



## CHAPTER 4

### Smooth Muscle Tumours

Smooth muscle tumours arising at non-cutaneous, non-uterine locations have been the focus of a considerable conceptual shift in recent years and this is ongoing. Specifically, it has been uncertain whether or not there exist benign leiomyomas of deep soft tissue, but these lesions are now becoming better recognized and defined. The vast majority of so-called smooth muscle tumours arising in the gastrointestinal tract, mesentery and omentum are, in fact, gastrointestinal stromal tumours defined by the presence of activating *KIT* mutations and expression of KIT protein. These lesions, described in the Digestive System volume, also account for most cases formerly classified as epithelioid smooth muscle tumours, or smooth muscle tumours of uncertain malignant potential.

During the past decade, it has been recognized, mainly through immunohistochemistry, that soft tissue leiomyosarcoma is more common than formerly believed and that a rare but histologically distinct subset of these lesions is related to Epstein Barr virus infection in immunocompromised patients.

Pilar leiomyoma and cutaneous leiomyosarcoma are described in the Skin volume. Smooth muscle tumours of the external genitalia (vulvovaginal region, scrotum and nipple), as well as leiomyomatosis peritonealis disseminata, are described in the respective WHO Blue Books.

# Angioleiomyoma

H. Hashimoto  
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## Definition

A frequently painful, benign subcutaneous or deep dermal tumour composed of mature smooth muscle bundles which surround and intersect between vascular channels. These tumours form a morphological continuum with myopericytoma and myofibroma.

**ICD-O code** 8894/0

## Synonyms

Angiomyoma, vascular leiomyoma.

## Epidemiology

Angioleiomyoma is a relatively common neoplasm. In the largest series reported by Hachisuga et al., 562 cases of angioleiomyoma accounted for approximately 4.4 % of a total of 12,663 cases of benign soft tissue tumours {863}.

## Sites of involvement

Most angioleiomyomas occur in the extremities, especially the lower extremity, and other sites include the head and the trunk {1309}. The tumours are usually located in the subcutis and less often in the deep dermis. Most of the solid

histological subtype (see below) develop in the lower extremity, and most of the cavernous subtype in the upper extremity {863}. Tumours of the venous type develop more often in the head than do the other subtypes. In contrast to pilar leiomyoma (see volume on Skin Tumours), almost all angioleiomyomas are solitary.

## Clinical features

Angioleiomyomas occur more frequently in women {555, 1500}, although tumours located in the upper extremity and the head appear more frequent in men than in women {863}. The lesions usually develop between the fourth and sixth decades of life.

Most angioleiomyomas present as a small, slowly enlarging mass usually of several years' duration. Pain is the most characteristic subjective complaint in about half of patients with angioleiomyoma {555}. In some patients the pain is exacerbated by wind, cold, pressure, pregnancy, or menses.

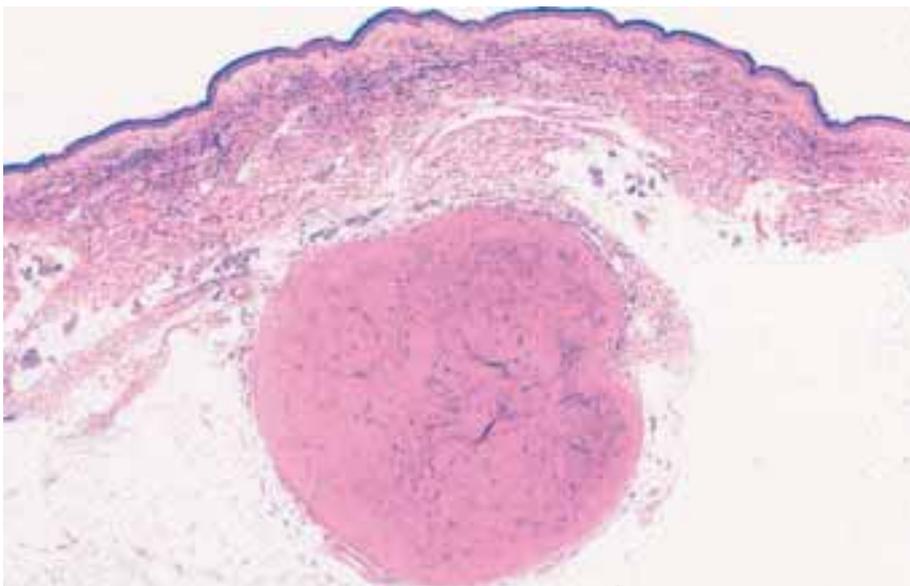
## Macroscopy

Angioleiomyomas are sharply demarcated, spherical, grey-white or brown

nodules, and most are less than 2 cm in diameter. Tumours of the solid type are smaller than those of the other two types.

