mass was performed. Three months later, he presented with a protruding mental region.

Diagnoses: Computed tomography revealed mental region mass and lung metastasis.

Interventions: After the failure of combination therapy of doxorubicin and ifosfamide, pazopanib was administered.

Outcomes: Shrinkage of both the mental region and lung mass continued for more than two months, but regrowth was confirmed at the fourth month.

Lessons: Lingual ASPS is an exceedingly rare subset of ASPS with distinct molecular and histological characteristics and appropriate therapy remains to be established. Our findings suggest a possible therapeutic strategy for lingual ASPS.

Abbreviations: ASPS = alveolar soft part sarcoma, CK = cytokeratin, CT = computed tomography, FDG = fluorodeoxyglucose, MITF = microphthalmia transcription factor, MRI = magnetic resonance imaging, PDGFR = platelet-derived growth factor receptor, PET = positron emission tomography, PFS = progression-free survival, RT-PCR = reverse transcription polymerase chain reaction, VEGFR = vascular endothelial growth factor receptor.

Keywords: alveolar soft part sarcoma, multitargeted tyrosine kinase inhibitor, pazopanib

1. Introduction

Alveolar soft part sarcoma (ASPS) is a very rare sarcoma which accounts for 0.4% to 1% of all soft tissue sarcomas and typically occurs in adolescent and younger adult patients.^[1] The tumors are found mainly in the deep tissues of the thighs, buttocks, and the abdominal wall, and in the head and neck region, mediastinum, and mammary gland. It is histologically characterized by a pseudoalveolar or organoid arrangement of cells and numerous delicate endothelial-lined vascular channels and septa.

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Although ASPS resembles a wide variety of neoplastic conditions, such as metastatic renal cell carcinoma, paraganglioma, granular cell tumor, and melanoma,^[2] the tumor specific chromosomal translocation der (17) t(X;17) (p11;q25), which causes the fusion of the transcription factor TEF3 located on Xp11.22 with a novel gene at 17q25, named ASPL is diagnostic for ASPS.^[3,4] Chimeric transcription factor caused by the translocation drives the overexpression of genes involved in angiogenesis and metastasis.

Despite its indolent behavior, ASPS has high potential for metastasis to the lungs, bone, liver, soft tissue, and brain. Only curative resection leads to a relatively better prognosis, whereas in cases where this is not possible prognosis is often poor, with a median survival of around 40 months.^[5] Given the known resistance to conventional chemotherapy and radiotherapy, new therapeutic options are strongly needed for advanced ASPS.

Recently, a potential therapeutic effect of molecularly targeted treatments for ASPS has been reported. The gene encoding the c-Met receptor (*MET*) was recently identified as a target of the ASPL–TFE3 transcriptional factor, with upregulation of *MET* expression by TFE3 resulting in increased cell proliferation. This observation has led to the investigation of a new drug targeted against c-Met.^[6] In addition, because of the prominent vascularity of ASPS, the antiangiogenic agent cediranib has been investigated and found to have antitumor activity.^[7]

Lingual ASPS is exceedingly rare and has been thought to be an independent subtype of ASPS, based on its characteristic features. The age for lingual ASPS is much younger than that for ASPS in other anatomical locations, and the lesions are associated with

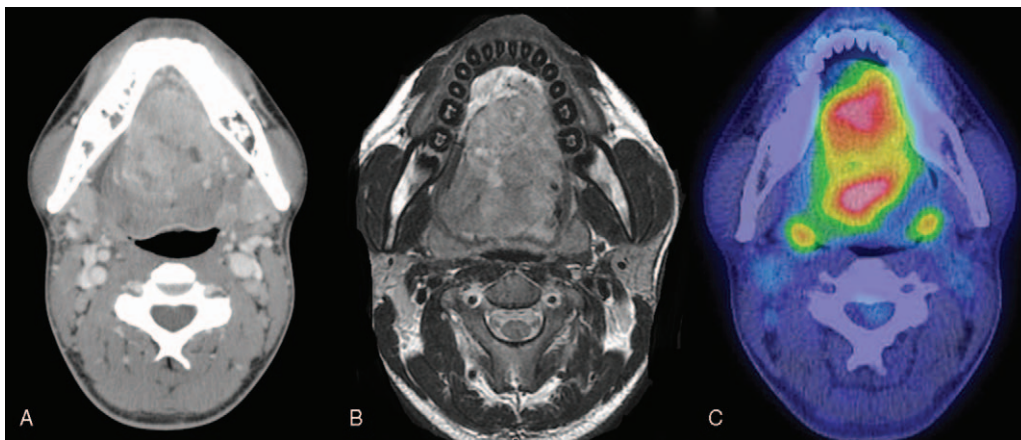


Figure 1. Computed tomography (A) and magnetic resonance imaging (B) revealed a mass lesion in the tongue. C, Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT indicated a high-uptake mass lesion in the tongue.

foci that present a solid ‘non-alveolar’ growth pattern.^[8] The multitargeted tyrosine kinase inhibitor pazopanib has been used in other types of ASPS but its efficacy in lingual ASPS has yet to be reported.^[9] In this study, we report the first case of lingual ASPS with demonstrated clinical response to pazopanib.

