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ORIGINAL STUDY

Outcomes of alveolar soft part sarcoma from a regional tumour unit

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We present six cases of alveolar soft part sarcoma (ASPS). All patients were identified from records at our regional institute and treated between 2000 and 2010. ASPS are slow growing highly malignant tumours, often with metastatic spread at initial presentation.

The mean age of the patients was 28.5 years (21 to 36), with four males and two females. Diagnosis was based on radiological and histological features. All patients had primary surgical resection (five wide local excisions, one marginal excision for extensive widespread disease) and adjuvant radiotherapy.

Four lesions involved the lower limb, one involved the upper limb and one originated from the retroperitoneal space. One patient presented late with pulmonary metastases and had marginal excision of the ASPS and died 2.6 years later. Recurrence occurred in two-fifths of the remaining patients at a mean of 6 months. Alveolar soft part sarcoma has a poor prognosis. Our data suggests that patients are managed with an agreed disease staging protocol, radical resection and kept under close surveillance with interval imaging in a specialist bone tumour unit.

Keywords : Alveolar soft part sarcoma; malignant tumours; surgical resection; radiotherapy; recurrence; protocol; surveillance.

INTRODUCTION

Alveolar soft part sarcoma (ASPS), originally described in 1952 by Christopherson *(2)*, is a highly malignant rare form of soft tissue sarcoma *(10)*. It is a slow growing indolent tumour that is not easily identified. It is primarily diagnosed in adolescents and young adults and carries an incidence of 0.5-1.0% of all soft tissue sarcomas. It has a female predilection and commonly presents as a painless swelling which is firm on palpation and well circumscribed. Primary tumours are anatomically distributed in the extremities (60%), trunk (20%), head & neck (12%) and retroperitoneum (8%) (10).

Molecular genetic studies *(7)* have demonstrated an unbalanced translocation, der(17)t(X;17)(p11:q25) causing fusion of the transcription factor TEF3 located on Xp11.22 with a novel gene at 17q25 (ASPL). This creates an ASPL-TFE3 fusion protein and with an antibody directed against the C-terminus of the TFE3, this has resulted in a highly sensitive and specific marker for ASPS *(7,13)*.

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Haematogenous metastatic spread to the lung, brain and bone can occur before initial presentation to a specialist. The proportion of patients presenting with metastatic deposits are as high as 65% in presenting adults and 30% in children *(8)*. Lymphatic metastatic spread is uncommon *(4)*. Metastases have been reported up to 15 years *(10)* after resection of primary tumour, irrespective of documented complete excision and the absence of local recurrence *(9)*. Typically local recurrence is associated with residual disease after incomplete excision *(8)*.

Alveolar soft part sarcoma conveys a poor prognosis. Lieberman et al *(8)* reported survival rates in patients without metastases at 2, 5, 10 and 20 years as 77%, 60%, 38% and 15% respectively. Kayton et al *(6)* reported that despite the occurrence of metastases in 70% of patients, the 5-year overall survival was around 80%.

Primary treatment is aggressive surgical excision of local disease *(8)*, with radiotherapy reserved for microscopic residual disease at the primary site. ASPS is reported to have moderate radiosensitivity *(1)* and is resistant to conventional chemotherapy in adults *(8)*. Studies have suggested that patients receiving chemotherapy and/or radiotherapy have no survival advantage *(6,8)*.

PATIENTS AND METHODS

A retrospective database search was undertaken at a regional bone tumour unit between 2000 and 2010. Clinical and histopathology records were reviewed of all patients identified. Only six cases were identified to have a histological diagnosis of ASPS. There were four males and two females with a mean age of 28.5 years (21 to 36 years). All cases underwent a multi-disciplinary team discussion prior to surgical excision and received adjuvant radiotherapy. Subsequent follow up and recurrence rates of all patients were reviewed.

RESULTS

Clinical Presentation

Primary presentation was a painful mass in two patients (33.3%) and painless swelling in four patients (66.7%). The mean presentation time was 15.8 months ; with five patients presenting within 8 months from the onset of symptoms (83.3%) and one patient presenting with established metastatic cerebral and pulmonary disease at 72 months (16.7%). There was a male predominance in our study group (66.7%). The anatomic distribution of primary tumour in our cohort included the anterior thigh in three patients, the triceps, the soleus and the retroperitoneal space. Although a small population size, this anatomic distribution equates to published reports *(10)*. If the tumour presents in an atypical location it can be misdiagnosed, hence a multi-disciplinary approach is necessary for the diagnosis of ASPS. One patient had distant metastases at initial presentation. Patient demographics are summarised in Table 1.

