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ORIGINAL ARTICLE

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Solitary fibrous tumour: clinicopathological, immunohistochemical, and ultrastructural analysis of 12 cases arising in soft tissues, nasal cavity and nasopharynx, urinary bladder and prostate

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Abstract The clinicopathological features of 12 extraserosal solitary fibrous tumours (SFT) are described. The age of the patients ranged from 18 to 72 years (mean: 48.2 years; median: 54 years); 5 were female patients. Seven lesions arose in soft tissue (5 in perifascial, and 1 each in subcutaneous and intramuscular tissues). They were situated in the groin (2 cases) and the neck, right buttock, left scapula, upper arm, and anterior abdominal wall (1 case each). One polypoid lesion was seen in in the nasal cavity and 1 in the nasopharynx; 2 neoplasms arose in the urinary bladder and 1 was located in the prostate and periprostatic tissue. Nine lesions were excised; in 1 patient wide excision was performed and in 2 patients, transurethral resection. Limited follow-up of 3 cases revealed a benign clinical course. The size of the neoplasms ranged from 1.7 cm to 20.0 cm (mean: 5.4 cm; median: 3.5 cm). Histologically, the neoplasms were well circumscribed and composed of cytologically bland spindle cells arranged without an obvious pattern; focally storiform or fascicular growth patterns were seen. Tumour cells were separated by thick bands of collagen demonstrating foci of keloid-like hyalinization. Prominent vascularity showing a haemangiopericytoma-like vascular pattern and vessels with thick, hyalinized vessel walls were seen in all cases. Increased mitotic activity was noted in 2 soft tissue cases (4–6 mitoses in 10 high-power fields); the other cases showed fewer than 2 mitotic figures in 10 high-power fields. Immunohistochemically, all cases tested stained positively for vimentin, CD34 and CD99, and 2 cases showed focal myofibroblastic differentiation. Two cases examined ultrastructurally showed a fibroblastic phenotype; focally pinocytic vesicles and microfilaments were identified. SFT represents a distinct neoplasm that should be included in the differential diagnosis of spindle-cell neoplasms in soft tissue, nasal cavity and nasopharynx, urinary bladder, and prostate. Strict diagnostic criteria are necessary to avoid overdiagnosis or confusion with more aggressive neoplasms in these locations.

Key words Solitary fibrous tumour · Soft tissue · Immunohistochemistry · Differential diagnosis

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Introduction

Solitary fibrous tumour (SFT) is an unusual but distinct spindle-cell lesion in adults, arising most commonly in the pleura [11] and more rarely on other serosal surfaces [10, 37]. In recent years this tumour has been reported in a variety of extraserosal sites, including thyroid [3], lung [19, 31], upper respiratory tract [36], nasal cavity and paranasal sinuses [38], the orbits [8, 24, 29, 33], mediastinum [35], major salivary glands [13], breast [6], meninges [4], kidney [12], renal capsule [18], liver [2], spermatic cord [14], and soft tissues [22, 30]. SFT from serosal and extraserosal sites is characterized histologically by uniform spindle cells that are arranged without an obvious growth pattern ("patternless" growth) or show a combination of this patternless growth with focal storiform, herringbone, haemangiopericytic, neural-like, or diffuse sclerosing growth patterns [20, 25]. Most recently, a so-called epithelioid variant has been described [34]. Given the well-known heterogeneity in mesenchymal neoplasms and the spectrum of clinical and morphological appearances of SFT, strict diagnostic criteria are necessary to avoid the establishment of a "new hotchpotch" in surgical pathology of mesenchymal lesions. In this report we present 12 extraserosal solitary fibrous tumours and discuss diagnostic criteria for this rare neoplasm and its differential diagnosis.

Materials and methods

All cases were identified in the consultation files of two of the authors (D.K., T.C.B.). For conventional microscopy, tissue was fixed

Table 1 Antibodies used in this study (*ASMA* alpha-smooth muscle actin)

Vimentin	V9	1:40	Dako
CD34	QBEND10	1:100	Dianova
CD99 (HBA71)	O13	1:30	Signet
CD31	JC/70A	1:30	Dako
ASMA	1A4	1:40	Dako
Actin	HHF35	1:150	Dako
S-100 protein	polyclonal	1:200	Dako
Cytokeratin	MNF 116	1:50	Dako
Ki-67	MIB-1	1:10	Dianova

in 10% buffered formalin, embedded in paraffin wax, cut and stained with haematoxylin and eosin, with periodic acid–Schiff (PAS) and with Goldner trichrome stains. For immunohistochemical studies, representative sections of all cases were examined by the APAAP technique using appropriate positive and negative controls throughout. The antibodies used, and the source and dilution of each are shown in Table 1. Because of the limited availability of slides vimentin (tested in 5 cases), CD99 (8 cases), alpha smooth muscle actin (10 cases), muscle actin (8 cases), Ki-67 (9 cases), CD31 (7 cases), cytokeratin (5 cases), and S-100 protein (9 cases) were not tested in all cases. The Ki-67 score was defined as the average number of cells with positive nuclear staining, divided by the total number of cells counted; quantification of the positive nuclear signal was not attempted. In 2 cases (cases 6 and 9) suboptimal material was available for electron-microscopic examination. Formalin-fixed tissue was washed in sodium cacodylate buffer, further fixed in 4% paraformaldehyde and then routinely processed. After selection of the appropriate blocks from toluidine blue-stained semithin sections, ultrathin sections were stained with uranyl acetate and lead citrate, and examined with a Zeiss Oberkochen EM 900 at 80 kV. The mitotic rate was expressed as the average mitotic count present in 10 high-power fields (HPF; 1 HPF = 0.159 mm^2 on the microscope used); 30 HPFs were counted in each case. Where possible, follow-up information was obtained from the hospital records, laboratory request forms, and referring pathologists (see Acknowledgements). Cases 3 and 6 will be published in more detail later [1].

