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ORIGINAL ARTICLE

Retroperitoneal synovial sarcoma: A clinicopathological study of 6 cases

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Summary

Purpose: *Synovial sarcoma (SS) arising in the retroperitoneum is a rare tumor. In this location it can be confused with other biphasic tumors and with other spindle and round cell sarcomas. We report 6 cases of SSs with emphasis on their clinicopathological findings.*

Patients and methods: *Six cases were studied, diagnosed as primary retroperitoneal SSs. Clinical, radiological and pathological findings were included in the study. Follow-up information was available in 5 out of 6 cases.*

Results: *The cases consisted of 5 males and 1 female (aged 27-42 years, median 34), who complained preoperatively for pain in the abdominal region (n=4) and dysuria (n=2). Clinical examination was negative. Abdominal X-ray showed a suspicious mass in 4 cases and computed tomography (CT) revealed the tumor mass in all cases. Surgical removal of the tumor was performed. Tumors ranged in size from 6.5 to 14 cm (median 11); histologically, all tumors were biphasic and 1 had poorly differentiated areas. Sarcomas were of high grade (n=3) and intermediate grade of malignancy (n=3). Immunohistochemical stains for cytokeratins AE1/AE3, CAM5.2, S-100, CD34, EMA, SMA and CD99 were performed. All tumors recurred or metastasized within the abdomen. Four patients died of disease within 8 -38 months.*

Conclusion: *Retroperitoneal SSs are very rare neoplasms that attain a large size, are difficult to excise and recur locally. Metastatic potential is low; however, mortality is very high.*

Key words: histology, prognosis, retroperitoneum, synovial sarcoma

Introduction

The term synovial sarcoma (SS) was first used by Knox in 1936 [1]. SS is a distinct soft tissue sarcoma that occurs in young and middle-aged adults and has a predilection for the extremities. It is a distinctive biphasic or monophasic tumor that occurs mainly near tendons/tendon sheaths and next to joint capsules. Despite its name, joint involvement is very uncommon, and most cases involve the extremities, especially the lower limb around the knee, which is the single most common location. SS may be more rarely found in unexpected sites, such as abdominal wall [2,3], head and neck regions [4], including pharynx, larynx [5], and orbit [6], retroperitoneum [7,8], mediastinum [9], as well as visceral organs such as lungs [10], kidneys [11], or prostate [12]. It is a highly malignant soft tissue sarcoma which is not a result of malignant transformation of normal synovium as the name would suggest, but it is believed to be a dedifferentiated mesenchymal tumor resembling normal synovial tissue. However, some patients develop metastases, particularly to the lungs, quite early after surgery and die of disease, whereas distinct groups of patients have prolonged clinical courses without recurrence or metastasis. Therefore, SS warrants accurate grading to determine the patient's prognosis.

In 1950, Pack and Ariel [13] reported the first 2 cases of SS arising in the abdominal wall. Most of the reported cases in the literature were cases with anterior abdominal wall localization [2,3]. Primary retroperitoneal SS is very rare; only few cases have been mentioned in the literature [7,8,14-20]. However, complete clinical and pathological data are available, to our knowledge, in only 8 published studies of retro-

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peritoneal SS [7,8,15,16,21-24]. The study by Fisher et al. [7] is the largest series to date, presenting 8 cases of retroperitoneal SS.

Retroperitoneum, embedded in a meshwork of loose connective tissue, contains the adrenal glands, kidneys and ureters, aorta and its branches, inferior vena cava and its tributaries, and numerous lymph nodes. This potentially large space allows both primary and metastatic tumors to grow silently before clinical signs and symptoms appear. Therefore, in recorded retroperitoneal SS cases, clinical signs and the precise anatomical origin was difficult to be defined. Usually these sarcomas are associated with a poor long-term survival rate, due to the extreme difficulty encountered in performing a complete surgical removal with a rim of normal tissue around the tumor [25]. In an attempt to evaluate clinical, surgical, pathological findings and prognosis, we studied 6 cases of SS arising within the retroperitoneum.

Patients and methods

Six cases, diagnosed as primary SS arising in the retroperitoneum, were selected from the archives at Hippokrateion Hospital, Department of Pathology, from 1997 to 2006. Clinical, laboratory, radiological, surgical, pathological findings and follow-up information were available in 5 out of 6 patients. Routine hematoxylin & eosin-stained slides were assessed in all cases for the following features: type of SS (monophasic fibrous type or biphasic), presence of poorly differentiated areas, presence of myxoid or haemangiopericytic areas, microscopic tumor necrosis, vascular invasion, type of tumor interface with surrounding tissue (pushing or infiltrative), number of mitoses per 10 high-power fields (HPF) (×400) (5 sets counted of most cellular and most mitotically active areas), and the presence of inflammatory cells. Tumor grade was assigned based on the French Cancer Centres System [26]. Architectural pattern of the growth was assigned a differentiation score of 3, numbers of mitoses were scored as 1-3 (0-9, 10-19 and ≥ 20, respectively), and 0-2 for percentage of necrosis (0, < 50%, > 50%). Grade 2 tumors had a total score of 4 or 5, and grade 3 tumors of 6, 7 or 8. There were no grade 1 tumors.

