Original Article

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Surgical Treatment of Alveolar Soft Part Sarcoma of the Extremity: Results of at Least 5 Years of Follow-up

Ekstremite Yerleşimli Alveolar Soft Part Sarkomların Cerrahi Tedavisi: En Az 5 Yıllık Takip Sonuçları

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ABSTRACT

Objective: Alveolar soft part sarcoma (ASPS) is a rare soft tissue tumor that usually affects young patients. Because of the rarity of the disease, most reports relating to ASPS are in the form of case reports or small series.

Methods: We performed a retrospective study to evaluate the clinic features, treatment and outcome in a consecutive series of patients with localized or metastatic ASPS between 2004 and 2014. Demographics, tumor sizes, sites of tumor and extent of disease, treatments provided, progression, and overall survival were evaluated.

Results: Total of 8 patients were identified. The clinical assumptive diagnosis of the doctor making first medical examination was benign soft tissue tumor like hemangioma in 3 cases (37.5%), delaying treatment. The most common loca¬tion of primary tumor was the thigh. The median diameter of the mass was 136.8±76.0 mm (range=4-572 mm). Median overall follow-up was 64 months.

Conclusion: It was found that age greater than 28 years at the time of diagnosis, and the non-thigh placement of the tumor on the limb were found to increase the risk of lung metastasis. It was found that 37.5% of the patients underwent inadequate operation with the pre-diagnosis of vascular-related benign tumors. So, a comprehensive preoperative evaluation for the differential diagnosis of ASPS is needed when interfering with hemangioma-like vascular associated tumors.

Keywords: Alveolar soft part sarcoma, extremity, thigh, prognostic factors, haemangioma

ÖZ

Amaç: Alveoler soft part sarkom (ASPS) genellikle genç hastaları etkileyen nadir görülen bir yumuşak doku tümörüdür. Hastalığın nadir olması nedeniyle, ASPS ile ilgili çoğu çalışma vaka raporları veya küçük seriler şeklindedir.

Yöntemler: Biz 2004 ve 2014 yılları arasında lokalize veya metastatik ASPS hastalarının klinik özelliklerini, tedavilerini ve tedavi sonuçlarını değerlendirmek için retrospektif bir çalışma yaptık. Demografik özellikler, tümör boyutları, hastalığın yerleri ve kapsamı, verilen tedaviler, prognoz ve genel sağkalım değerlendirildi.

Bulgular: Toplam 8 hasta tespit edildi. İlk tıbbi muayene doktorunun klinik ön tanısı, 3 olguda (%37,5) hemanjiyom gibi benign yumuşak doku tümörleri idi ve tedaviyi geciktirdi. Primer tümörün en sık yerleşim yeri uyluktu. Kitlenin ortanca çapı 136,8±76,0 mm (aralık=4-572 mm) idi. Ortalama genel takip süresi 64 aydı.

Sonuç: Hastanın yaşının tanı anında 28 yaşından büyük olması ve tümörün uyluk dışı ekstremite yerleşiminin akciğer metastazı riskini artırdığı tespit edildi. Hastaların %37,5'inin damar ilişkili benign tümör ön tanıları ile yetersiz operasyona tabi tutulduğu tespit edildi. Bu nedenle, hemanjiyom benzeri damar ilişkili tümörler ile ilgili ön tanılar düşünüldüğünde, ASPS'nin ayırıcı tanısı için iyi bir preoperatif değerlendirme gereklidir.

Anahtar Sözcükler: Alveoler sort part sarkom, ekstremite, uyluk, prognostik faktörler, hemanjiyom

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Introduction

Alveolar soft part sarcoma (ASPS) is a very rare type of soft tissue sarcoma (STS). It was first described in 1952 by Christopherson et al. (1).

The incidence of ASPS is 0.5-1% among all soft tissue sarcomas with a very young peak age, and unusual features such as frequent metastasis to the brain (2,3).

