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Original Article

Alveolar soft part sarcoma: Clinical presentation, treatment, and outcome in a series of 13 patients

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Abstract

Background: Alveolar soft part sarcoma (ASPS) is a rare soft tissue tumor that typically affects young patients. Similar to other soft tissue sarcomas, it has high pulmonary metastasis ability, whereas compared with other soft tissue sarcomas, it has high brain metastasis ability. Because of the rarity of the disease, most studies on ASPS have been case reports and small series studies.
Method: We performed a retrospective study to evaluate the clinical and pathological features and oncological results in a consecutive series of patients with localized or metastatic ASPS treated at our institute between 1994 and 2014. Demographics, location, severity of disease, treatment provided, progression-free survival, and overall survival were evaluated.
Results: A total of 13 patients were investigated. The most common locations of primary tumor were the thigh ($n = 6$, 47%), followed by the flank ($n = 3$, 23%), forearm ($n = 2$, 15%), and calf ($n = 2$, 15%). Three patients were initially diagnosed as having hemangiomas elsewhere. These patients received unplanned intralesional excision. All the patients received wide tumor resection at our institute. Over the average follow-up period of 80.5 months (range: 36−133 months), the 5-year overall survival rate was 67.5%. Four patients were continuously disease free (31%), six were living with disease (46%), and three died of disease (23%). Of nine patients who presented with distant pulmonary metastasis, two had bony and brain metastases. The 5-year survival rate was 66.7% in patients who received chemotherapy and those who did not ($p = 0.941$).
Conclusion: The treatment strategy for ASPS is wide resection, and postoperative chemotherapy may be crucial for long-term survival. In addition, this type of tumor has a high distant metastasis rate at the time of diagnosis, particularly in the lungs and brain.

Keywords: Alveolar soft part sarcoma; Chemotherapy; Metastasis; Surgery

1. Introduction

Alveolar soft part sarcoma (ASPS) is a rare, clinical, and distinctive soft tissue sarcoma that typically affects young patients and was initially described by Christopherson in 1952.[1] It is generally believed to account for 0.5%−1% of all soft tissue tumors.[2,3] ASPS typically occurs in adolescents and young adults aged 15−35 years, particularly in females, who

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exhibit an incidence rate of 60%.[4,5] The location of the tumor is typically in the deep soft tissue, primarily in the thighs or buttocks; however, it is also found in the arms, breasts, genital area, chest, and retroperitoneal tissue.[6] Radiographically, ASPS is characterized by calcification through plain radiography. In addition, magnetic resonance imaging (MRI) has revealed high signals in both T1- and T2-weighted images and internal and external multilobulated signal changes (Fig. 1).[7,8] Histopathologically, periodic acid-Schiff-positive findings may reveal rhomboid-shaped crystalline material, and ASPS cells also have round, regularly placed nuclei with vesicular chromatin and a prominent central nucleolus (Fig. 2).[9] Genetically, ASPS is caused by an unbalanced translocation, namely der(17)t(X:17)(p11;p25), which results in the formation of an ASPL−TFE3 fusion gene.[10] Because of the rarity of this disease, most studies on ASPS have been case reports and small series studies. In the present study, we first analyzed the patients' demographic and tumor characteristics in Taiwan. Second, we evaluated the factors related to clinical outcomes of ASPS.

2. Methods

The medical records of 23 patients pathologically diagnosed as having ASPS who received surgical treatment between June 1994 and July 2014 were analyzed in our hospital. Those treated at other departments ($n = 10$) were excluded. Two patients were diagnosed as having ASPS in other areas such as the nasopharyngeal area ($n = 1$) and retroperitoneal tissue ($n = 1$). Eight were receiving chemotherapy without surgical intervention. No patients received the treatment protocol in our department. A total of 13 patients were enrolled in this study. The mean age of the patients was 21 years (range: 9−52 years). The mean follow-up period was 80.5 months (range: 36−133 months). We performed a retrospective study to evaluate the patients' demographic and tumor characteristics. In addition, the clinical outcomes were analyzed and compared based on several factors.