## Histopathology

Angioleiomyomas may be separated into three subtypes according to the dominant histological pattern: solid, venous and cavernous. Smooth muscle cells of angioleiomyoma are mature and well differentiated. Mitotic figures are usually absent or very rare. In tumours of the solid type smooth muscle bundles are closely compacted, and intersect with one another. Vascular channels in this type of tumour are large in number but usually small in size and slit-like. Tumours of the venous type have vascular channels of venous type with thick muscular walls, and lesional smooth muscle bundles are not so compact. The outer layers of the smooth muscle in the vascular walls blend with intervascular smooth muscle bundles. Tumours of the cavernous type are composed of dilated vascular channels with small amounts of smooth muscle, and the muscular walls of these vessels are difficult to distinguish from intervening smooth muscle bundles. Although two different histological patterns are seen occasionally in the same tumour, one of the above histological subtypes is generally identified as the dominant histology. According to this subclassification, the angioleiomyomas reported by Hachisuga et al. were separated into 374 cases (66%) of the solid type, 127 (23%) of the venous type, and 61 (11%) of the cavernous type {863}. Rarely, the nuclei of smooth muscle cells are enlarged and hyperchromatic, probably displaying degenerative nuclear atypia {307,1076,1344}. Areas of hyalinization, calcification, myxoid change, haemorrhage, and small groups of mature fat cells may be seen {863}. Because there is no evidence of any relationship between those fat-containing angioleiomyomas and renal or retroperitoneal angiomyolipomas, nor with tuberous sclerosis, they should not be labelled "subcutaneous angiomyolipoma".



**Fig. 4.01** Solid type angioleiomyoma located in the subcutis showing sharp demarcation.

### Immunohistochemistry

Most cells are positive for alpha-smooth muscle actin, desmin, vimentin and collagen type IV. According to a study by Hasegawa et al., in more than half of cases, small nerve fibres positive for both S100 protein and PGP9.5 are seen within the capsule of tumours and tumour stroma [899]. The peculiar pain of angioleiomyomas is

possibly mediated by these nerve fibres. In contrast to renal and retroperitoneal angioleiomyoma, angioleiomyomas (including the fat-containing examples) are consistently negative for HMB45.