ASPS is mostly seen on the trunk and extremities, although it can also occur all over the body such as tongue, uterus, stomach and vagina (4). Tumor progression is painless and slow, as a result of this, distant metastasis is often detected at the time of first medical examination of the patients (5). It mostly metastasizes to the lung, brain, bone and lymph nodes (6).

This tumor is highly-vascularized; therefore, and its murmur can sometimes be misinterpreted as arteriovenous malformations (7,8).

Surgical treatment in non-metastatic tumors is the basis of treatment. Adjuvant radiotherapy and chemotherapy are the options used to provide local control of the tumor and in case of the presence of metastasis (8,9).

In this article, we reported 8 cases of ASPS who were detected among the patients treated due to soft tissue sarcoma in our clinic between January 2004 and January 2014.

Methods

In this article, we performed a retrospective analysis in order to evaluate the demographic characteristics of the patients and the characteristics of the tumor.

Between January 2004 and January 2014, the medical records of 8 patients who were diagnosed as having ASPS pathologically and underwent surgery in the orthopedics and traumatology clinic of our hospital were examined. Demographic data of the patients are summarized in the Table 1. Written informed consent was obtained from the patient's legal custodian or first-degree relatives to use the individual medical records.

All patients underwent wide resection. The mean age of the patients was 33.5± 17 years (19-74 years). The mean follow-up period was 64.0 months (range=21 to 145 months). Every living patient had a follow-up period of at least 5 years.

We noted the anatomical location of the tumor and the depth of the tumor in all patients. If the tumor invasion of the deep fascia was shown in magnetic resonance imaging (MRI) before the operation, the lesion was considered to be deeply localized.

The preoperative MRI scans and the excisional biopsy reports of some patients who underwent surgery at other hospitalswere used and the length, width and depth of the tumor were recorded and the tumor volume (V) was calculated using the cylinder formula.

In order to identify pulmonary or other distant metastasis and local tumor recurrence in two years after surgery, MRI scan of the extremity was performed every three months, and lung computed tomography (CT) and a full-body bone scintigraphy were performed every six months. MRI scan of the extremity was performed every six months, chest CT and bone scan were performed once a year for up to 5 years in the following period. After 5 years, patients were called up for screening once a year. The presence and absence of pulmonary or other organ metastasis or local recurrence in all patients were examined and recorded.

An excisional biopsy was performed in 3 out of 8 patients with a diagnosis of benign tumor. When the pathology reports were examined, no residue was left in any patient but the microscopic surgical margins were all positive. After the transfer to our hospital, 3 patients underwent extensive tumor resection. The other 5 patients were diagnosed as having ASPS preoperatively, and extensive tumor resection was performed.

Table 1. Baseline demographics

Characteristic	Total n=8
Age, year	
Mean ± SD	33.5±17.8
Median (min-max)	27.5 (19.0-74.0)
Age, n (%)	
<28	4 (50)
≥28	4 (50)
Sex, n (%)*	
Female	3 (37.5)
Male	5 (62.5)
Location, n (%)	
Thigh	4 (50)
Non- thigh	4 (50)
Tumor volume, mL	
Mean ± SD	136.8±76.0
Median (min-max)	187.8 (4.0-572.0)
Tumor volume	
<30	3 (37.5)
≥30	5 (62.5)
Pulmonary metastasis, n (%)	
Yes	5 (62.5)
No	3 (37.5)
Exitus, n (%)	
Yes	5 (62.5)
No	3 (37.5)

*Column percentage, SD: Standard deviation

The excision limit was assessed by microscopic examination as positive (tumor located within 1 mm from the edge of the excision) or negative (no tumor located within 1 mm from the edge of the excision).

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 (Chicago IL) package program. In statistical analysis, categorical variables were given as numbers and percentages, and continuous variables as mean ± standard deviation (SD) and median [minimum-maximum (min-max value)] for descriptive analyses. Fisher's chi-square test was used for comparison of categorical variables between groups. Mann-Whitney U test was used for comparison of datasets which were not normally distributed for the variables. Receiver operating curve (ROC) analysis was used to determine cut-off values of age and tumor volume in distinguishing patients with pulmonary metastasis (Figure 1, Table 2). Survival analyses were performed with Kaplan-Meier methods and Log-rank test. $P<0.05$ was considered to be statistically significant.

