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Case Report

Treatment of Alveolar Soft-Part Sarcoma with Bevacizumab: A Case Report and Review of the Literature

Heinz Läubli[1,6], Benjamin Kasenda[1], Daniel Baumhoer[2], Johanna Maria Lieb[3], Christoph Kettelhack[4], Markus Gross[5] and Fatime Krasniqi[1]*

[1]Department of Medical Oncology, University Hospital Basel, Switzerland

[2]Bone Tumor Reference Center at the Institute of Pathology, Switzerland

[3]Department of Neuroradiology, University Hospital Basel, Switzerland

[4]Department of Visceral Surgery, University Hospital Basel, Switzerland

[5]Department of Radiation Oncology, University Hospital Basel, Switzerland

[6]Department of Biomedicine, Cancer Immunology Laboratory, University of Basel, Switzerland

***Corresponding author:** Fatime Krasniqi, Department of Medical Oncology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland, Tel: +41 61 265 5074; Fax: +41 61 265 5316; Email: fatime.krasniqi@usb.ch

Received: October 24, 2014; **Accepted:** November 21, 2014; **Published:** November 24, 2014

Abstract

Alveolar Soft-Part Sarcoma (ASPS) is a rare disease and accounts for approximately 0.5-1% of soft tissue sarcomas. While many localized ASPS in younger adults occur in the lower extremities, patients with advanced stages often present with lung and central nervous system metastasis. ASPS are strongly vascularized tumors and few cases, mainly pediatric patients, were reported to respond to anti-angiogenic therapy. We present a case of a 29-year old malepatient with stage IV ASPS with a primary lesion in his right lower leg and pulmonary and cerebral metastasis. After induction treatment (doxorubicin, methotrexate, bevacizumab) and radiotherapy to the cerebral metastasis and the primary site, the disease was stabilized by bevacizumab maintenance therapy over 10 months. Here, we discuss this case within the context of the current literature on ASPS and trials that include anti-angiogenic strategies to treat soft tissue sarcomas.

Keywords: Alveolar soft-part sarcoma; Bevacizumab; Methotrexate

Introduction

Alveolar soft-part sarcoma (ASPS) was first described as a distinct tumor type by Christopherson and Stewart in 1952 [1]. ASPS accounts only for approximately 0.5-1% of soft tissue sarcomas [2] and generally affects patients between 15 and 35 years of age [3,4]. ASPS often occur in the head and neck region in children [3,5]. The deep soft tissues of the thigh or buttock are the primarily involved sites in adults [4,6-10]. Although tumors grow rather slowly, patients often present with advanced disease. Patients presenting with stage IV disease reach nearly two thirds of the analyzed cases in some series [8,9]. In patients with advanced stages, metastases are often found in lungs, but in contrast to other soft tissue sarcomas, ASPS also preferentially metastasizes to the brain [4,6-9].

Histologically, ASPS has a pseudoalveolar appearance with round-polygonal tumor cells separated by fibrous trabeculae [10-12]. Dilated thin-walled vessels are present and the tumor cells typically contain PAS positive and diastase-resistant, membrane bound, rhomboidal crystals and pre-crystalline granules [11,12]. These pre-crystalline granules contain monocarboxylate transporter 1 and CD147 [13]. ASPS is characterized by the unbalanced translocation del (17) t (X; 17) (p11; q25) that leads to the fusion of the N-terminal region to the *ASPL* gene (17q25) to the C-terminal region of the transcription factor E3 (TFE3) located on Xp11 [14]. This fusion results in ASPL-TFE3 type 1 or type 2 transcripts and proteins that function as aberrant transcription factors and activate MET signaling [14,15]. Although not entirely specific, the detection of TFE3 by immunohistochemistry is therefore a useful tool in the diagnosis of ASPS [16].