2. Case presentation

A 23-year-old man presented in March 2016 with articulation disorder and a reporting swelling of the tongue since 2014. After gradual worsening of the symptoms, he consulted an otolaryngologist in May 2016. The patient had no significant past medical history, was a social drinker, and had smoked until the age of

23 years. There were no reported allergies and no family history of malignant tumors. Though computed tomography (CT) and magnetic resonance imaging (MRI) revealed a mass lesion in the tongue (Fig. 1A & B), scraping cytology and tissue biopsy failed to reach any diagnosis. He was referred to the Kyushu University Hospital (Fukuoka, Japan) for further investigation in late May.

Fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT indicated a high-uptake mass lesion in the tongue (Fig. 1C), and lung nodular shadows that did not accompany FDG uptake. To confirm the diagnosis, incisional biopsy was performed in early June. Histological examination revealed proliferation of tumor cells having oval vesicular nuclei and abundant eosinophilic cytoplasm, arranged in alveolar or organoid pattern (Fig. 2A).

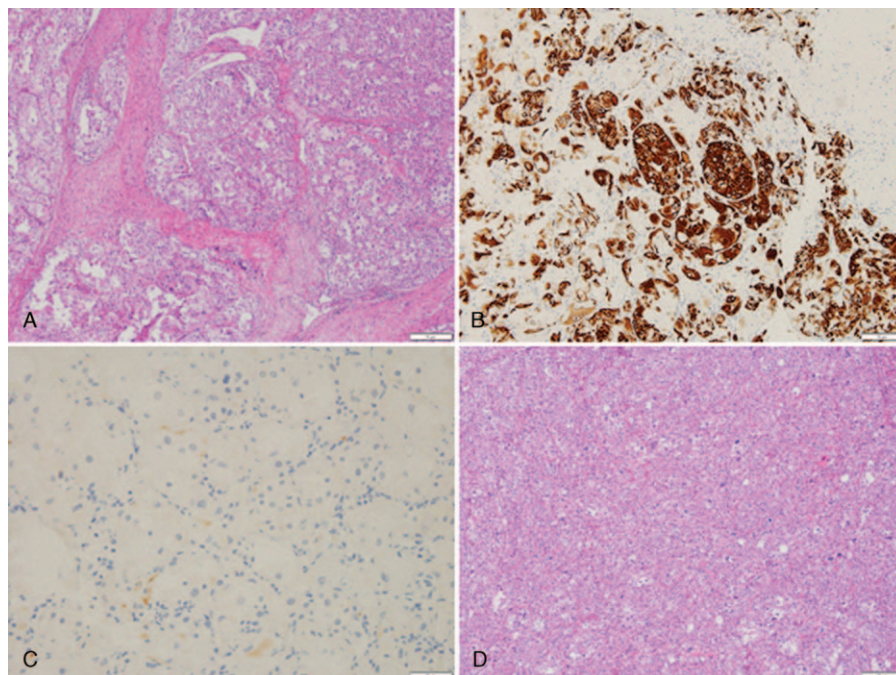


Figure 2. A, Hematoxylin and eosin staining showing proliferation of tumor cells having oval vesicular nuclei and an abundant eosinophilic cytoplasm, arranged in an alveolar or organoid pattern. The tumor cells stained positive for (B) desmin, but negative for (C) cytokeratin (CK) AE1/AE3. D, Hematoxylin and eosin staining of lung metastasis showed alveolar growth with no solid pattern.