Results

Demographic Data and Tumor Characteristics of Patients

The mean age of 5 male (62.5%) and 3 female (37.5%) patients was 33.5±17 years (19-74 years). The mean tumor volume was 129±201 mL (4-572 mL). The most common primary tumor localization was thigh (n=4, 50%) (Figure 2a-c), other localizations were hip (n=1, 12.5%), proximal humerus (n=1, 12.5%), fibula (n: 1, 12.5%) (Figure 3a-e) and forearm (n=1, 12.5%).

Metastases

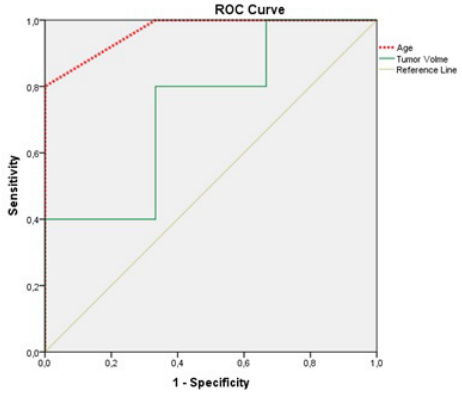

Figure 1. ROC curve of age and tumor volume for distinguishing patients with pulmonary metastasis

Five patients (62.5%) had pulmonary metastasis. Two of these 5 patients had metastasis in vertebrae in addition to lungs; one had liver, and one had liver and brain metastasis at the same time. Of these 5 patients, 3 were male and 2 were female. The mean age of these 5 patients was 40.6 years (range=24-74 years).

Development Time of Metastasis

Only 1 of the 3 patients who had no metastasis at the time of diagnosis developed lung metastasis at 53rd month after the operation.

Chemotherapy And Thoracotomy

IMA (ifosfamide, mesna, adriamycin) was given to 5 patients, and doxorubicin was given to 1 patient. Two patients were not given chemotherapy. No patient underwent thoracotomy because the patients did not accept or the lesion in the lung was inoperable.

Radiotherapy

In 3 patients (cases 5, 7 and 8) , radiotherapy was performed to the operation area, post-operatively. Two patients received radiotherapy because of vertebral metastases and 1 patient because of brain metastasis.

Local Recurrence

No local recurrence was detected in any of the patients.

Overall Survival Rate

The median overall survival time was 61.0 [95% confidence interval (CI)=1.9-120.1] months (Table 3). The 5-year overall survival rate of 8 patients was 62.5% (Figure 4a). The 5-year survival rate in patients without pulmonary metastasis

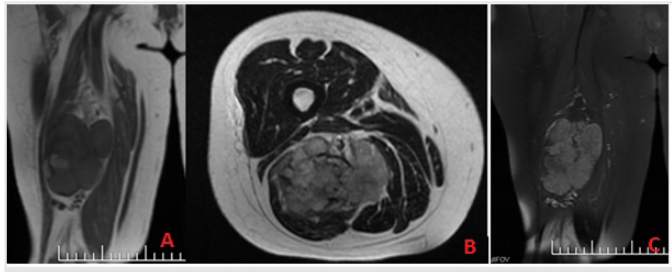

Figure 2. A) MRI images of posterior muscle plans of right lower thigh. The lesion seemed mildly hyperintense on T1-weighted sequences **B)** hypointense on t2-weighted sequences and showed **C)** no prominent contrast enhancement after intravenous contrast-material was injected to a lesion with lobulated contour with a size of approximately 74x39 mm

Table 2. The ability of age and tumor volume to distinguish pulmonary metastasis

	AUC (95% CI)	p	Cut-off	Sensitivity	Specificity
Age	0.967 (0.845-1.000)	0.037	≥28	80%	100%
Tumor volume	0.733 (0.352-1.000)	0.297	≥30	80%	67%