Case Report

A 29-year old male patient presented with progressing fatigue and vertigo to the medical outpatient department. On examination,

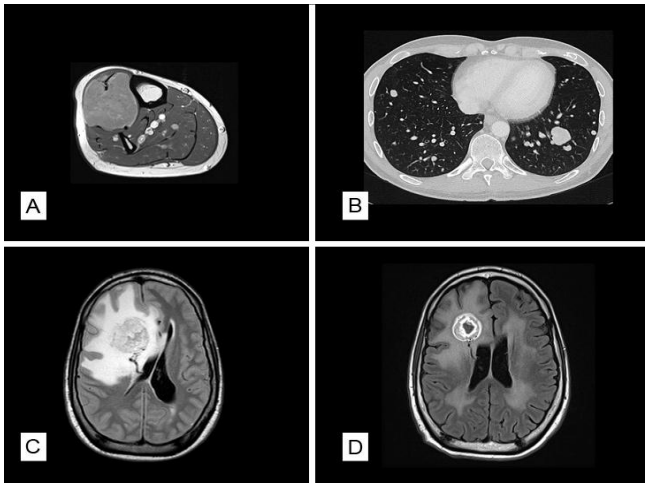

Figure 1: Magnetic imaging and computed tomography.
Initially, the MRI of the lower right leg showed a contrast material-enhancing lesion lateral of the tibia (A). Multiple 2-3 cm large lesions were found within the lung by computed tomography of the chest (B). MRI of the brain showed 3 lesions with the largest being depicted here (C and D, fluid attention inversion recovery, FLAIR). Before radiotherapy and start of anti-angiogenic therapy, the lesion led to a pronounced midline shift, edema and compression of the lateral ventricle (C). Five months after radiotherapy and initiation of anti-angiogenic therapy, no midline shift was observed anymore and the edema regressed significantly (D).

Citation: Läubli H, Kasenda B, Baumhoer D, Lieb JM, Kettelhack C, et al. Treatment of Alveolar Soft-Part Sarcoma with Bevacizumab: A Case Report and Review of the Literature. Sarcoma Res Int. 2014;1(2): 3.

a swelling on the lateral right lower leg was noted. No laboratory abnormalities were found. Imaging of the right leg showed a mass suspicious for soft tissue sarcoma and small lesions in the tibia (Figure 1A). Computed tomography of the thorax, abdomen and pelvis revealed multiple and bilateral pulmonary nodules and a small lesion in the right gluteus maximus muscle (Figure 1B). While magnetic resonance imaging of the brain showed three large supratentorial lesions with a mass effect and deviation of the midline (Figure 1C), an electroencephalogram exhibited no signs of hyperexcitability or an increased risk for seizures. A core needle biopsy from the tumor on the lower leg was performed. The histology showed a well-vascularized malignant tumor with a lobular architecture and PAS positive, diastase resistant inclusions (Figure 2A-C). Immunohistochemically, the cells were negative for S-100 and cytokeratins, but demonstrated a strong nuclear positivity for TFE3 (Figure 2D). Consequently, stage IV ASPS with metastatic spread mainly to the brain and the lungs was diagnosed.

After an interdisciplinary discussion of the case, a whole brain radiation with 30 Gray and a radiation of the primary lesion with 39 Gray were started. Under this treatment the largest brain metastasis diminished in size while the other two intracerebral lesions remained stable (Figure 1D). After four cycles of chemotherapy with doxorubicin (60 mg/m^2 over 24 hours) and high-dose methotrexate (8 g/m^2) in combination with bevacizumab (10 mg/m^2), the disease remained stable and a maintenance therapy with bevacizumab (3 weekly, 10 mg/m^2) was initiated. After 9 weeks of maintenance therapy with bevacizumab, one nodule in the left lower lobe of the lung was growing slowly while all other manifestations of the disease were stable. We decided to treat the singular enlarging lesion in the lung by stereotactic radiation therapy and to continue the maintenance therapy with bevacizumab. The bevacizumab maintenance led to a stabilization of the disease for another 6 months with an excellent quality of life for the patient, who did not experience any side effects. After 6 months, another metastatic lesion in the right tibia plateau was found slightly enlarged, while all other lesions remained stable. The patient is currently undergoing local radiotherapy for this lesion and maintenance therapy with bevacizumab is being continued.

Discussion

Patients with ASPS often present with advanced stage of the disease [4,6-9]. While resection of localized ASPS usually leads to a recurrence free survival of 60-80% at 5 years (4, 8), patients with distant metastasis have a poor prognosis with 5-year survival rates around 20% [8,9]. The prognosis seems more favorable for children and adolescents with ASPS [3]. AJCC stage and tumor size are the main prognostic factors [4,6-9].