The anatomic location and depth of each tumor were evaluated and recorded by the first medical doctor. A tumor was classified as deep if it invaded the deep fascia in the

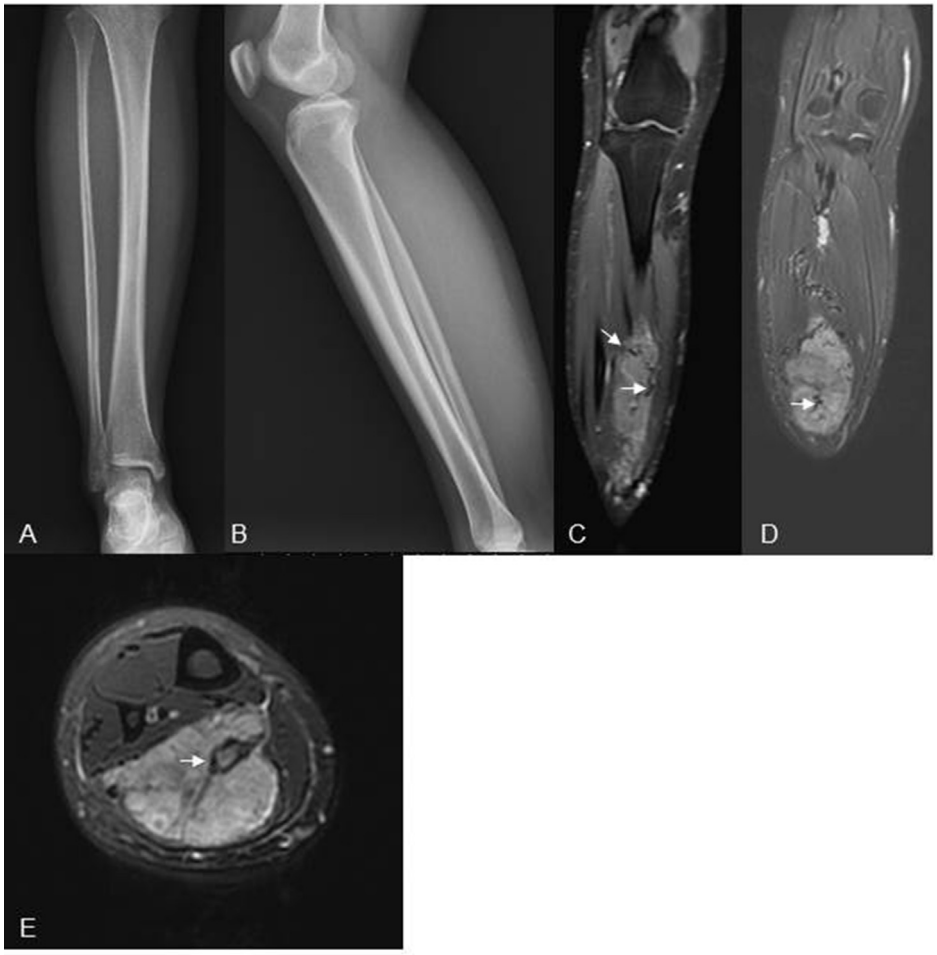

Fig. 1. Image showing a right calf mass present for 16 months in a 19-year-old women. (A) Radiography showing the anterior-posterior view of the right lower leg. No obvious calcification or bone erosion can be observed. (B) Radiography showing the lateral view of the right lower leg. Soft tissue mass over the calf area can be observed. (C) Coronal post-contrast T1-weighted image showing inhomogeneous enhancement of the tumor in the right lower calf with ill-defined margin and tortuous vessel (arrow). (D) Coronal fat-suppressed T2-weighted image revealing the irregular signal tumor with intra-tumoral signal voids (arrow). (E) Axial fat-suppressed T2-weighted image revealing the tortuous vessel with flow voids (arrow).