Results

Clinical findings

Clinical data are summarized in Table 2. The age of the patients, 5 female and 7 male, ranged from 18 to 72 years (mean: 48.2 years; median: 54 years). In 7 cases the lesion arose in soft tissues: 2 neoplasms were situated in the groin and 1 each in the neck, right buttock, region of the left scapula, upper arm, and anterior abdominal wall, and 5 of the 7 tumours in soft tissues were located in perifascial tissues; in case 7 a subcutaneous mass and in case 12 an intramuscular lesion was described. One polypoid neoplasm was located in the nasal cavity, and 1 lesion arose in nasopharynx. Interestingly, 2 cases were found in the urinary bladder and 1 in the prostate and periprostatic tissue. The preoperative duration was only known in 3 cases and ranged from 1 year (case 10) to 16 months (case 6). In none of the cases of soft tissue lesions were specific clinical symptoms noted; patients 1, 3 and 6 complained of genitourinary symptoms and "pelvic pressure". In none of the cases was hypoglycaemia recorded. Nine neoplasms were treated by simple excision, in case 6 wide excision was performed, and in cases 1 and 3 transurethral resection was done. Follow-up information was only available in 3 cases; duration of follow-up ranged from 3 to 18 months. No systemic metastases or tumour-related deaths of patients have been reported.

Pathological findings

Grossly, tumours in soft tissues, nasal cavity and nasopharynx were described as well-circumscribed or encapsulated lesions with firm, grey-white cut surfaces. In case 6 an encapsulated neoplasm of soft consistency with numerous small cysts was noted. The tumours ranged in size from 1.7 cm to 20 cm (mean: 5.4 cm; median: 3.5 cm).

Histologically, in all cases for which excisional material was available (cases 2, 4–12) well-circumscribed lesions were found. In all but 2 cases the lesions were characterized by varying cellularity; hypocellular, sclerosed areas were adjacent to more cellular areas (Fig. 1). Two lesions (cases 1 and 11) were rather hypocellular throughout. The tumours were composed of cytologically bland spindle cells with a small rim of amphophilic or pale eosinophilic cytoplasm and slender nuclei with tapered edges and finely distributed chromatin (Fig. 2). In 7 cases (cases 1–3, 6, 10–12) scattered cells with nuclear pseudoinclusions were identified. Case 7 showed foci

Table 2 Clinical data in 12 cases of extraserosal solitary fibrous tumour (*M* male, *F* female, *TUTUR* transurethral tumour resection, *NA* not available, *NSR* no sign of recurrence)

Case (no.)	Age (years)	Sex	Site	Size (cm)	Treatment	Follow-up
1	72	M	Prostate	NA	TUTUR	NA
2	51	M	Anterior abdominal wall	4.8	Excision	NA
3	50	F	Bladder	5.0	TUTUR	NSR at 18 months
4	25	F	Nasopharynx	3.5	Excision	NSR at 5 months
5	57	M	Groin	4.0	Excision	NA
6	42	M	Bladder	20.0	Wide excision	NSR at 3 months
7	69	M	Left scapula	3.0	Excision	NA
8	18	F	Right buttock	2.5	Excision	NA
9	44	M	Neck	NA	Excision	NA
10	31	F	Nasal cavity	1.7	Excision	NA
11	66	M	Groin	3.0	Excision	NA
12	54	F	Upper arm	7.0	Excision	Recent case