We searched PubMed for case series and trials on ASPS (search term "alveolar soft part sarcoma"). Only reports of retrospective case series were found. According to the literature, ASPS seems resistant to conventional chemotherapy [4,6-9]. Frequently used regimens include different combinations of active substances for soft tissue sarcomas such as anthracyclins (doxorubicin or epirubicin), oxazaphosphorines (ifosfamide, cyclophosphamide), vincristine, cisplatin, methotrexate and etoposide [6-9]. In most published case series, no or only a minimal objective response to chemotherapy could be observed [6-9]. Only one patient with lung metastasis achieved a long-term remission after receiving adjuvant chemotherapy

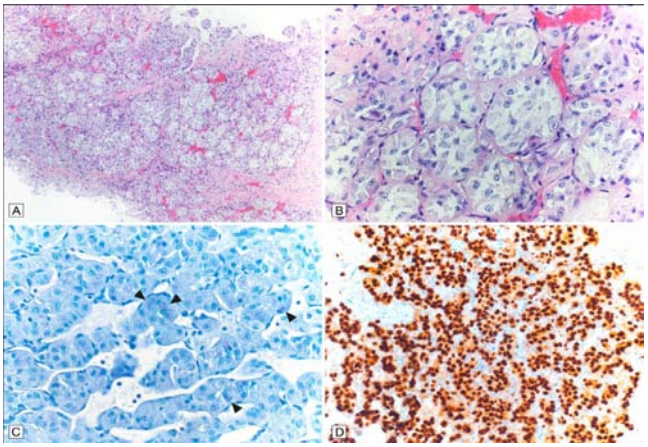

Figure 2: Histological analysis and immunostaining.
Histology shows epitheloid tumor cells arranged in nests and divided by collagenous bands (HE staining, A: x100, B: x400). Focally, PAS positive and diastase resistant deposits are detectable in the cytoplasm (C: Diastase-PAS, x400), immunohistochemistry against TFE3 demonstrates strong and nuclear positivity (D: x200).

with doxorubicin, vincristine and cyclophosphamide and an R2 metastectomy [8]. The available series thus strongly suggest that alternative treatment approaches for patients with advanced stage ASPS are urgently needed.

ASPS are heavily vascularized and it was proposed that angiogenesis is an important driver of ASPS tumor progression and anti-angiogenic agents were reported effective in different cases as treatment for ASPS [17,18]. In a preclinical mouse model of transplanted human ASPS tissue from a patient, a good anti-tumor activity of anti-angiogenic therapy was demonstrated [19]. In a 5-year old boy, bevacizumab was used in combination with celecoxib to downstage an ASPS of the tongue with reduction of the tumor size of 30 % before an R0 resection [17]. In another case report, an 8-year old boy with central nervous system metastasis bevacizumab was used successfully by achieving a partial remission after a previous treatment with interferon-alpha and conventional chemotherapy (doxorubicin, ifosfamide, dactinomycin and vincristine) failed [18]. In a phase I trial that tested the anti-angiogenic Tyrosine Kinase Inhibitor (TKI) cediranib in combination with bevacizumab in patients with advanced soft tissue sarcomas, three patients had an ASPS and they responded well to the treatment [20]. The PALETTE phase III trial tested the activity of the multitargeted tyrosine kinase receptor pazopanibin soft tissue sarcoma [21]. Pazopanib also inhibits angiogenic receptors, but the contribution of ASPS to the cohort was unfortunately not specified [21].

Here, we present a case of a patient with stage IV ASPS treated with an induction chemotherapy containing doxorubicin and methotrexate in combination with bevacizumab after local therapy of the primary lesion and brain metastases by radiation therapy. This treatment was followed by a maintenance therapy with bevacizumab, with disease stabilization over 10 months, except for two lesions that were treated with additional radiation therapy.

Conclusion

Although we cannot exclude spontaneous disease stabilization,

this patient tolerates bevacizumab with virtually no side effects and describes a very good quality of life. Reports of the efficacy of anti-angiogenic agents in ASPS are promising and prospective studies are currently testing anti-angiogenic tyrosine kinase inhibitors cediranib and sunitinib (NCT01337401, NCT01391962) in this rare disease.