AUC: Area under curve, CL: Confidence interval

Table 3. Median survival times according to factors

	Median OS months (95% CI)
All patients	61.0 (1.9-120.1)
Patients with pulmonary metastases	16.4 (6.8-71.2)
Age ≥28 years	24.0 (0-63.2)
Tumor volüme ≥30 mL	16.4 (6.7-71.2)
Tumor volüme ≥50 mL	24.0 (0-63.2)

CI: Confidence interval, OS: Overall survival

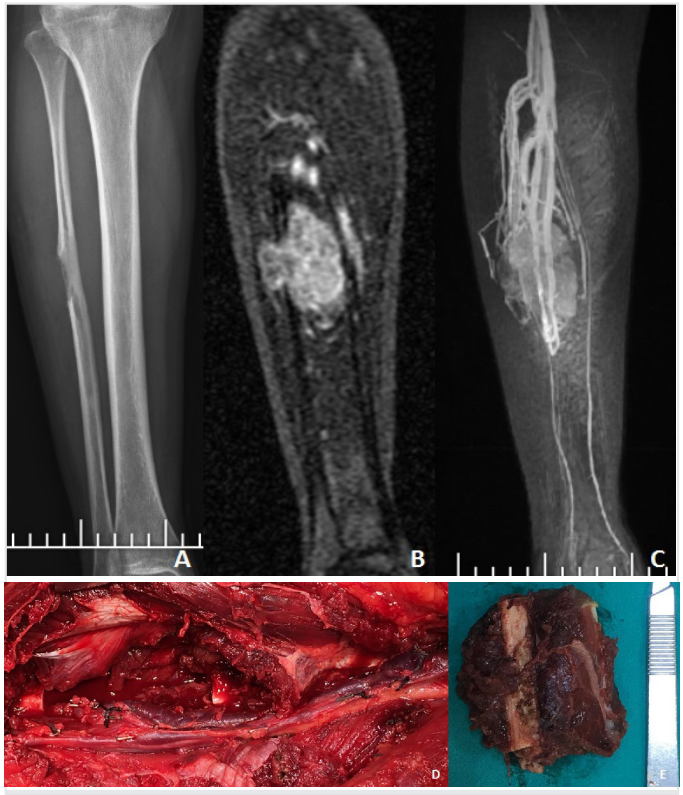

Figure 3. A, B, C) Right cruris direct X-ray and MRI angiography cross sections, a mass lesion was observed between the tibia and the fibula, filling and expanding the soft tissue at the middle part of the cruris. The integrity of the fibular cortex at the mass level could not be clearly selected in some regions. Therefore, it was thought that the mass could have a vascular origin. Fibular artery, tibialis anterior and posterior artery branches could not be clearly distinguished from the current mass. **D, E)** Medical surgery was performed first, intraoperative evaluation revealed that only fibular artery was associated with the tumor. This artery was ligated proximally and sacrificed. The tibial arteries were preserved, then the lateral fibula was osteotomized from the proximal and distal of the tumor and the tumor was removed with wide surgical margins.

was 100% and was only 40% in patients with pulmonary metastasis. However, the difference was not statistically significant (log-rank test; p=0.053; Figure 4b) (Table 4).

The 5-year survival rate for those under 28 years of age was 75% while it was 50% for those over 28 years of age. There was no significant difference in survival rates according to age groups (log-rank test; p=0.171; Figure 4c).

Table 4. Evaluation of baseline demographics according to pulmonary metastasis

	Patients without pulmonary metastases (n=3)	Patients with pulmonary metastases (n=5)	p
Age year			
Mean ± SD	21.7±2.5	40.6±19.5	0.036[1]
Median (min-max)	22.0 (19.0-24.0)	34.0 (24.0-74.0)	
Age n(%)			
<28	3 (100.0)	1 (20.0)	0.143[2]
≥28	0	4 (80.0)	
Sex n (%)*			
Female	1 (33.3)	3 (60.0)	1.000[2]
Male	2 (66.7)	2 (40.0)	
Location n (%)			
Thigh	3(100.0)	1 (20.0)	0.143[2]
Non- thigh	0	4 (80.0)	
Tumor volume mL			
Mean ± SD	55.7±73.7	185.4±226.1	0.297[1]
Median (min-max)	23.0 (4.0-140.0)	115.0 (18.0-572.0)	
Tumor volume			
<30 mL	2 (66.7)	1 (20.0)	0.464[2]
≥30 mL	1 (33.3)	4 (80.0)	
Exitus N (%)			
Yes	2 (66.7)	1 (20.0)	0.464[2]
No	1 (33.3)	4 (80.0)	