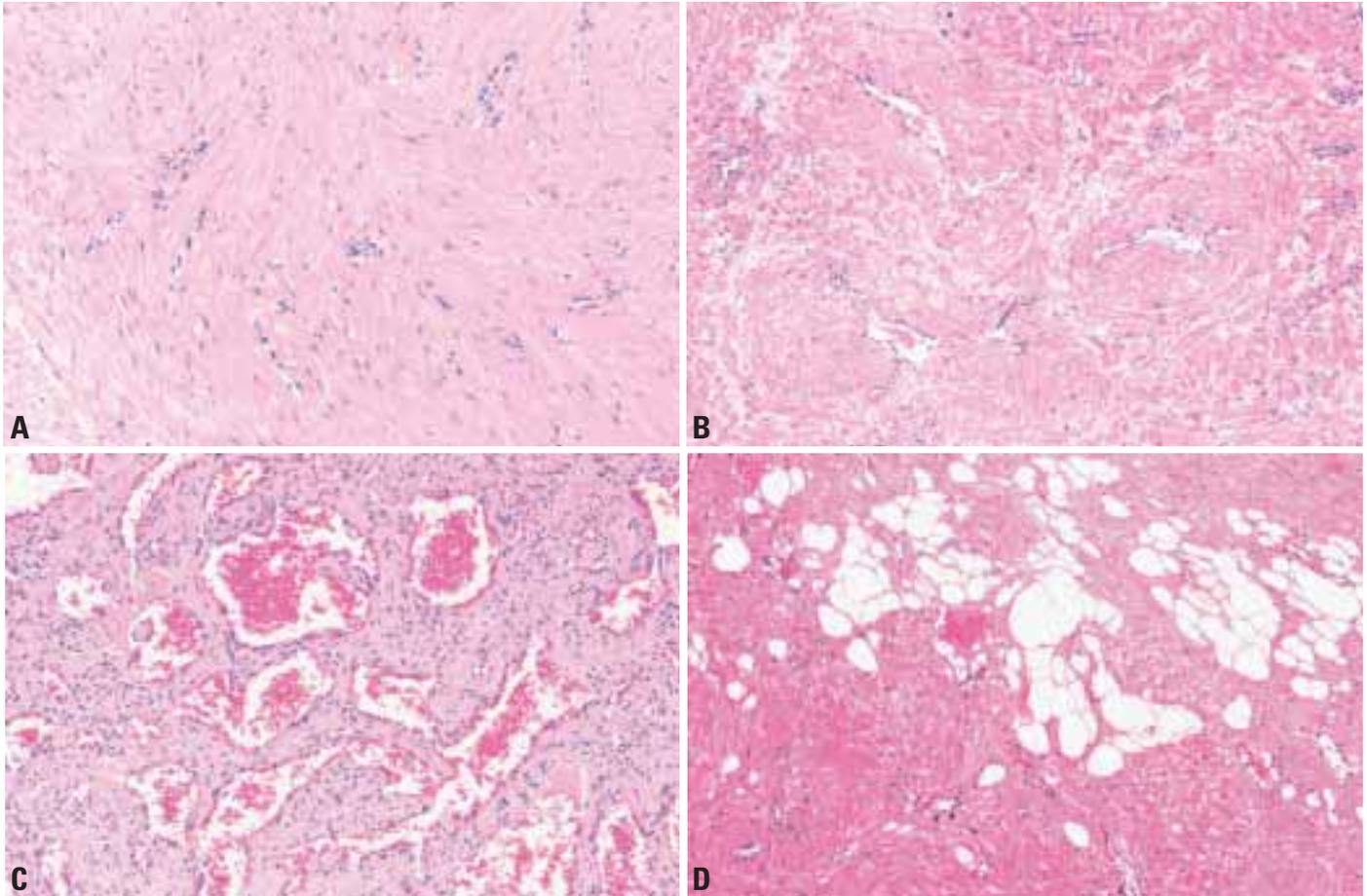
### Genetics

Cytogenetic data exist for only four angioleiomyomas from different sites.

All had near-diploid karyotypes, but no consistent abnormality has been detected among them [926,936,1567,1989].

### Prognostic factors

Angioleiomyoma is benign. Simple local excision is adequate treatment, and recurrence after excision is exceptional.



**Fig. 4.02** **A** Angioleiomyomas are typically composed of monomorphic well differentiated smooth muscle cells. **B** Solid type angioleiomyoma composed of closely compacted vascular and muscle elements. **C** Cavernous type angioleiomyoma showing dilated vascular channels with little muscular thickening of the walls. **D** Angioleiomyoma with groups of mature fat cells.

# Leiomyoma of deep soft tissue

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## Definition

A very rare type of leiomyoma that occurs in the deep somatic soft tissue or retroperitoneum/abdominal cavity.

**ICD-O code** 8890/0

## Epidemiology

The existence and diagnostic criteria of leiomyomas of deep soft tissue have been controversial, and only sporadic cases reports of leiomyomas arising in the deep soft tissue have been reported, except for the recent three large series by Kilpatrick et al. {1106}, Billings et al. {196}, and Paal and Miettinen {1636}, respectively.

## Sites of involvement

The extremities are the most common site in the deep somatic soft tissue. They arise in the deep subcutis or skeletal muscle. Pelvic retroperitoneum and abdominal cavity, including the mesentery and omentum, are other deep soft tissues where leiomyomas may occur. They are always distinct from the uterus and independent soft tissue primaries rather than parasitic leiomyomas of the uterus.

## Clinical features

Leiomyomas of the deep somatic soft tissue affect both sexes equally, whereas leiomyomas of the retroperitoneum or abdominal cavity occur almost exclusively in women {196,1636}. Most patients in both groups are young adults or middle-aged. Many lesions are calcified, so they may be detected radiographically.

## Macroscopy

Leiomyomas of the deep soft tissue are well circumscribed, grey-white tumours. The greatest diameter of 11 leiomyomas of the deep somatic soft tissue reported by Kilpatrick et al. ranged 2.5 – 15 cm (mean 7.7 cm), and most measured 5 cm or more, exceeding the usual size of angioleiomyomas {1106}. Twenty retroperitoneal and 3 abdominal leiomyomas

reported by Billings et al. ranged in size 3.2-37 cm (mean 14 cm) {196}. The greatest diameter of 51 retroperitoneal leiomyomas reported by Paal and Miettinen ranged 2.5 - 31 cm (mean 16.2 cm), and the tumour weight ranged 28 - 5400 g (mean 1600 g) {1636}. Myxoid change is common.