Immunohistochemistry

The specimens were fixed in 10% buffered formalin, embedded in paraffin and cut in 4-μm sections. The following available antibodies were used: monoclonal mouse antibodies for cytokeratin (AE1/AE3 1:20, DAKO, Glostrup, Denmark), and for CAM5.2 (Becton Dickinson, Oxford, UK, 1:10), monoclonal mouse antibody for epithelial membrane antigen (EMA, DAKO E29, 1:100), α-smooth muscle actin (1A4, 1:50, DAKO), S-100 protein (1:500, DAKO), CD34 (1:30, Novocastra, Newcastle, UK), and CD99 (1:25, DAKO). Sections were studied immunohistochemically with automated immunostainer (Biogenex, San Ramon, USA), using a standard labelled streptavidin-biotin method, followed by a 3.3'-diamino-benzidine enzymatic development. Representative sections were examined by using positive and negative controls.

Results

Clinical features

The findings for the 6 cases are summarized in Table 1. Five cases involved male patients aged 27-39 (median 32.8) and 1 female patient aged 42. In 2 cases (1 tumor fixed in the right ureter and 1 tumor fixed in the left ureter) patients experienced pain, dysuria, and recurrent urinary infections. In 2 cases the tumor occupied the upper pole of the right kidney and adrenal gland, causing a feeling of weight and pain in the upper abdominal area. In the remaining 2 cases, the tumor site was not further specified, because the tumors were very large and the patients experienced dyspepsia and vague pain in the upper abdominal area. All patients mentioned that tumors became painful and increased rapidly in size. The general examination was negative, except a moveable mass (in 4 cases) in the abdominal wall. No other masses were detected anywhere else. Liver and spleen were not palpable and rectal examination was negative. Examination and investigation of the genitourinary system yielded positive results in the 2 dysuric cases, and negative results in the other cases. Abdominal X-ray and CT revealed the tumor masses in all cases. Surgical removal of the retroperitoneal tumors was carried out in all of the patients.

Pathological findings

1. Gross features

Pathological examination revealed grey-colored tumors, sharply circumscribed, multilobular, limited by a smooth pseudocapsule (in 5 cases), with size ranging from 6.5 to 14 cm (median 11) in maximum dimension. Four tumors had macroscopic cysts on their cut surface. One tumor was notably myxoid on section, with very soft areas and multiple cysts filled with yellowish gelatinous material. In 5 cases there was visible necrosis.

Table 1. Retroperitoneal synovial sarcomas in the present study

Case	*Site*	*Sex*	*Age (years)*	*Clinical symptoms*	*Histological type*	*Behavior*	*Lenght of follow-up (months)*
1	Retroperitoneum, fixed in right adrenal gland	M	29	pain and/or mass	Bi	intrabdominal recurrence 15 months	DOD, 38
2	Retroperitoneum, fixed in right kidney	F	42	pain and/or mass	Bi	intrabdominal recurrence 12 months	DOD, 16
3	Retroperitoneum, fixed in right ureter	M	33	dysuria	Bi	NK	NK
4	Retroperitoneum, fixed in left ureter	M	27	dysuria	Bi	intrabdominal recurrence 8 months	DOD, 28
5	Retroperitoneum	M	39	pain and/or mass	Bi	intrabdominal recurrence 16 months	AWD
6	Retroperitoneum	M	36	pain and/or mass	Bi	peritoneal sarcomatosis 5 months	DOD, 8

M: male, F: female, Bi: biphasic, DOD: died of disease, NK: not known, AWD: alive with disease