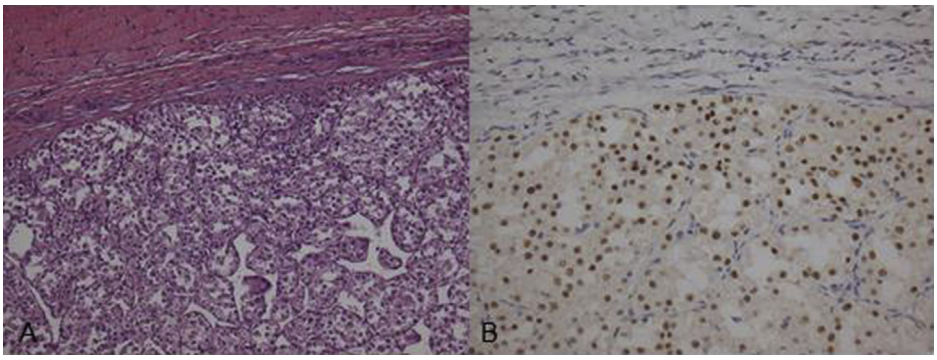

Fig. 2. (A) Alveolar soft part sarcoma. Hematoxylin and eosin staining revealed well-defined nests separated by delicate fibrous tissue. The tumor cells are large with vesicular nuclei, prominent nucleoli, and a granular cytoplasm. Mitoses are exceptional. (B) Transcription factor E3 staining in alveolar soft part sarcoma revealed strong nuclear staining.

imaging examinations performed before surgery. Tumor length, width, and depth were measured on preoperative MRI scans and tumor volume (V) was calculated using the cylinder formula. To identify pulmonary metastasis and local tumor recurrence, plain radiography and chest computed tomography (CT) were performed at the time of diagnosis, every 3 months for the first 2 years postsurgery, every 6 months in the third to fifth years postsurgery, and annually after the fifth year postsurgery. The presence of pulmonary metastasis and local recurrence was observed and recorded.

Of the 13 patients, three were initially diagnosed as having hemangiomas elsewhere and two initially received unplanned intralesional curettage. After transfer to our hospital, the three patients with hemangiomas elsewhere received wide tumor resection. The remaining 10 patients were preoperatively diagnosed as having ASPS in our hospital and received wide tumor excision. The excision margin was confirmed through microscopic examination as positive (tumor within 1 mm from the edge of excision) or negative (tumor not within 1 mm from the edge of excision) (Table 1).

The 5-year survival rate was estimated using the Kaplan−Meier method. A p value of <0.05 was considered statistically significant, and all analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient demographics and tumor characteristics

Of the 13 patients, six were men and seven were women, and their mean age was 21 years (range: 9−52 years). Information on tumor size was available for all patients. The mean volume was 118.8 mL (range: 7.0−306.2 mL). The most common primary tumor locations were the thigh ($n = 6$, 47%), followed by the flank ($n = 3$, 23%), forearm ($n = 2$, 15%), and calf ($n = 2$, 15%).

3.2. Metastasis

Nine patients (69.2%) developed pulmonary metastasis. One of these patients also presented with brain metastasis and another presented with bone metastasis. Of these nine patients, five were male and four were female. Their mean age was 20.8 years (range: 11−52 years). To evaluate age, a cutoff point of 15 years was used to divide the patients into younger and older age groups. In the younger age group, 80% of the patients developed pulmonary metastasis, compared with only 62.5% in the older age group, and the difference was not statistically significant ($p = 0.690$). Furthermore, tumor location was not related to pulmonary metastasis (Table 2). The mean tumor volume increased to 161.62 mL in patients with pulmonary metastasis, compared with 22.31 mL in patients without pulmonary metastasis ($p = 0.016$; Table 2). Based on a diameter of >5 cm as the cutoff point for tumor size, seven patients (87.5%) exhibited pulmonary metastasis in the large tumor group, whereas only 40% of the patients exhibited pulmonary metastasis in the small tumor group ($p = 0.083$; Table 2).

3.3. Timing of metastasis

Of the nine patients with pulmonary metastasis, five exhibited primary pulmonary metastasis (metastasis at initial diagnosis). The mean time span from initial diagnosis to occurrence of pulmonary metastasis was 28.8 months in the remaining three patients (Table 1).

3.4. Chemotherapy and thoracotomy

Seven patients received chemotherapy with an alkylating agent (ifosfamide) and doxorubicin. Four patients received thoracotomies for metastatic pulmonary lesions. One patient (case 3) exhibited primary metastasis and underwent six thoracotomies. Two patients did not undergo thoracotomies for metastatic pulmonary lesions because of poor medication conditions (cases 9 and 10). One patient exhibited lesion regression during chemotherapy (case 13).

3.5. Radiotherapy

Two patients (cases 2 and 13) received local radiotherapy after wide excision. The first patient (case 2) without pulmonary metastasis had approximately 7 mL of tumor over the left

Table 1
Patient profiles and outcomes.