References

1. Christopherson WM, Foote FW Jr, Stewart FW. Alveolar soft-part sarcomas; structurally characteristic tumors of uncertain histogenesis. Cancer. 1952; 5: 100-111.
2. Enzinger FM, Weiss SW. Malignant tumors of uncertain type. In: Soft tissue tumors. St Louis. 1995; 1067–1074.
3. Casanova M, Ferrari A, Bisogno G, Cecchetto G, Basso E, De Bernardi B, et al. Alveolar soft part sarcoma in children and adolescents: A report from the Soft-Tissue Sarcoma Italian Cooperative Group. Ann Oncol. 2000; 11: 1445-1449.
4. Lieberman PH, Brennan MF, Kimmel M, Erlandson RA, Garin-Chesa P, Flehinger BY. Alveolar soft-part sarcoma. A clinico-pathologic study of half a century. Cancer. 1989; 63: 1-13.
5. Hunter BC, Devaney KO, Ferlito A, Rinaldo A. Alveolar soft part sarcoma of the head and neck region. Ann Otol Rhinol Laryngol. 1998; 107: 810-814.
6. Reichardt P, Lindner T, Pink D, Thuss-Patience PC, Kretzschmar A, Dörken B. Chemotherapy in alveolar soft part sarcomas. What do we know? Eur J Cancer. 2003; 39: 1511-1516.
7. 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.
8. Portera CAJ, 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: 585–591.
9. Pennacchioli E, Fiore M, Collini P, Radaelli S, Dileo P, Stacchiotti S, Casali PG. Alveolar soft part sarcoma: clinical presentation, treatment, and outcome in a series of 33 patients at a single institution. Ann Surg Oncol. 2010; 17: 3229-3233.
10. Ordóñez, NG, Ladanyi, M. Alveolar soft part sarcoma. In: WHO Classification of Tumours of Soft Tissue and Bone. Fletcher CDM, Bridge JA, Hogendoorn PCW, et al WHO Press. 2013; 218–220.
11. Zarrin-Khameh N, Kaye KS. Alveolar soft part sarcoma. Arch Pathol Lab Med. 2007; 131: 488-491.
12. Fisher C. Soft tissue sarcomas with non-EWS translocations: molecular genetic features and pathologic and clinical correlations. Virchows Arch. 2010; 456: 153-166.
13. Ladanyi M, Antonescu CR, Drobnjak M, Baren A, Lui MY, Golde DW, et al. The precrystalline cytoplasmic granules of alveolar soft part sarcoma contain monocarboxylate transporter 1 and CD147. Am J Pathol. 2002; 160: 1215–1221.
14. Ladanyi M, Lui MY, Antonescu CR, Krause-Boehm A, Meindl A, Argani P, 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.
15. Tsuda M, Davis IJ, Argani P, Shukla N, McGill GG, Nagai M, 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: 919–929.
16. 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: 11–17.
17. Conde N, Cruz O, Albert A, Mora J. Antiangiogenic treatment as a pre-operative management of alveolar soft-part sarcoma. Pediatr Blood Cancer. 2011; 57: 1071-1073.
18. Azizi AA, Haberler C, Czech T, Gupper A, Prayer D, Breitschopf H, 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: 521–523.
19. Vistica DT, Hollingshead M, Borgel SD, Kenney S, Stockwin LH, Raffeld M, Schrump DS. Therapeutic vulnerability of an *in vivo* model of alveolar soft part sarcoma (ASPS) to antiangiogenic therapy. J Pediatr Hematol Oncol. 2009; 31: 561-570.
20. Hong DS, Garrido-Laguna I, Ekmekcioglu S, Falchook GS, Naing A, Wheler JJ, et al. Dual inhibition of the vascular endothelial growth factor pathway: a phase 1 trial evaluating bevacizumab and AZD2171 (cediranib) in patients with advanced solid tumors. Cancer. 2014; 120: 2164–2173.
21. van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2012; 379: 1879–1886.

Sarcoma Res Int - Volume 1 Issue 2 - 2014
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