2. Microscopic features

Microscopic examination of the surgical specimen in all cases showed a biphasic growth pattern composed of epithelial and spindled areas (Figure 1a, 1b). The epithelial component of the biphasic tumors was usually glandular and sometimes formed solid cords. The epithelial cells were predominantly cuboidal and had a moderate amount of pale-staining cytoplasm with distinct cellular borders, and round to oval vesicular nuclei. The lumina of the glands contained eosinophilic mucinous material, which was not digestible with diastase or hyaluronidase. Also, in 3 cases, focal keratinization with squamous metaplasia was observed (Figure 1c). One neoplasm had poorly differentiated areas, mostly composed of small round cells. Nuclear pleomorphism and multinucleated tumor cells were absent. Mitotic activity ranged from 5 to 30 mitoses/10 HPF, but without abnormal forms. Necrosis was present in 4 cases, but only focally. In 1 case, the tumor displayed myxoid appearance. The surrounding spindle cells (Figure 1b) or fibrous components forming solid and compact sheets, were composed of densely packed, elongated fusiform cells with small amounts of indistinct cytoplasm and oval dark staining nuclei. In most tumors inflammation was rare. Finally, 3 sarcomas were high-grade (grade 3) and 3 were of intermediate-grade (grade 2).

Immunohistochemical findings

Immunohistochemically, cytokeratins (AE1/AE3 and CAM5.2) and EMA were positive in all (100%) cases in the cytoplasm and in the membrane of the epithelial tumor cells (Figure 2a, 2b). The glandular epithelium and solid cords stained with cytokeratin and EMA, and occasional spindle cells were positive for both markers. The spindle cells were positive for CD99 with focal membranous staining. The tumor cells were consistently negative for α-smooth muscle actin (α-SMA), S-100 and CD34.

Follow-up information

Follow-up information ranging from 8 to 38 months was available for 5 patients. All patients underwent initial surgical excision, which was described as complete in 3 cases. No patient had postoperative chemotherapy or radiotherapy. In 5 cases, the disease recurred or metastasized within the abdomen between 5 and 16 months postoperatively. No case metastasized outside the abdomen. Four patients died of disease within 8-38 months after surgery. One patient is alive, after disease recurrence (at 16 months). Three patients were operated again after recurrence (with no postoperative chemotherapy or radiotherapy; Table 1, patients no. 1, 4 and 5).

Discussion

Although the most common location for SS includes the soft tissues of the extremities and the head & neck region, examples of this entity have now been reported in almost all parts of the body [7,9,27]. In most reported cases with retroperitoneal SS the tumor had large size and this obscured its precise anatomical origin. SS is said to represent about 1% of retroperitoneal tumors [28]. The true incidence, however, is likely to be higher