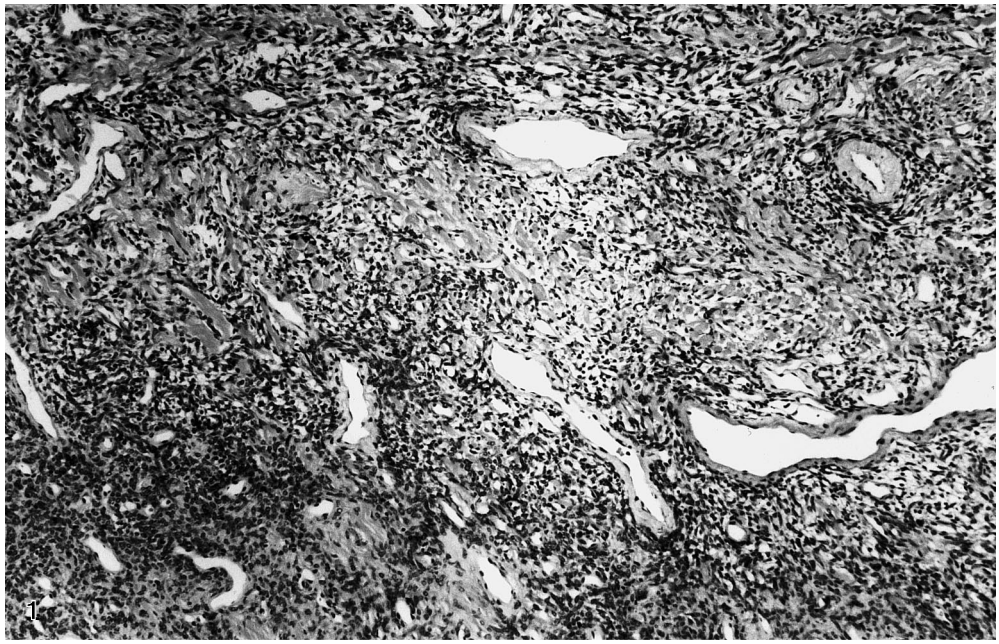


Fig. 1 Varying cellularity, "patternless" growth pattern of the tumour cells and a prominent vascularity with thin-walled, haemangiopericytoma-like vessels and blood vessels with hyalinized vessel walls are histological hallmarks of SFT (case 2). H&E, ×100

Fig. 2 SFT is composed of spindle-shaped tumour cells with slender, slightly bent nuclei with tapered edges and finely distributed chromatin (case 4). H&E, ×425

with nuclear palisading reminiscent of the appearance of neural neoplasms. Focally, plump fusiform and polygonal tumour cells with more rounded nuclei were noted in cases 3 and 6. The tumour cells were mainly arranged in a patternless growth pattern, storiform and fascicular areas or tumour cells arranged in a more linear fashion being found only focally (Fig. 3). In case 12 a predominately fascicular growth pattern was identified. Tumour cells were separated to varying degrees by thick bands of collagen showing foci of keloid-like hyalinization (Fig. 4). It seemed especially in hypocellular lesions (cases 1 and 11) that the tumour cells permeated between the collagen bundles (Fig. 5). One of the cases in the urinary bladder (case 6) showed a myxoid stroma with microcystic-like features (Fig. 6). Typically, a prominent vascularity with thin-walled, branching blood vessels (haemangiopericytoma-like pattern) and frequently hyalinized, thick-walled vessels was noted in all cases examined (Fig. 1). The mitotic count ranged from fewer than 2 mitoses in 10 HPFs (10 cases) to 4–6 mitoses in 10 HPFs in cases 8 and 9. All lesions with increased mitotic activity were located in soft tissues. Neither necrosis nor prominent atypia was identified in any of the cases. Scattered inflammatory cells were seen in 4 cases, while small areas of haemorrhage were identified in 2 lesions.

An interesting finding in two soft tissue neoplasms (cases 5 and 7) was the evidence of islands of mature fatty tissue distributed throughout the tumour (Fig. 7). The adipocytes varied only slightly in size and shape; lipoblasts and hyperchromatic nuclei were not found in these areas.