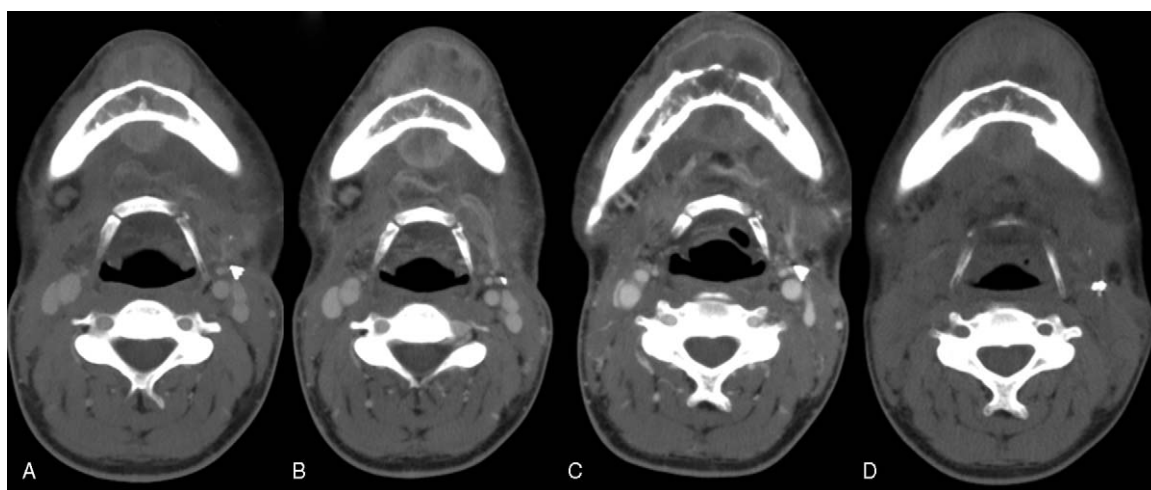


Figure 3. A, Computed tomography revealed protruding mental region. B, Rapid growth of the tumor was observed after the treatment of doxorubicin and ifosfamide. Following administration of pazopanib, shrinkage of the mass was observed (C), but regrowth was confirmed at the fourth month (D).

Immunohistochemical staining showed that the atypical cells were positive for desmin and transcription factor E3, but negative for cytokeratin (CK) AE1/AE3, CAM5.2, synaptophysin and chromogranin A (Fig. 2 B & C). The tumor-specific ASPL-TFE3 fusion gene was confirmed by reverse transcription polymerase chain reaction (RT-PCR) and sequencing, which led to the final diagnosis of lingual ASPS, T2bN0M2, Stage IIB, according to the 7th edition of the TNM Classification of Malignant Tumors.^[10]

Complete excision of the mass was carried out in June, but postoperative CT revealed swelling of the lung nodules and the patient was diagnosed with lung metastasis. Complete excision of the lung lesion was performed in August, with histological examination of the excised nodules showing alveolar growth with no solid pattern (Fig. 2D). Though the curative resection was completed macroscopically, the patient presented with a protruding mental region in late September, with multiple lung nodules again revealed by CT (Fig. 3A), resulting in a diagnosis of ASPS recurrence.

As progression was very rapid, which is atypical for ASPS, combination therapy of doxorubicin and ifosfamide was administered (doxorubicin at 30mg/m² on days 1 and 2; ifosfamide at 2g/m² on days 1–5), but the mass continued to grow rapidly which was confirmed by CT scan (Fig. 3B). The regimen was thus withheld after the first course, and second-line treatment was considered. Since pazopanib is approved by the Ministry of Health, Labor and Welfare in Japan against sarcoma but sunitinib and cediranib are not, pazopanib monotherapy (800mg/day, per oral) was started in late October. The mental region shrunk promptly within 10 days, achieving a reduction ratio of about 20% in maximum diameter, and shrinkage of multiple lung nodules was also observed (Fig. 3C). As the tumor shrunk, the articulation disorder was significantly ameliorated. Pazopanib was well tolerated and the patient experienced no severe adverse events other than Grade 1 malaise, aspartate aminotransferase elevation (56U/l) according to the Common Terminology Criteria for Adverse Events, version 4.0.^[11] The shrinkage of both the mental region and lung mass was maintained for longer than two months. However, a gradually protruding mass in the jaw was observed, and regrowth was confirmed at the 4th month by CT (Fig. 3D). At this point the patient was referred to another hospital to be enrolled on a

clinical trial for a new anticancer agent. The patient provided a signed informed consent regarding the publication of the case details and associated images.

3. Discussion

Lingual ASPS is well-known as a subset of head and neck ASPS, as it was reported in the original description of the disease, but it is exceedingly rare, and to date has been described mainly in case reports.^[8] It is observed in young patients and has focal prevalence of a solid ‘nonalveolar’ growth pattern, which is characteristic of the lingual subtype. In a retrospective study of lingual ASPS, in which the median age of presentation was 5 years, an alveolar growth pattern was usually seen in older patients, with the younger patients showing a solid pattern.^[8] Interestingly, a spectrum of solid growth pattern has been reported, from sheet-like to solid and organoid, which changes over time. The 23-year-old case described in the present study showed focal prevalence of a solid growth pattern consistent with these previous reports. The early diagnosis and small tumor size may explain the relatively good outcome of lingual ASPS, but it is not yet known whether histological differences in these cases have an impact on outcome.