No.	Age (y)	Gender	Initial diagnosis	Location	Tumor volume (mL)	Index surgery	Margin	Chemotherapy	Lung metastasis	Brain metastasis	Metastasis time (months)	Recurrence	Status	Follow-up (months)
1	17	M	ASPS	Flank	150.0	nil	negative	No	Yes	Yes	3	No	DOD	124
2	20	F	ASPS	Forearm	7.0	nil	negative	No	No	No	Nil	No	NED	84
3	11	M	ASPS	Thigh	28.1	nil	negative	Yes	Yes	No	At diagnosis	Yes	AWD	42
4	20	F	Hemangioma	Thigh	240.0	Intralesional excision	negative	Yes	Yes	No	At diagnosis	No	AWD	133
5	11	F	ASPS	Thigh	219.2	nil	negative	Yes	Yes	No	41	No	AWD	124
6	34	M	ASPS	Flank	60.0	nil	negative	No	No	No	Nil	No	NED	95
7	9	F	ASPS	Forearm	8.3	nil	negative	No	No	No	Nil	No	NED	96
8	21	M	ASPS	Thigh	174.0	nil	negative	No	Yes	No	At diagnosis	No	AWD	84
9	52	M	Hemangioma	Thigh	180.0	Intralesional excision	negative	Yes	Yes	No	At diagnosis	Yes	DOD	83
10	24	M	ASPS	Ankle	141.1	nil	negative	Yes	Yes	No	6	Yes	DOD	36
11	13	F	ASPS	Ankle	16.0	nil	negative	No	Yes	No	At diagnosis	No	AWD	60
12	23	F	ASPS	Thigh	14.0	nil	negative	Yes	No	No	Nil	No	NED	26
13	18	F	Hemangioma	Flank	306.2	Intralesional excision	negative	Yes	Yes	No	At diagnosis	Yes	AWD	28

Abbreviations: ASPS = Alveolar soft part sarcoma, AWD = alive with disease, NED = no evidence of disease, DOD = died of disease.

Table 2
Factors related to lung metastasis.

	Patients with lung metastases (n = 9)	Patients without lung metastases (n = 4)	*p*
Age (y/o), mean	20.8	21.5	0.866
Gender, male/female	4/5	3/1	0.327
Tumor volume (mL), mean	161.62	22.31	0.016
Tumor size >5 cm	7 (87.5%)	2 (40.0%)	0.083
Local recurrence	3 (33.3%)	0 (0%)	0.206
Location			
limb	7	3	0.916
axial	2	1	

forearm, and the other (case 13) with pulmonary metastasis had approximately 306.2 mL of tumor over the right buttock. After local radiotherapy, no local recurrence occurred.

3.6. Local recurrence

Of three patients who had local recurrence after wide excision, one (case 9) initially received unplanned intralesional curettage at another hospital and subsequently received wide excision at out institute. However, the tumor recurred 6 months after wide excision. The other two patients (cases 3 and 10) received wide excision after receiving a diagnosis of ASPS at our hospital. Local recurrence occurred at 9 and 13 months postsurgery, respectively. Two patients (cases 9 and 10) died 53 and 36 months after wide excision, respectively.

3.7. Survival rate

The 5-year overall survival rate of the 13 patients was 67.5% (Fig. 3A). The 5-year survival rate for patients without pulmonary metastasis was 100%, compared with only 51.4% for patients with pulmonary metastasis. However, the difference was not statistically significant ($p = 0.184$; Fig. 3B). The 5-year survival rate of patients who underwent chemotherapy and those who did not was 66.7% ($p = 0.941$; Fig. 3C).

4. Discussion

ASPS was originally described by Christopherson in 1952[1] as a relatively large tumor with a tube-shaped nucleolus and eosinophilic cytoplasm. Subsequently, Masson et al.[16] demonstrated the ultrastructural appearance of ASPS with intracytoplasmic crystals. ASPS is a rare disease that accounts for <1% of all soft tissue tumors.[2,3,12] The most common invasive locations are the thighs and buttocks.[6] ASPS primarily affects adolescents and young adults.[4,5] A slight female preponderance is observed in patients aged ≤30 years.[13] In our study, the number of female patients was almost identical to that of male patients (F/M = 6/7).