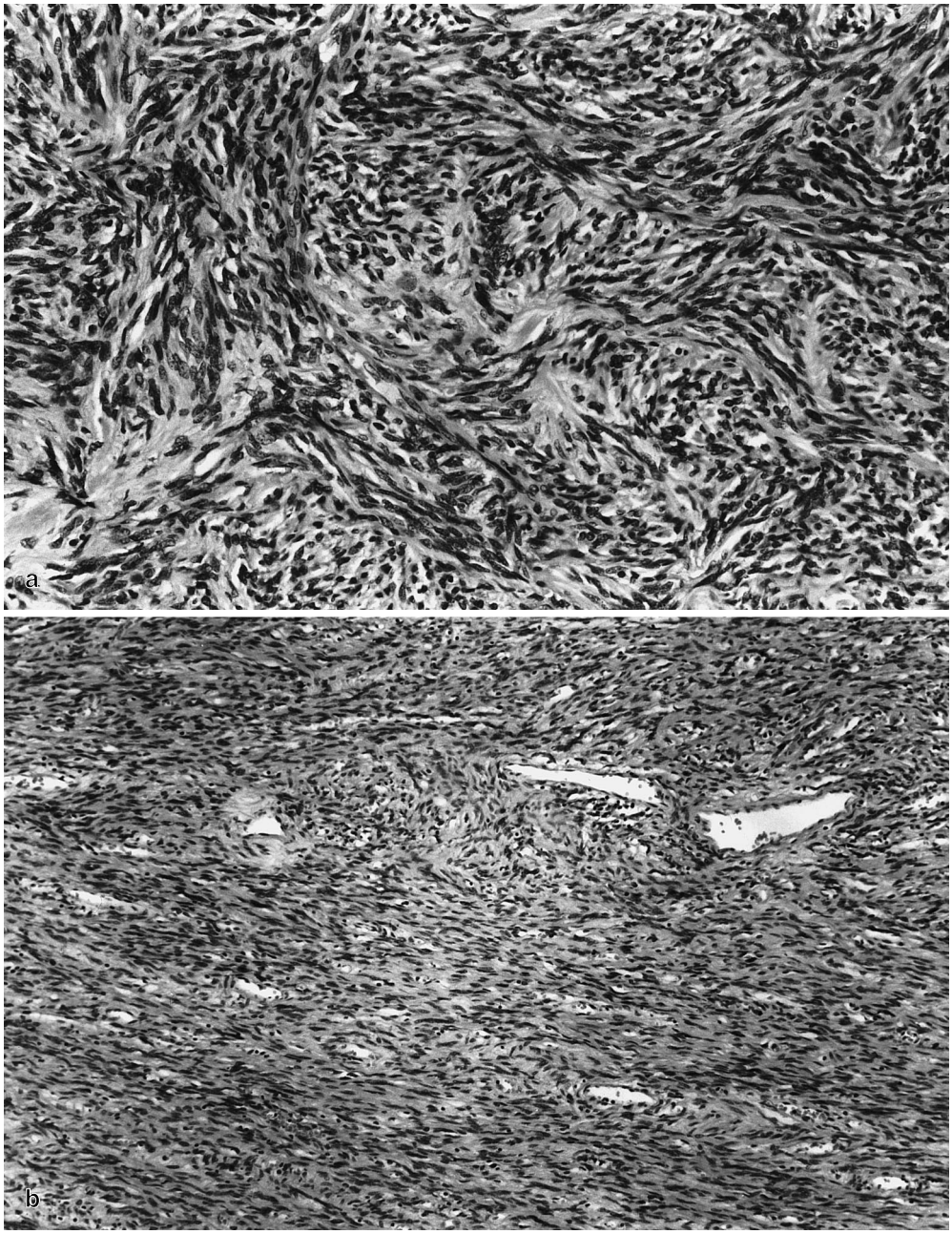


Fig. 3 Focally, **a** a storiform growth pattern or **b** tumour cells arranged in a somewhat linear fashion are seen (case 4). H&E, **a** ×250, **b** x100

Immunohistochemically, all cases examined stained positively for vimentin. The tumour cells in all cases were positive for CD34 and CD99 (Fig. 8). In cases 1 and 3 focal positive staining for alpha smooth muscle actin and muscle-specific actin was noted in scattered fusiform tumour cells with more eosinophilic cytoplasm, suggesting focal myofibroblastic differentiation. Stains for S-100 protein, cytokeratin and CD31 were negative in all cases tested. The percentage of Ki-67-positive tumour cells was highly heterogeneous in each tumour examined and ranged from less than 5% in cases 4, 6, 10, and 12 to 10–15% in cases 1, 2, 8, 9, and 11.

Both cases examined ultrastructurally showed similar features. The fusiform tumour cells had spindle-shaped or irregularly shaped nuclei with scattered condensed chromatin. The cytoplasm contained rough endoplasmic reticulum and and mitochondria. Focally, numerous pinocytic vesicles and bundles of microfilaments (between 4 and 6 nm) without densities were noted (Fig. 9). The tumour cells did not show long cytoplasmic processes, a basal lamina, cell-to-cell junctions, or subplasmalemmal attachment plaques, suggesting a specialized line of differentiation.

Discussion

After a long debate concerning the histogenesis of pleural SFT, it is now commonly accepted that this neoplasm is derived from mesenchymal rather than mesothelial