As ASPS tumors appear to be hypervascular on angiography and CT scans, early biopsy is essential to differentiate it from arteriovenous malformation and angioma. FDG-PET/CT findings in ASPS have rarely been reported, but one study indicated that high FDG uptake may indeed be useful in distinguishing ASPS from angioma.^[12] In the current case, although high FDG uptake was seen in primary lesion, the small nodule in the lung, which was suspicious of metastasis, was negative for FDG uptake. CT is generally thought to be more sensitive than FDG-PET/CT in detecting lung metastasis of soft tissue sarcomas, and a significant portion of known pulmonary metastases greater than 1.0cm on CT, are negative for FDG uptake.^[13] In the current case, as the possibility of false negative results from FDG-PET/CT could not be ruled out, the lung nodules were closely monitored by CT scans. These lung nodules were found to grow rapidly and eventually became unresectable.

It has been demonstrated that tumors with the chromosomal translocation der (17) t(X;17) (p11; q25) highly express TFE3.

This protein is a member of the microphthalmia transcription factor (MITF) family and its overexpression is thought to be related to tumorigenesis.^[14] Although ASPS, clear cell sarcoma of soft tissue, and translocation-associated renal cell carcinoma are all defined as MITF-associated tumors, they are morphologically and clinically distinct, yet share certain clinical features such as a disproportionate incidence among younger individuals and a strong propensity to metastasize. MITF-associated tumors are typically refractory to current chemotherapy and new treatment alternatives, such as tivantinib, a selective inhibitor of MET, are now under investigation.^[6]

In soft tissue sarcomas, monotherapy with anthracyclines has been reported to result in response rates of 18% to 25%,^[15] whereas combination regimens of anthracyclines and high-dose ifosfamide have been associated with response rates up to 52%.^[16] Although similar regimens have been examined in ASPS, the currently used chemotherapies must be ineffective given the tumor responses observed.^[17] Radical resection is therefore the therapy of choice in these cases, not only for localized disease, but also for metastatic disease. If curative resection is obtained, good prognosis can be expected, but the prognosis for patients with evidence of metastasis at the time of initial diagnosis is poor, with median survival time for this group reported to be around 40 months.^[5] In the current case, the initially identified lung metastases were completely resected, but both local and metastatic recurrence was subsequently observed, with these lesions proving unresectable. The 5-year recurrence-free survival rate for patients with local disease at diagnosis has been reported to be 84%,^[5] with median progression-free survival (PFS) of Stage IV patients who underwent chemotherapy being reported as 36 months.^[17] Such statistics are indicative of the indolent nature of ASPS, but the current case is distinct in this regard, as the clinical course was very aggressive. As the growth of the tumor was atypically rapid, we expected that cytotoxic chemotherapy may be effective and thus administered a combination regimen of doxorubicin and ifosfamide. Consistent with the findings of previous studies, cytotoxic chemotherapy was ineffective for ASPS.

Portera et al^[5] proposed that newly diagnosed patients with unresectable or metastatic ASPS should be enrolled in phase I and II chemotherapy trials in an attempt to identify novel active agents, and clinical efficacy of molecularly targeted treatments against ASPS has now been reported.^[7,18–20] Because of the prominent vascularity of ASPS, anti-angiogenic agents were expected to be effective in this disease, and this has been shown to be true for bevacizumab.^[18] In addition, 2 recent preclinical investigations have highlighted the role of unregulated TFE3 expression resulting from the ASPL-TFE3 fusion event, which leads to activation of *MET* and its downstream signaling pathway, and which in turn represents a potential target for receptor tyrosine kinase inhibitors.^[19] In a clinical trial of the tyrosine kinase receptor inhibitor cediranib, administered to 46 ASPS patients, objective response rate was 35%.^[7] In other trial, Sunitinib malate was administered to fifteen ASPS patients, and the median PFS reached 19 months.^[20] Although these data are preliminary, the observations are promising and further investigation is needed in the future.