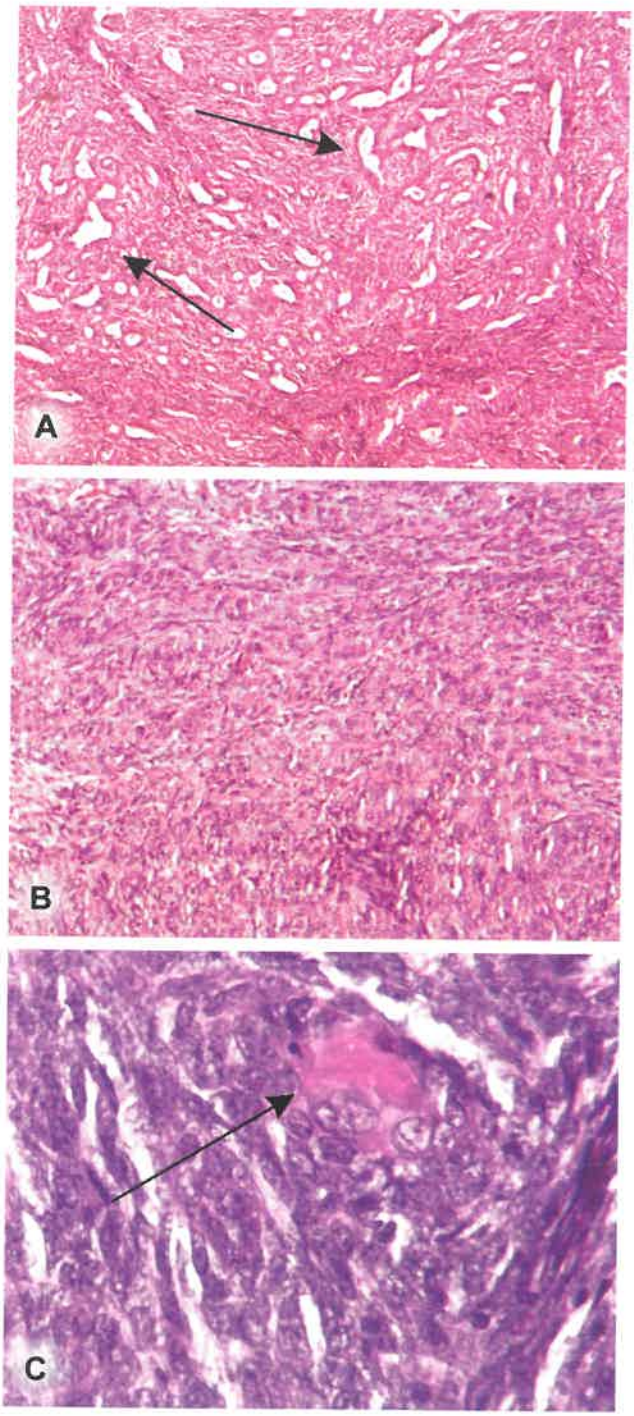


Figure 1. Biphasic synovial sarcoma with: A: gland formations (arrows) (H&E ×4); B: spindle cells (H&E ×4); C: focal keratin formation (arrow) (H&E ×40).

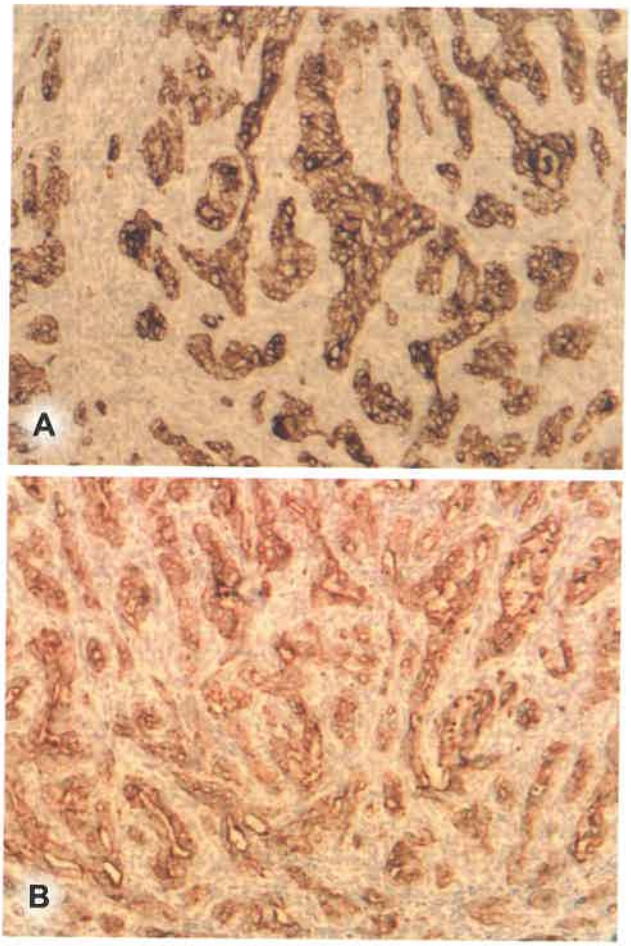


Figure 2. Immunohistochemical stains. A: Positive cytoplasmic staining for AE1/AE3 (×4); B: Positive cytoplasmic staining for CAM5.2 (×4).

since cases formerly diagnosed as haemangiopericytoma, fibrosarcoma or other types of spindle cell sarcoma might, with adequate investigation, be reclassified as monophasic SS. Retroperitoneum is a large space which allows both primary and metastatic tumors to grow silently before clinical signs and symptoms appear.

Morphologically, classic biphasic SS is diagnostically obvious, with spindle cell and epithelial components and rarely creates a diagnostic dilemma. Poorly differentiated SS has more hyperchromatic nuclei which can resemble small round cell sarcomas or carcinomas, but there is typically little pleomorphism and the cytoplasm is sparse, except the plumper cells seen in clusters in some tumors. The differential diagnosis for the retroperitoneal SS should include other biphasic neoplasms, spindle cell sarcomas, metastatic carcinoma and small round cell tumors. Biphasic SS must be distinguished from carcinosarcoma, Wilm's tumor, extragonadal germ cell tumors and mesothelioma. Müllerian adenosarcoma and carcinosarcoma arise mostly in gynecological organs in older patients, are more pleomorphic than SS and have more diffuse cytokeratin positivity. Biphasic peritoneal mesotheliomas are closely related to long-term exposure to asbestos [29], occurring in an older age group and having larger and less uniform nuclei [7]. Also, gross morphologic findings can be quite helpful in such cases; SS will usually present as a lobular mass

as opposed to mesothelioma, which has a tendency to grow as a diffuse, plaque-like tumor mass [9]. Furthermore, both epithelial and sarcomatoid components of mesotheliomas are positive for vimentin, cytokeratin and EMA [29]. Monophasic SSs can resemble a wide variety of other neoplasms, including solitary fibrous tumor [30], malignant peripheral nerve sheath tumor, leiomyosarcoma and gastrointestinal stromal tumor arising in the retroperitoneum or omentum [31]. These can be distinguished by their specific morphology and immunophenotype. Adult fibrosarcoma displays a herring bone pattern, can be pleomorphic and produces intercellular collagen. Many SSs have a haemangiopericytomatous pattern and have been misdiagnosed as haemangiopericytoma. The latter, however, is regarded as a diagnosis of exclusion. Metastatic carcinoma can be generally ruled out by identifying the atypical spindle cell component surrounding the glands. Also, the nuclei in metastatic adenocarcinoma are more pleomorphic and less uniform than those generally encountered in the glandular elements of SS [9].