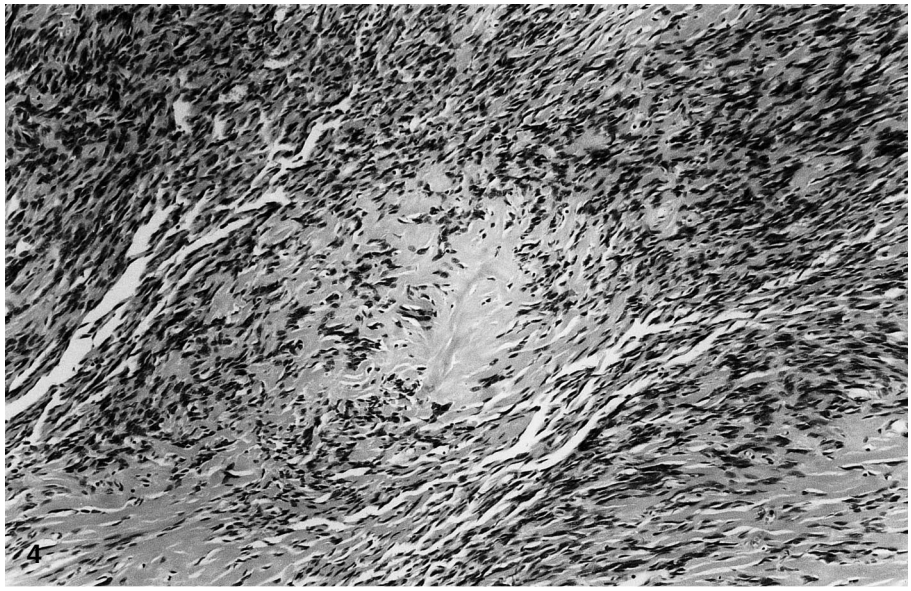


Fig. 4 Foci of keloid-like hyalinization are seen (case 11). H&E, ×100

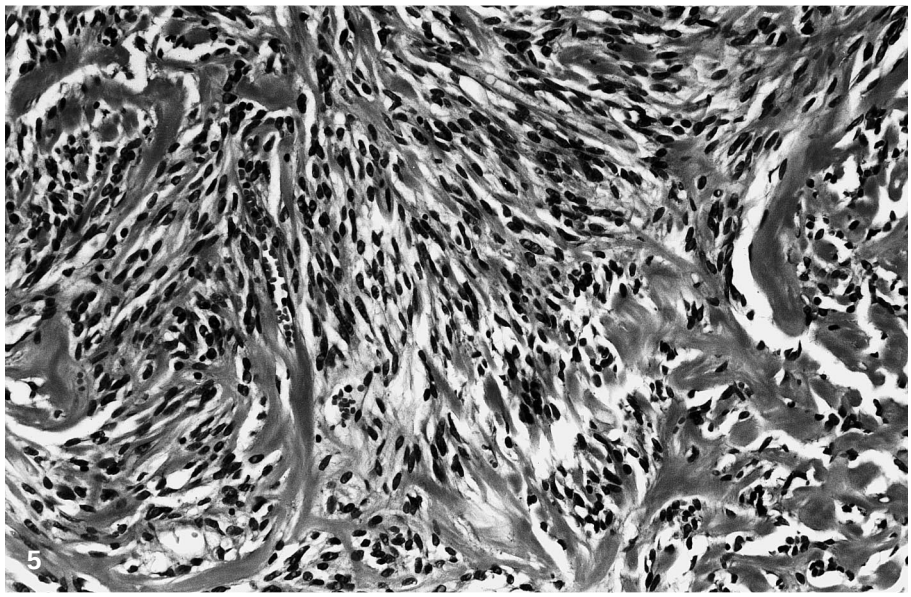


Fig. 5 In hypocellular areas tumour cells permeate between collagen bundles in a characteristic fashion. Note nuclear pseudoinclusions in a number of cells (case 1). H&E, ×250

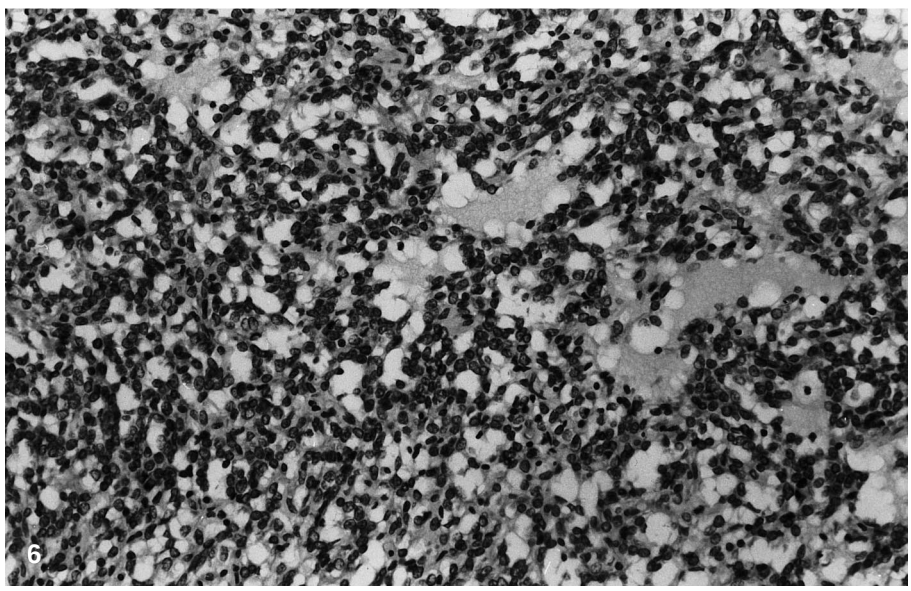


Fig. 6 In case 6 myxoid stromal changes and, focally, tumour cells with rather round nuclei are identified. H&E, ×250