ASPS exhibits slow-growth characteristics but has a high metastatic rate at the time of diagnosis of 20%−40% .[11] The lungs are the most frequent sites of metastasis through the hematogenous route, followed by the brain and bones.[6] In one study, the incidence of brain metastasis due to ASPS was

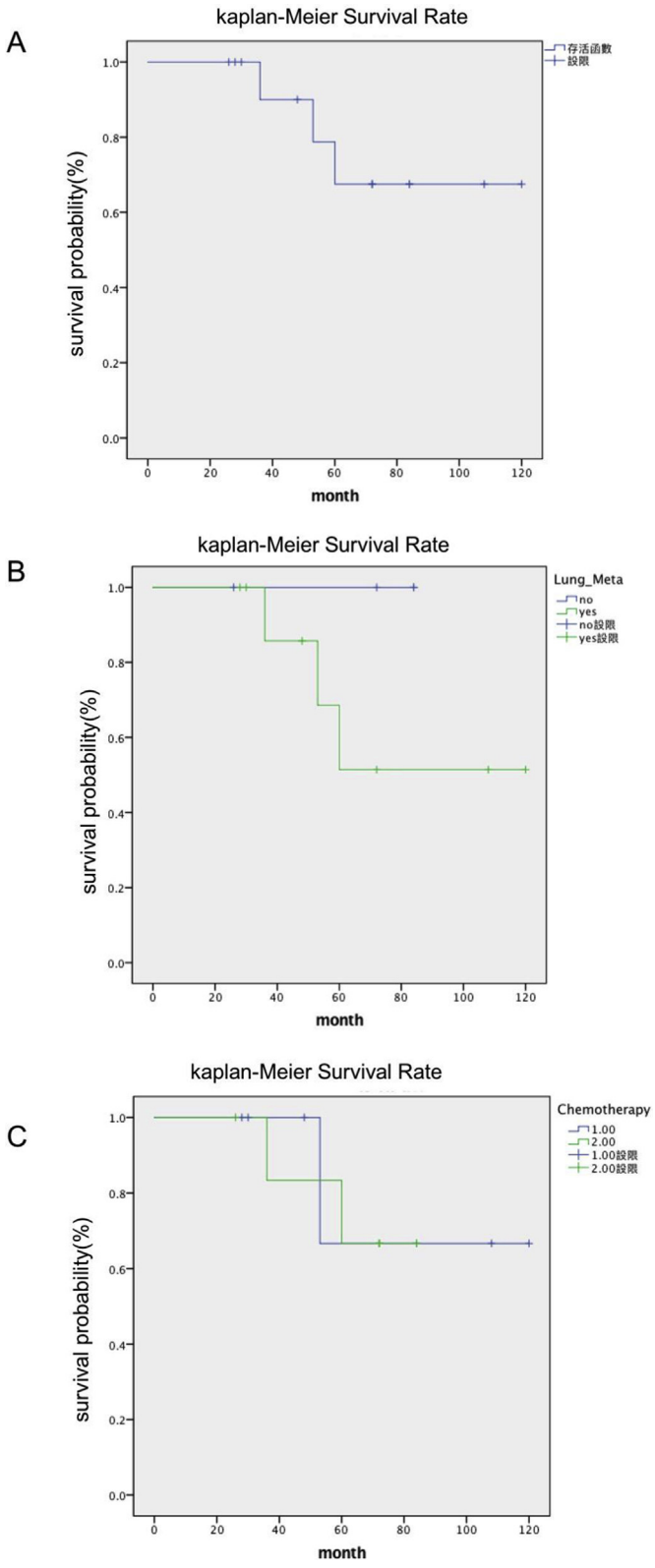

Fig. 3. Kaplan−Meier modeling for the 5-year survival rates of (A) all 13 ASPS patients, (B) patients with ASPS with or without pulmonary metastasis, and (C) patients with ASPS who did and did not receive chemotherapy.

reported to be approximately 30%, and the survival rate was low (median survival of 12 months) after diagnoses of brain metastasis.[13] Nine patients (69.2%) developed pulmonary metastasis in our study; one of these patients also had brain metastasis (7.7%) and another also had bone metastasis (7.7%). The prognoses of chemotherapy were poor for those with brain metastasis because of the failure of several chemotherapeutic agents to cross the blood−brain barrier.[24] One patient with brain metastasis in our study received Gamma Knife treatment, but died 60 months later.