*Column percentage, [1]Mann-Whitney U test, [2]Fisher chi-square test, SD: Standard deviation

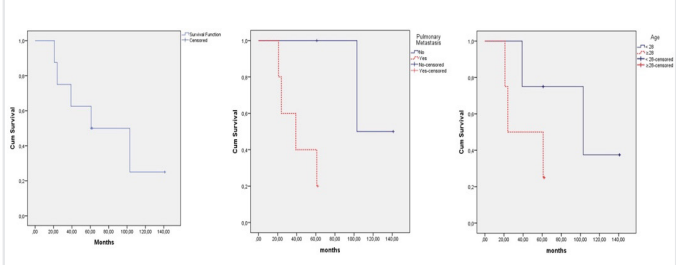

Figure 4. a) Kaplan-Meier curve for overall survival **b)** Kaplan-Meier curves for overall survival according to pulmonary metastasis **c)** Kaplan-Meier curves for overall survival according to age groups

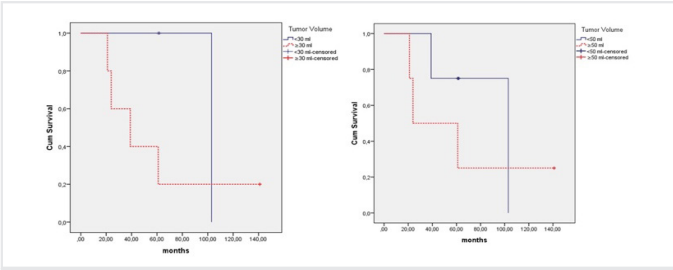

Figure 5. a) Kaplan-Meier curves for overall survival according to tumor volume **b)** Kaplan-Meier curves for overall survival according to tumor volume

In addition, tumor localizations were divided into two groups as thigh and non-thigh localizations. While only 1 of the 4 patients with tumor localized in thigh had metastasis, all of the patients with tumor localized in regions other than thigh were metastatic, but the difference was not statistically significant (p=0.143).

The 5-year survival rate was 100% in patients whose tumor volume was below 30 mL and 40% in patients with tumor volume of 30 mL or above, and there was no significant difference in survival rates (log-rank test; p=0.204; Figure 5a). The 5-year survival rate was 75% in patients with tumor volume below 50 mL and 50% in patients with tumor volume of 50 mL or above, and there was no significant difference in survival rates (log-rank test; p=0.446; Figure 5b).

Discussion

Vascular anomalies are a heterogeneous group consisting of conditions associated with abnormal growth or expansion of the vessels (10). Due to the diversity of these pathological structures and the similar appearance of many of these diseases, the indefinite terminology is prevalent in these lesions thus causes misdiagnoses, inappropriate interventions and treatment delays. Many vascular lesions are called hemangiomas with incorrect use, and the rate of use of misnamed lesion as hemangioma is reported to be as high as 71.3% (11,12).

ASPS is a rare, highly-vascularized malignant soft tissue tumor. Sometimes a murmur can be heard clinically and may be confused with arteriovenous malformations (7,8). Furthermore, according to a recently published study, MRI findings of ASPS may be misdiagnosed as benign tumors, pseudo-tumors, particularly intramuscular benign vascular tumors or vascular malformations (13).