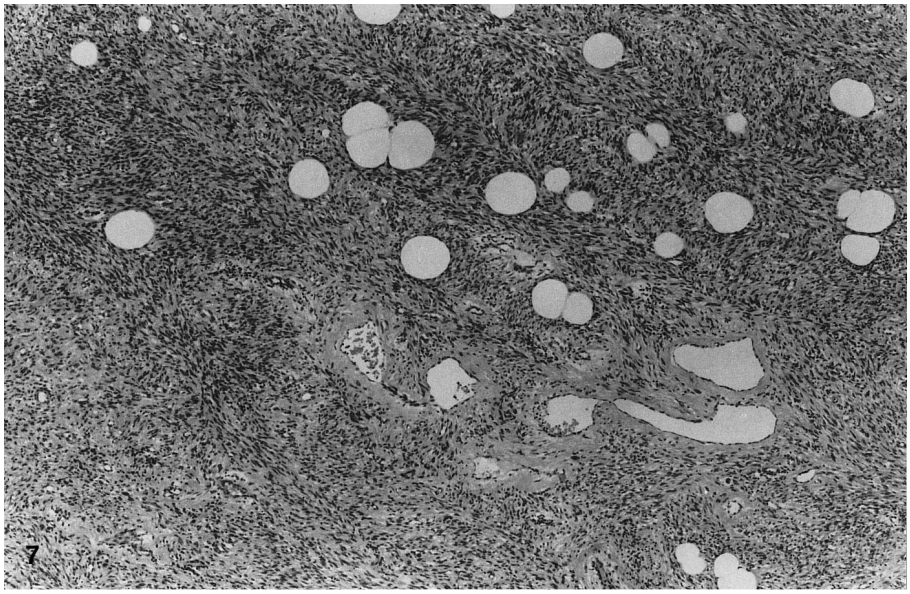
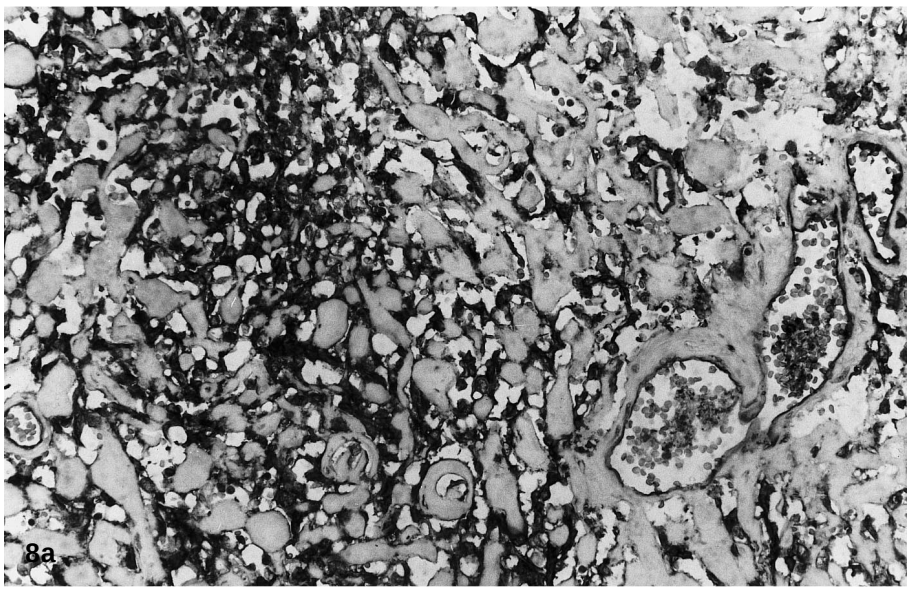


Fig. 7 In two cases islands of fatty tissue are distributed throughout the tumour tissue (case 7). H&E, ×63



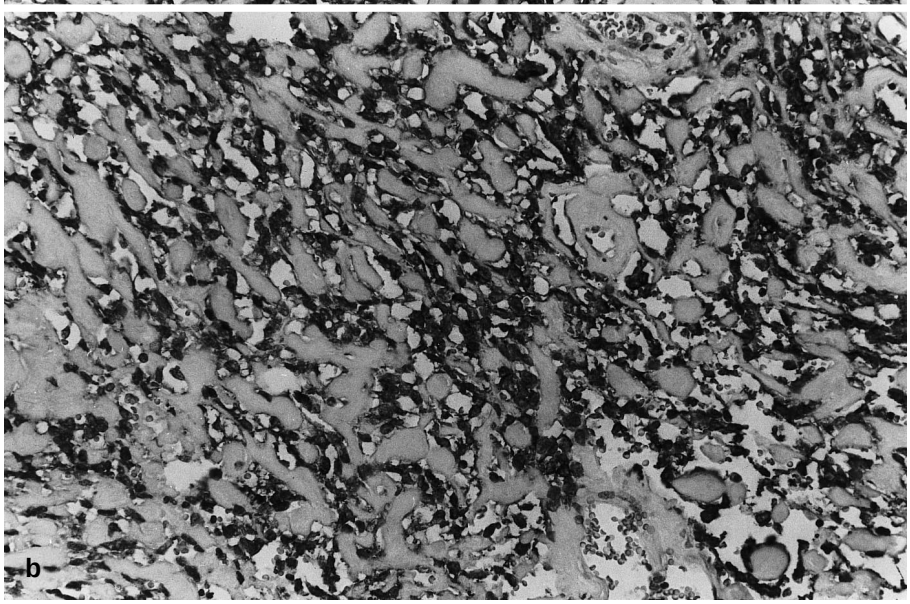


Fig. 8 Tumour cells stained positively for **a** CD34 and **b** CD99 in all cases examined. APAAP, ×250