Management

Our protocol consisted of staging computed tomography (CT), technectium-99 bone scan, brain magnetic resonance imaging (MRI) and tissue biopsy. Two patients had ultrasound scans of their lesions prior to referral to our institute with a provisional diagnosis of arteriovenous malformation and rhabdomyosarcoma, which reiterates the dif-

Table 1: Summary of patient presentation & demographics

Patient	Sex	Age	Presenting Symptoms (mass)	Duration of Symptoms	Site
1	F	34	Painful	1	Left triceps
2	M	29	Painless	4	Right soleus
3	M	26	Painful	72	Left vastus medialis
4	M	36	Painless	8	Right adductors
5	F	25	Painless	2	Retroperitoneal
6	M	21	Painless	8	Left quadriceps

ficulty in diagnosing these tumours. All six patients underwent primary surgical resection with adjuvant radiotherapy to any residual disease. Five patients with extremity tumours had wide local excisions (WLE) from the upper limb (triceps) and lower limb (soleus, vastus medialis and adductors). One patient with infiltrative inguinal disease had marginal excision of ASPS from the quadriceps and inguinal lymph node block dissection. The mean follow up after surgery was 23 months (9 to 58 months) although this figure is limited by failure of patients to attend scheduled clinics and hence were lost to follow up. Average length of inpatient stay was 4 days. No metastectomies were performed. We had no significant post-operative complications.

Radiological Features

Both MRI and CT of the tumours demonstrated presence of intra- and peri-tumoral vessels, with flow voids at the peripheral and central parts of the tumour (83.3%), which are distinct imaging features of ASPS. Most of the tumours had sharp margins with occasional poorly defined margins at both superior and inferior poles in the presence of high vascularity. Such highly vascular findings are also demonstrated on angiography, but this is not part of our routine imaging protocol. Magnetic resonance T1-weighted (MR T1W) images show that ASPS is either isotense, or more commonly hypertense to muscle *(5)* (Figure 1). Some tumours also demonstrated lobulated contours and nodular internal architecture. Other features after contrast administration include intense to moderate enhancement and occasional thick enhancing peripheral rims with around central necrosis *(9)*.

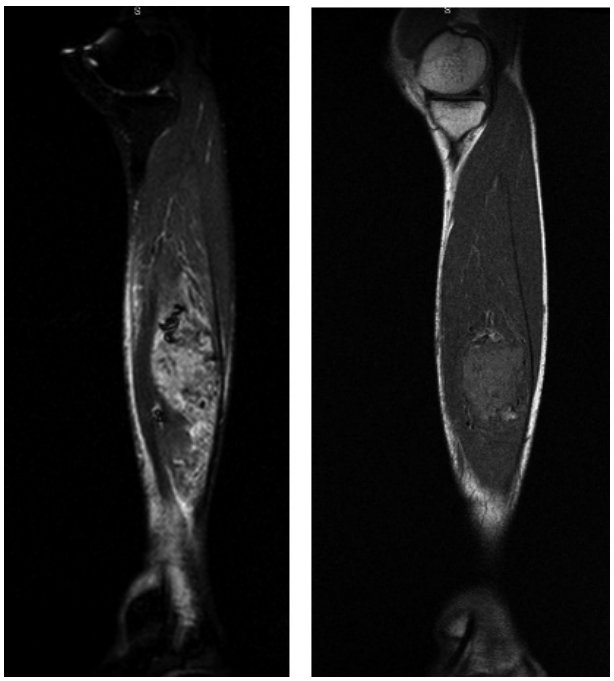

Figure 1. — MRI T2W (a) and (b) sequences : demonstrating typical alveolar appearances of the tumour in the soleus muscle bulk.

Histological findings

There was very little variation from case to case, as is witnessed in other reported series *(3)*. Pathological specimens were analysed with Haemotoxylin & Eosin (H&E) staining in paraffin embedded tissue samples. The mean tumour size at resection was 9.4 × 9.4 × 6.3 cm. There was no correlation between the size of the lesion and duration of symptoms. Tumour morphology governed the main diagnostic features*(14)*. Tumours were composed of nests of classic large cells with centralised areas of necrosis and a pseudo-alveolar appearance. The histological diagnosis of alveolar soft tissue (ASPS) can be difficult to establish. Morphologically, ASPS may be misdiagnosed as malignant epithelial tumours, primary or metastatic adenocarcinoma, paraganglioma and Xp11 neoplasms with melanocytic differentiation (which was recently recognized). Histological appearances may resemble renal adenocarcinoma *(1)*, due to prominent clear cell changes with cells having distinct borders with abundant clear cytoplasm that results in an epithelioid appearance *(3)*. Microscopic findings show a uniform pattern characterized by a pseudo-alveolar or organoid arrangement of polygonal tumour cells separated by fibro-vascular septa and delicate capillary sized vascular channels (Figure 2) *(9)*.