The small-molecule pazopanib is a multitargeted tyrosine kinase inhibitor, with activity against vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, and platelet-derived growth factor receptor (PDGFR).^[21] In the PALETTE trial, pazopanib achieved significantly longer PFS than placebo, with a median PFS of 4.6 months (95% CI 3.7–4.8) for pazopanib compared with

1.6 months (0.9–1.8) for placebo [hazard ratio (HR) 0.31; 95% CI 0.24–0.40; $P < .0001$], and the drug has thus become an important treatment option for metastatic soft tissue sarcoma.^[22] Pazopanib has also been reported to be effective in ASPS, with one study involving nine patients showing a mean treatment duration of 312 days.^[9] High levels of activated tyrosine kinase receptors such as PDGFR, EGFR, MET family members, and RET have been observed in ASPS.^[23] Though the precise mechanism remains unknown, we speculate that the observation may explain why pazopanib is effective in ASPS.

In summary, the current report is the first to show evidence of clinical efficacy of pazopanib in lingual ASPS, a distinct subset of the ASPS family. The findings suggest not only a possible therapeutic strategy for lingual ASPS, but also contribute to our understanding of the molecular mechanisms of tumorigenesis in this exceedingly rare disease.

References

- Sandberg A, Bridge J. Updates on the cytogenetics and molecular genetics of bone and soft tissue tumors: alveolar soft part sarcoma. *Cancer Genet Cytogenet* 2002;136:1–9.
- Ordóñez NG, Mackay B. Alveolar soft-part sarcoma: a review of the pathology and histogenesis. *Ultrastruct Pathol* 1998;22:275–92.
- Covell DG, Wallqvist A, Kenney S, et al. Bioinformatic analysis of patient-derived ASPS gene expressions and ASPL-TFE3 fusion transcript levels identify potential therapeutic targets. *PLoS ONE* 2012;7:e48023.
- 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.
- 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.
- Wagner AJ, Goldberg JM, Dubois SG, et al. Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: results of a multicenter phase 2 trial. *Cancer* 2012;118:5894–902.
- Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol* 2013;31:2296–302.
- Fanburg-Smith JC, Miettinen M, Folpe AL, et al. Lingual alveolar soft part sarcoma; 14 cases: novel clinical and morphological observations. *Histopathology* 2004;45:526–37.
- Kobayashi E, Kawai A, Chuman H. Pazopanib treatment in alveolar soft part sarcomas. *Ann Oncol* 2015;26:108–10.
- TNM Classification of Malignant Tumours 7th edition. Published: 2009. P157–161. Available online: http://www.inen.sld.pe/portal/documentos/pdf/educacion/13072015_TNM%20Classification.pdf. Accessed October 22, 2017.
- National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Published: May 28, 2009. P23 and P41. Available online: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed October 22, 2017.
- Dong A, Wang Y, Cheng C, et al. CT, MRI, and FDG PET/CT in a patient with alveolar soft part sarcoma. *Clin Nucl Med* 2014;39:265–7.
- Iagaru A, Chawla S, Menendez L, et al. 18F-FDG PET and PET/CT for detection of pulmonary metastases from musculoskeletal sarcomas. *Nucl Med Commun* 2006;27:795–802.
- Davis IJ, Fisher DE. MiT transcription factor associated malignancies in man. *Cell Cycle* 2007;6:1724–9.
- Mouridsen HT, Bastholt L, Somers R, et al. Adriamycin versus Epirubicin in advanced soft tissue sarcomas. A randomized phase II/phase III- study of the EORTC Soft tissue and Bone Sarcoma group. *Eur J Cancer Clin Oncol* 1987;23:1477–83.
- Reichardt P, Tilgner J, Hohenberger P, et al. Dose-intensive chemotherapy with ifosfamide, epirubicin and filgrastim for adult patients with metastatic or locally advanced soft tissue sarcoma: a phase II study. *J Clin Oncol* 1998;16:1438–43.
- Reichardt P, Lindner T, Pink D, et al. Chemotherapy in alveolar soft part sarcomas. What do we know? *Eur J Cancer* 2003;39:1511–6.
- Azizi AA, Haberler C, Czech T, et al. Vascular-endothelial-growth-factor (VEGF) expression and possible response to angiogenesis inhibitor bevacizumab in metastatic alveolar soft part sarcoma. *Lancet Oncol* 2006;7:521–3.

- [19] Tsuda M, Davis IJ, Argani P, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. *Cancer Res* 2007;67:919–29.
- [20] Jagodzińska-Mucha P, Świtaj T, Kozak K, et al. Long-term results of therapy with sunitinib in metastatic alveolar soft part sarcoma. *Tumori* 2017;103:231–5.
- [21] Schutz FA, Choueiri TK, Sternberg CN. Pazopanib: clinical development of a potent anti-angiogenic drug. *Crit Rev Oncol Hematol* 2011;77:163–7.
- [22] van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379:1879–86.
- [23] 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.