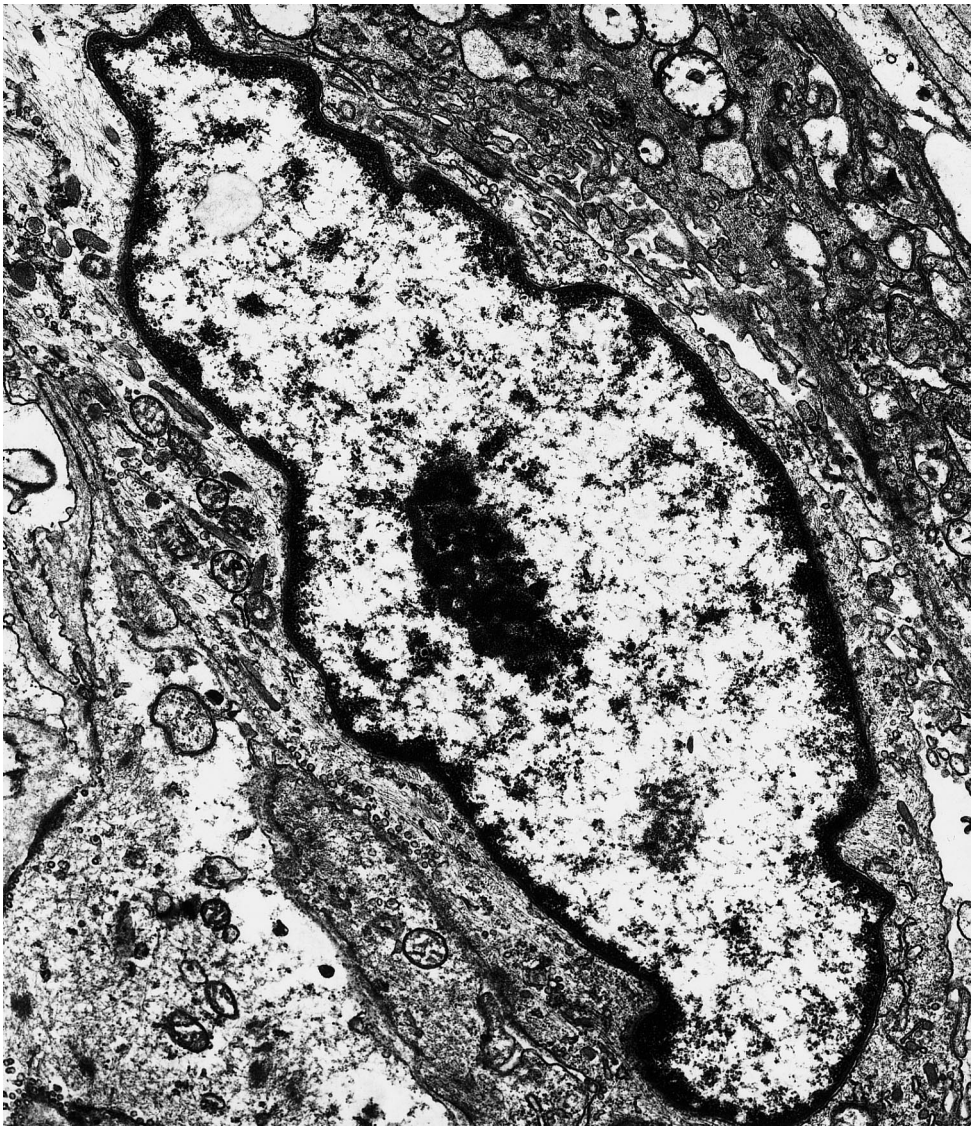


Fig. 9 Ultrastructurally, fusiform tumour cells contained occasional irregularly shaped nuclei. Note numerous pinocytic vesicles and bundles of microfilaments. x13,200

cells and shows fibroblastic (and possibly myofibroblastic) differentiation [11, 25]. In the last decade extraserosal examples of SFT have been reported with increasing frequency. However, because of the variability of morphological patterns seen in SFT and the lack of stringent diagnostic criteria, SFT may be misdiagnosed, especially if it occurs in an unusual location. Different mesenchymal neoplasms may be included under the "popular" term of SFT unless strict diagnostic criteria are applied.

Whereas in the past the designation "patternless growth pattern" was used to describe the histological appearance of SFT, the combination of different histological patterns (patternless, storiform, fascicular, neural-type, diffuse sclerosing, and herringbone growth patterns) seems even more characteristic of SFT [33]. The tumours are well circumscribed and composed of cytologically bland spindle cells set in a collagenous matrix with typical keloid-like hyalinizations and show varying degrees of cell density (from loose tissue to cell-rich areas). They have haemangiopericytoma-like vascularity as well as blood vessels with thickened, hyalinized walls. Comparable to other mesenchymal neoplasms, SFT cannot be diagnosed by means of a specific immunohistochemical marker; however, combined markers are of use. In addition to vimentin, tumour cells of SFT from varying anatomical sites stain positively for CD34 [31, 33] and for CD99, an immunohistochemical marker which was originally believed to be specific for the Ewing's sarcoma/MPNET tumour family and is now found in several spindle cell neoplasms [28].

The reported 12 extraserosal cases fulfil diagnostic criteria of SFT and expand their clinicopathological spectrum. The 7 cases arising in somatic soft tissues bring the number of reported SFT in this location to 23 cases [22, 27, 30]. SFT in the nasal cavity and nasopharynx are rare [38], and our cases in the urinary bladder and prostate extend the range of anatomical locations of SFT. In addition to the variety of histological features described, in 2 of the 7 cases in soft tissue reported herein scattered islands of mature fatty tissue were noted. A

recent paper reported fatty islands only in the tumour periphery [22], but, in our 2 cases fatty tissue was distributed throughout the neoplasms. We feel that this lipomatous component is more likely to be an integral part of the tumour than entrapped normal adipose tissue.