The immunohistochemical profile of SS helps determine the precise diagnosis. It has been suggested that positivity of EMA, cytokeratin AE1/AE3, and E-cadherin, in combination with CD34 negativity, are the most useful and sensitive markers for diagnosing monophasic fibrous and poorly differentiated SS [32]. In our study, cytokeratins (AE1/AE3 and CAM5.2) and EMA were positive in all (100%) cases. The tumor cells were negative for α-SMA, S-100 and CD34. The pattern and extent of the immunohistochemical staining, in conjunction with clinical, radiologic and microscopic features, will usually lead to correct diagnosis [2].

The pathogenesis of SS is unresolved. Its frequent association with para-articular regions indicates that these tumors could be originated from synovial cells [33]. Yet, the presence of SS of the abdominal wall, as well as those of other extra-articular sites where normal synovial, bursal, or tendon sheath structures do not exist, argues against an origin from arthrogenous mesenchyme [34]. However, many examples have been described, indicating that these tumors are not related to normal synovium, but rather show features of epithelial differentiation [35,36]. These examples, coupled with their documented occurrence at extra-articular sites, have led to the speculation that these neoplasms could arise from a mutated pluripotential mesenchymal cell present in diverse locations [35,36].

The characteristic chromosomal translocation t(x;18) (p11.2;q11.2) found in about 90% of SSs has been interpreted as being specific to SSs and is probably related to the genesis of this tumor [36]. Two different types of breakpoint on chromosome X, which correspond to the chimeric genes SYT-SSX1 and SYT-SSX2, have been reported in SSs [34]. These two chimeric genes may be related to the histological subtypes: monophasic and biphasic. Monophasic tumors have either SSX1 (about 60%) or SSX2 in their rearrangement, but the majority of biphasic tumors (defined as having distinct gland formation with lumina) have the SSX1 rearrangement [37].

SSs can recur locally, usually within 2 years, but sometimes many years later [38]. Metastases occur mainly to the lungs, and less commonly to lymph nodes and bone. All of the previously reported cases of primary retroperitoneal SS died between 7-24 months with local recurrence or extension, but without metastases outside the abdomen. In our study, local intraabdominal recurrence was identified at intervals of 5-16 months in all cases and without any distant hematogenous metastasis. Despite their large size, none of them metastasized outside the abdomen. In 3 cases, surgical margins were not adequate. In 2 of them tumors recurred in 5 and 8 months, respectively. In the third patient, follow-up was not available. In the other 3 cases with adequate surgical margins, intraabdominal recurrence was noted after 12-16 months. This demonstrates that adequate surgical margins may delay the time of intraabdominal recurrence. Also, 2 cases with earlier recurrence had higher histological grade and 1 of them died within 8 months. These findings suggest that the difficulty of surgical excision with adequate margins and high histological grade may bear a worse outcome.

The role of radiation therapy or chemotherapy in the outcome and prognosis of patients with SS is controversial. In one study [38], non-adjuvant radiation therapy and chemotherapy did not influence local control or outcome of patients with SS. In another study [39], adjuvant chemotherapy showed no clear impact on patients' survival. Furthermore, patients with SS can be divided into distinct low and high risk groups, based on morphology, tumor size, and patient age. The low risk group (classical morphology, tumor < 5 cm, patient age < 25 years) seems to be best treated by surgery alone, whereas the high risk group (poorly differentiated morphology, tumor > 5 cm, patient age > 40 years) needs postoperative chemotherapy. In our study, none of the patients received additional adjuvant therapy, demonstrating that the preferred treatment was local excision with wide margins of normal tissue.

In conclusion, we described 6 cases of retroperitoneal SSs, which - to our knowledge - is the 9th study available with clinical and pathological data, and emphasis on their clinicopathological findings. Like other retroperitoneal sarcomas, they reach a large size before presentation, are difficult to excise and recur locally.

Also, they do not usually metastasize outside the abdomen. The mortality rate is high due to the local disease extension.

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