## Histopathology

Leiomyomas of deep soft tissue are composed of cells that closely resemble normal smooth muscle cells because they have eosinophilic cytoplasm with haematoxylin and eosin, fuchsinophilic, red-staining cytoplasm with Masson's trichrome technique and bland, uniform blunt-ended, cigar-shaped nuclei. They are arranged in orderly intersecting fascicles. They are highly differentiated, possess little or no atypia and, at most, an extremely low level of mitotic activity. In limb lesions and intra-abdominal lesions in males, mitoses number less than 1/50 HPF. In peritoneal / retroperitoneal lesions in females (showing positivity for hormonal receptors) mitoses may number up to 5/50 HPF. Necrosis should not be present in deep leiomyoma. Most lesions are paucicellular, and degenerative or regressive changes, such as fibrosis, hyalinization, calcification and myxoid change, are common in large leiomyomas. Ossification, focal epithelioid change, clear cell change and fatty differentiation {1393} are also occasionally seen. If the fatty change is prominent, such tumours should be termed myolipoma (see page 29). The significance of focal degenerative nuclear atypia is as yet not fully defined and should always prompt a careful search for mitoses and additional sampling.

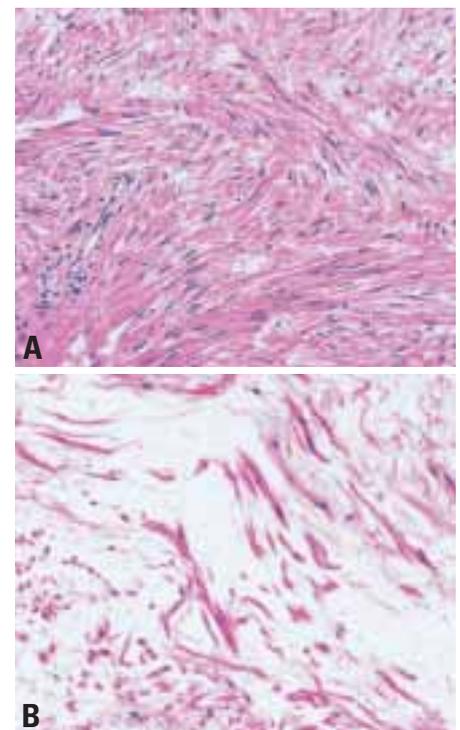
## Immunohistochemistry

Tumour cells are always positive for actin, desmin and h-caldesmon at least focally. S100 protein is negative. Billings et al. reported that all six of the retroperitoneal leiomyomas tested were positive for progesterone receptors and five

of six were positive for oestrogen receptors, probably indicating that the tumours arise from hormonally sensitive smooth muscle {196}, whereas none of the somatic leiomyomas {196} or retroperitoneal leiomyosarcomas {1636} expressed either hormone receptor protein.

## Prognostic factors

Tumours categorized as leiomyomas of the deep soft tissue should be cured by complete excision. If they recur, the recurrence should be nondestructive. Long-term follow-up did not reveal metastases, but one of 29 patients reported by Billings et al {196} and two of 36 patients reported by Paal and Miettinen {1636} had local recurrence; however, none of the patients with recurrence demonstrated disease progression in follow-up.



**Fig. 4.03** **A** Leiomyoma of the retroperitoneum composed of interlacing fascicles of bland smooth muscle cells. **B** Leiomyoma of the retroperitoneum showing myxoid change.

# Leiomyosarcoma

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## Definition

Leiomyosarcoma is a malignant tumour composed of cells showing distinct smooth muscle features.

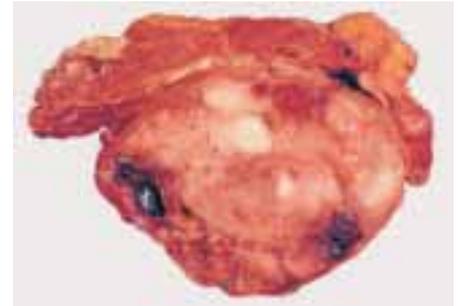
**ICD-O code** 8890/3

## Epidemiology

Soft-tissue leiomyosarcoma usually occurs in middle-aged or older persons, although it may develop in young adults and even in children {1839, 2066}. Leiomyosarcoma forms a significant percentage of retroperitoneal (including pelvic) sarcomas {906,1749,1754,1945, 2268} and is the predominant sarcoma arising from larger blood vessels {166, 1095,1243,2192}. Aside from these locations, it is a comparatively less common sarcoma, accounting for perhaps 10-15% of limb sarcomas. The sex incidence depends on tumour location, with women forming a clear majority of patients with retroperitoneal and inferior vena cava leiomyosarcomas but not of those with leiomyosarcomas in other soft tissue sites.