It is estimated that 90% percent or more of vascular anomalies can be diagnosed simply by anamnesis and physical examination. Indications for imaging tests include the diagnosis of atypical lesions, the examination of larger and deeper lesions, and planning treatment for mixed lesions (venous or lymphatic malformations, etc.). An incisional biopsy is essential for the diagnosis before the final treatment plan in cases in whom anamnesis, physical examination and imaging findings do not match. Three of the 8 cases in this study were operated in other centers with a pre-diagnosis of a benign vascular lesion and required bed resection. In case of preliminary diagnosis of a vascular lesion, we recommend a more careful preoperative evaluation for malignancy, and if necessary, referring the patient to a hospital experienced in tumoral diseases (2,5,6,9,12,14)

The aim of this study was to investigate the factors affecting the prognosis of patients with ASPS whichwas a very rare soft tissue sarcoma. It is known that ASPS is an insidious disease and is often metastatic at the time of diagnosis (9,15-17). In ASPS, we examined the risk factors for the presence of lung metastases, and when we considered $p<0.05$ as significant, we could not find a significant result. Because this was a very rare tumor, we analyzed the data with a significance level of $p<0.20$ and found that the age at the time of diagnosis and tumor localization were significant prognostic factors in terms of lung metastasis.

ASPS is typically more common in adolescents and young adults and women aged between 15 and 35 years (15). However, patients can be seen in a wide range of age. Recently, ASPS has been reported in the tongue in a 11-month- girl (18). In our study, the mean age was 33.5 years, but 62% of the patients were male, which was not consistent with the literature. When we divided the patients into two groups as patients over 28 years of age and under 28 years of age, age older than 28 years was found as a risk factor for lung metastasis (Table 3).

ASPS is most commonly seen in the thigh (16,17,19) and it was seen in 50% of the patients in our study. In our study, when we divided the patients into two groups as patients with primary tumor located in the thigh and patients with non thigh localization , non-thigh localization was found as a risk factor for lung metastasis (Table 3).

ASPS has slow growth characteristics, but 20% to 40% of patients have a high metastatic rate at the time of diagnosis. Metastasis occurs primarily in the lung, including the bone and brain. Five-year survival was reported to be between 52% and 88% (8,9). In our study, the rate of metastatic patients was high (62%) and at the time of diagnosis, 5 of the 8 patients had lung metastases. In all cases in our study, the removal of the primary tumor with wide margins could be performed and the 5-year survival rate was 62.5%.

Previously, factors affecting survival in the literature have been reported as stage, surgical margins and tumor size (3,15,17). We reported that age older than 28 years and non-thigh localization of tumor in extremity were the risk factors for lung metastasis Treatment of primary, non-metastatic soft tissue sarcomas is resection with wide margins. Chemotherapy is recommended for advanced, inoperable and/or metastatic soft tissue sarcomas (STS) (20). However, advanced or metastatic ASPS is generally not sensitive to conventional cytotoxic chemotherapy. Current studies have

shown that ASPS is characterized by its sensitivity to the effect of vascular endothelial growth factor receptor (VEGFR)-predominant tyrosine kinase inhibitors (TKIs) compared with other STSs (21,22). Especially in recent years, there have been studies indicating that antiangiogenic agents such as pazopanib, crizotinib, sorafenib, anlotinib, sunitinib and cedirranib could be effective in ASPS (23).

There were some limitations in this study. Firstly, the study was retrospective . Also, since it was a very rare tumor, the number of cases was relatively low. The low number of cases reduced the statistical power of the study, and therefore, the survival rates reported in our article were poor in reflecting the reality.

Conclusion

When the demographic data were analyzed, the average age in our study was similar with the literature, but in contrast with the literature , the tumor was more common in men in our study. It was found that age older than 28 years at the time of diagnosis and the non- thigh location of the tumor inextremity increased the risk of lung metastasis. It was found that 37.5% of the patients underwent inadequate operation with the pre-diagnosis of vascular related benign tumors. So, a good preoperative evaluation for the differential diagnosis of ASPS is needed when interfering with hemangioma-like vascular associated tumors.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Written informed consent was obtained from the patient's legal custodian or first-degree relatives to use the individual medical records.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: Concept: Design: Data Collection or Processing: Analysis or Interpretation: Literature Search: Writing:

Conflict of Interest: No conflict of interest was declared by the authors.

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