Immunohistochemical analysis of ASPS, demonstrate they are generally negative for epithelial markers (cytokeratins and epithelial membrane antigen) ; negative for specific neuroendocrine markers (chromogranin A and synaptophysin) ;

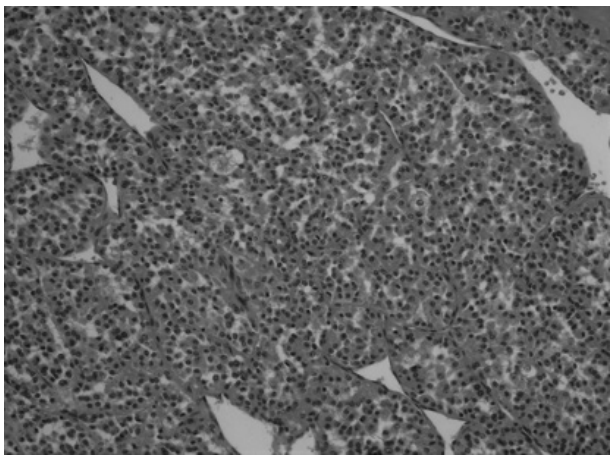

Figure 2. — Microphotograph showing the classical alveolar architecture (4x magnification ; H&E stain).

and negative for specific melanocytic markers (HMB45 and Melan-A). Neurone-specific enolase and vimentin are non-specific markers that can be detected in up 30-50% of cases (3). ASPS can thus be distinguished from renal cell carcinoma by expression of ASPL-TFE3 fusion gene and lack of cytokeratin expression.

Rates of Recurrence

Two patients out of five, (40%) developed post-operative metastatic disease at a mean of 6 months (range 1 to 11 months) despite having complete resection margins after surgical resection. The mean survival time was 2.6 years (Table 2). One patient had pulmonary metastases (20%) and both patients had cerebral metastases (40%) at time of recurrence. One of these patients received additional chemotherapy following tumour excision for recurrence of skin metastases at the scar site. One patient presented late with distant disease spread and received palliative surgery only. This patient is therefore not accounted for in our reported recurrence rates.

DISCUSSION

ASPS is a challenge to diagnose and management is often neglected due to its low incidence *(11)* and variable presentation. As evidenced by the radiological findings, these tumours are highly vascular and although not observed in our series, clinicians should be aware that they occasionally present with bruits.

Our results concur with published reports that most patients present with painless swelling. In contrast to reported literature, within our group there were more males than females however, this can be accounted for by the small number of patients in our study and is therefore not an absolute reflection of disease prevalence. Current literature suggests there is a genetic predisposition for females *(3)*.

The referrals received at our unit suggest that interpretation of radiological features of ASPS can be difficult with one third of cases reported incorrectly at local units. This may be attributed to the rarity of this disease and highlights the potential pitfalls in diagnosis. In cases when tumour is suspected we recommend early involvement of specialist centres. The need for thorough radiological staging was highlighted by studies reported by Portera et al *(10)* and Kayton et al *(6)*, with patients presenting with cerebral metastases having concurrent lung lesions. Hence imaging protocols should be established in units managing these tumours.

There were three deaths in our series. Two of these occurred in a patient with extensive metastatic spread, and the other in a delayed presentation that received palliative surgery. Studies *(6,8)* have shown that large tumours (lesions >5 cm) had an adverse

Table 2. — Summary of patient treatment, recurrence and death

Patient	Procedure	Post-Radiotherapy	Follow up	Recurrence	Mortality
1	WLE	Y	12	Y	N
2	WLE	Y	9	N	N
3	WLE	N	20	Y	N
4	WLE	Y	12	N	N
5	WLE	Radical	24	N	N
6	Marginal excision	Radical	58	Y	Y

effect on survival in addition to metastases. The mean tumour size in our study was almost double this and is likely to have affected the outcomes in our series. Furthermore, in accordance to published reports, we experienced recurrence in half of our patients despite obtaining clear margins at surgery.

Some of the larger published studies have been retrospective and spanned many decades, which can lead to variability in data collection, biopsy techniques and changes in management strategies. Many of these were published more than 15 years ago *(8,10)*. Surgical options have remained fundamentally unchanged since then, but adjuvant treatment regimens have advanced, potentially impacting survival outcomes. Although we have a small population size we report the outcomes from a single institute and hence better consistency of interpretation.

Alveolar soft part sarcoma is a highly malignant tumour with significant metastatic potential. Despite early detection and appropriate management, ASPS is associated with a high recurrence and mortality rate. Whilst surgery remains the mainstay of treatment, adjuvant therapies have not significantly improved outcomes. Newer molecular targeted therapies such as anti-angiogenic approaches and tyrosine kinase inhibitors appear promising and may be novel adjuncts to future treatments *(12)*.

We recommend management of these rare tumours in specialist units in a multi-disciplinary environment. All patients should be investigated with MRI and CT of the tumour, MRI brain, staging CT and tissue biopsy to confirm the diagnosis and establish the extent and burden of the disease. Careful analysis and interpretation with prompt surgical intervention at a bone tumour unit is paramount. Recent practice guidelines have also recommended routine intracranial imaging as part of the initial staging evaluation *(8)*. We suggest that patients should be closely followed up with repeat interval imaging regularly for life.

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