Radiologically, the plane view may reveal soft tissue calcification. ASPS exhibits hypervascular lesions on contrast-enhanced CT or angiography with a dense tumor stain and tortuous, dilated draining veins.[8,9] Because of the hypervascular lesions, making differential diagnoses of hemangioma, arteriovenous malformation, clear-cell sarcoma, metastatic malignant melanoma, and other soft tissue sarcomas with internal bleeding is critical. MRI typically reveals a high signal intensity on T1- and T2-weighted images, and contrast-enhanced MRI reveals multiple peritumoral and intratumoral tortuous signal voids and intense enhancement.[8,9,14,15] In our study, three patients were initially diagnosed as having hemangiomas. Two of these patients (cases 4 and 9) underwent unplanned surgery elsewhere. Subsequently, after rewide excision at our hospital and postoperative chemotherapy, one of them (case 4) was alive with disease status (pulmonary metastasis) after 133 months of follow-up.

Studies have reported that the 5-year overall survival is rate is 52.6%−88% for ASPS (Table 3) and that several factors are related to the outcomes, such as the stage, size, and surgical margin.[13,17−20] Ogura et al.[13] reported a 5-year survival rate of 64% of a patient cohort after surgical resection of ASPS, suggesting that tumor size and American Joint Committee on Cancer stage are related to disease progression. Cho et al.[20] reported that the long-term survival rate was higher in patients with tumors ≤50 mm in diameter than in those with tumors >50 mm in diameter. Ogose et al.[21] reported that the 5- and 10-year survival rates in patients with tumors <50 mm in diameter were 72% and 65%, respectively, whereas those in patients with a tumors >50 mm in diameter were 46% and 9%, respectively. Other studies have reported that a larger tumor size indicates a higher incidence of organic metastasis.[22,23] Based on tumor size, the survival rate was 89% in patients with tumors <50 mm in diameter and 50% in patients with

Table 3
5-Year survival rate of previous reference and out study.

Reference	Year	No. of patient	5-year survival (%)		
			All	M0	M1
Anderson et al.	2005	15	75	NA	NA
Daigeler et al.	2008	11	88	88	–
Pennacchioli et al.	2010	33	69	NA	NA
Koichi Ogura et al.	2012	26	64	100	37
Yong Jin Cho et al.	2014	19	52.6	81	46
Our study		13	67.5	100	68.6

tumors >50 mm in diameter. The local recurrence rate was 37.5% (3/8) for tumors >50 mm in diameter and 0% (0/5) for tumors <50 mm in diameter.

The surgical margin influences the prognosis. Pennacchioli et al.[19] reported that the quality of surgery is basically related to the prognosis of ASPS and demonstrated a 10-year survival rate of 53.4%. Lieberman et al.[3] suggested that if residual tumor cells are still observed over the surgical margin according to pathological reports, the recurrence rate of ASPS is >20%, and thus patients would require more aggressive treatments after surgery. In our series, all the pathological reports revealed negative surgical margins. Sherman et al.[27] suggested that radiation therapy may play a beneficial role in enhancing the local control of limited surgery for ASPS.

The local recurrence rate of ASPS ranges from 11% to 50%.[24,25] In our study, all the patients received wide-margin resection, and the local recurrence rate was 23% (3/13). The survival rate of patients without local recurrence was 90% (9/10), whereas that of patients with local recurrence was 33% (1/3). Two patients (cases 2 and 13) received local radiotherapy after wide excision, and no local recurrence was observed over the surgical site.

No studies have reported significant survival benefits for patients undergoing adjuvant chemotherapy after surgery.[3,26,28,29] Reichardt et al.[29] analyzed 68 patients who received chemotherapy with drugs such as anthracyclines and ifosfamide and demonstrated complete remission in 4%, partial remission in 3%, stable disease in 41%, and progressive disease in 51% of the patients. In our study, six patients received chemotherapy with an alkylating agent (ifosfamide) and an antibiotic agent (doxorubicin), and the results revealed partial remission in 16.7% (1/6), stable disease in 50% (3/6), and death in 33.3% (2/6) of the patients.

The demographics and tumor characteristics of the patients in the present study were similar to those in other studies. The factors that affect clinical outcomes included large tumor size and distant metastasis. The treatment strategy for ASPS is wide resection, and postoperative chemotherapy may be crucial for long-term survival. Because of the radiological presentation, differential diagnoses of ASPS should be considered while treating hemangiomas.

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