The differential diagnosis of SFT in soft tissues involves a number of benign and malignant neoplasms. Fibrous histiocytoma arising in deep soft tissue is a mainly well-circumscribed lesion composed of relatively uniform tumour cells and may show a prominent haemangiopericytoma-like vascularity. However, a more uniform storiform growth pattern and CD34-negative tumour cells are seen in deep benign fibrous histiocytoma [15]. The recently described giant cell angiofibroma shares histological and immunohistochemical features with SFT [7] but shows angiectatic spaces and multinucleated giant cells. Spindle-cell lipoma is a further CD 34-positive mesenchymal neoplasm, and the evidence of fatty islands in 2 of our cases raises additional differential problems. However, spindle-cell lipoma develops predominantly in subcutaneous tissue on the neck, shoulder or upper back of mainly male patients and does not have the collagenous background with focal keloid-like hyalinizations and the characteristic vascular pattern of SFT. The very rare haemangiopericytoma [16] is another tumour that must be discussed in differential diagnosis. Haemangiopericytoma lacks the combination of varying growth patterns and the collagenous stroma with foci of hyalinization, and is characterized by a dense pericellular reticulin staining pattern. In contrast to SFT with strong and generalized CD34 immunopositivity, it has been said that haemangiopericytoma is characterized by weak and patchy immunopositivity for CD34 [33]. Most recently three cases of so-called lipomatous haemangiopericytoma have been described [26]. Given the reported fatty islands in 2 otherwise typical SFT in our series, the question arises as to whether lipomatous haemangiopericytoma is a true distinct entity or rather a variant of SFT with a more prominent adipocytic component. In the breast SFT may show features overlapping with those of myofibroblastoma of the breast, and it has been proposed that mammary myofibroblastoma should be subsumed under the term SFT [6]. However, myofibroblastoma of the breast differs from SFT in this location in having a more prominently myoid morphology, and it is said to be positive for desmin [23]. Dermatofibrosarcoma protuberans (DFSP), especially its fibrosarcomaous variant [5], can be recognized from its dermal/subcutaneous location and its characteristic honeycomb infiltration of the surrounding fatty tissue.

Malignant peripheral nerve sheath tumours (MPNST) are only partly positive for CD34 [32], and are characterized by perivascular tumour cell whorls and elongated, slender and wrinkled tumour cell nuclei, which stain positively for S-100 protein in at least 50% of cases. Further differential diagnoses include monophasic synovial sarcoma, leiomyosarcoma, and fibrosarcoma. Monophasic fibrous synovial sarcoma is characterized by focal positivity of tumour cells for cytokeratin and epithelial membrane antigen. Leiomyosarcoma is a fascicular neoplasm composed of tumour cells with cigar-shaped nuclei and paranuclear vacuoles and stains positively for myogenic markers. Fibrosarcoma is a very rare tumour in adults and is characterized by cellular tumour fascicles (herringbone pattern) composed of spindle-shaped tumour cells that are negative for CD34.

Schwannoma of the nasal cavity and paranasal sinuses and sinonasal haemangiopericytoma are additional differential diagnoses for SFT in this location. Schwannomas in this anatomical site are very rare and characterized by lack of encapsulation [21]. The typical Antoni A and B pattern and the consistent immunopositivity for S-100 protein are features distinguishing them from SFT. Sinonasal haemangiopericytoma consists of spindle-shaped tumour cells with more eosinophilic cytoplasm and stains in a third of cases positively for actin; ultrastructurally, most cases show features suggesting myoid/pericytic differentiation [9].

SFT arising in the urinary bladder and prostate requires further differentiation from pseudosarcomatous fibromyxoid tumour, postoperative spindle-cell nodule, inflammatory pseudotumour, and pseudosarcomatous myofibroblastic tumour. Although all these pseudosarcomatous proliferations show a spectrum of clinicopathological features, they are characterized by a looser architecture, mixed inflammatory infiltrate, proliferation of reactive-appearing blood vessels and increased proliferative activity; there is no CD34 and CD99 immunopositivity in these lesions.

As to the behaviour of SFT, in a large series of pleural SFT the criteria of high cellularity, more than 4 mitoses in 10 HPFs, cellular pleomorphism, evidence of haemorrhage and necrosis were established to predict malignancy [11]. Owing to the small number of reported extraserosal SFT with long follow-up, these criteria cannot be applied per se. Lesions presenting in extrapleural sites appear to be characterized by an indolent clinical behaviour, and malignant cases are very rare [17, 20]. Long-term follow-up studies of additional cases are required to establish reliable morphological criteria predicting clinical behaviour.

In summary, SFT represents a distinct spindle cell neoplasm with a broad range of clinical and morphological features. In combination, immunohistochemical markers are of great value in the diagnosis of SFT, which appears to be consistently positive for vimentin, CD34, and CD99. In extraserosal locations SFT seems to be an indolent neoplasm regardless of its large size. Strict diagnostic criteria are necessary to avoid confusion of SFT with more aggressive lesions, especially in extraserosal anatomical locations. SFT is easily overdiagnosed if these criteria are not carefully applied.

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