## Sites of involvement

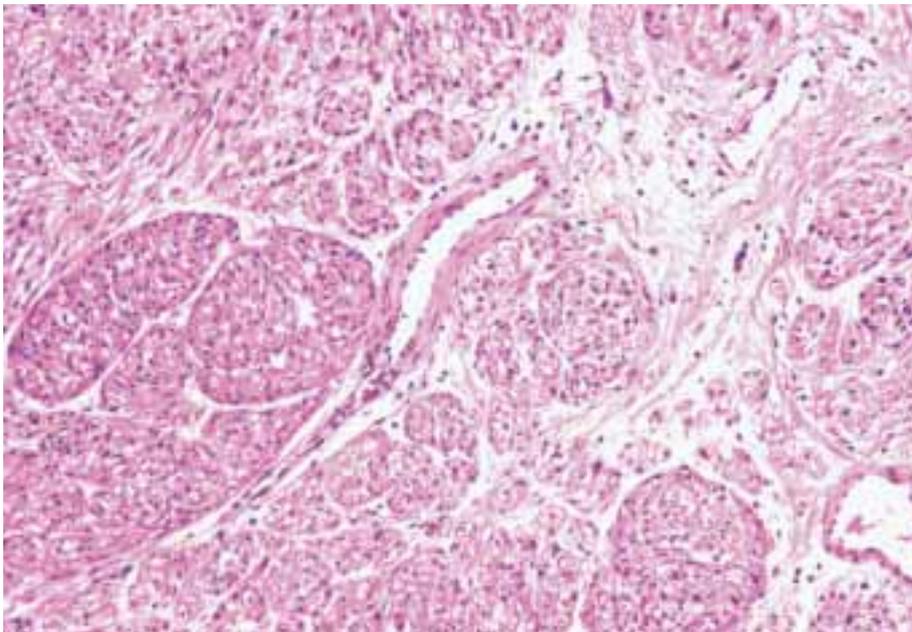
The most common location of soft tissue leiomyosarcoma is the retroperitoneum, including the pelvis. Another distinctive subgroup consists of leiomyosarcomas that arise in large blood vessels, most commonly the inferior vena cava and the large veins of the lower extremity. Arterial origin occurs but is rare; sarcomas of the pulmonary artery and other large arteries generally do not have the features of leiomyosarcoma and are better classified as intimal sarcomas (see page 223). Leiomyosarcomas involving nonretroperitoneal soft tissue sites constitute a third group {423,642,903,2039}. These are found most frequently in the lower extremity but may develop elsewhere. Intramuscular and subcutaneous localizations occur in approximately equal proportion, and some of these tumours show evidence of origin from a small to medium sized (unnamed) vein. Leiomyosarcomas also develop in the dermis, but these are discussed in the volume on tumours of the skin.



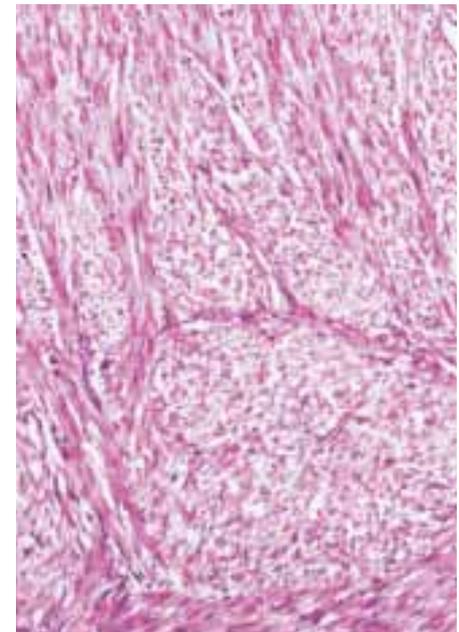
**Fig. 4.04** Leiomyosarcoma. This high grade lesion (19 cm) from the quadriceps muscle shows extensive necrosis and haemorrhage.

## Clinical features

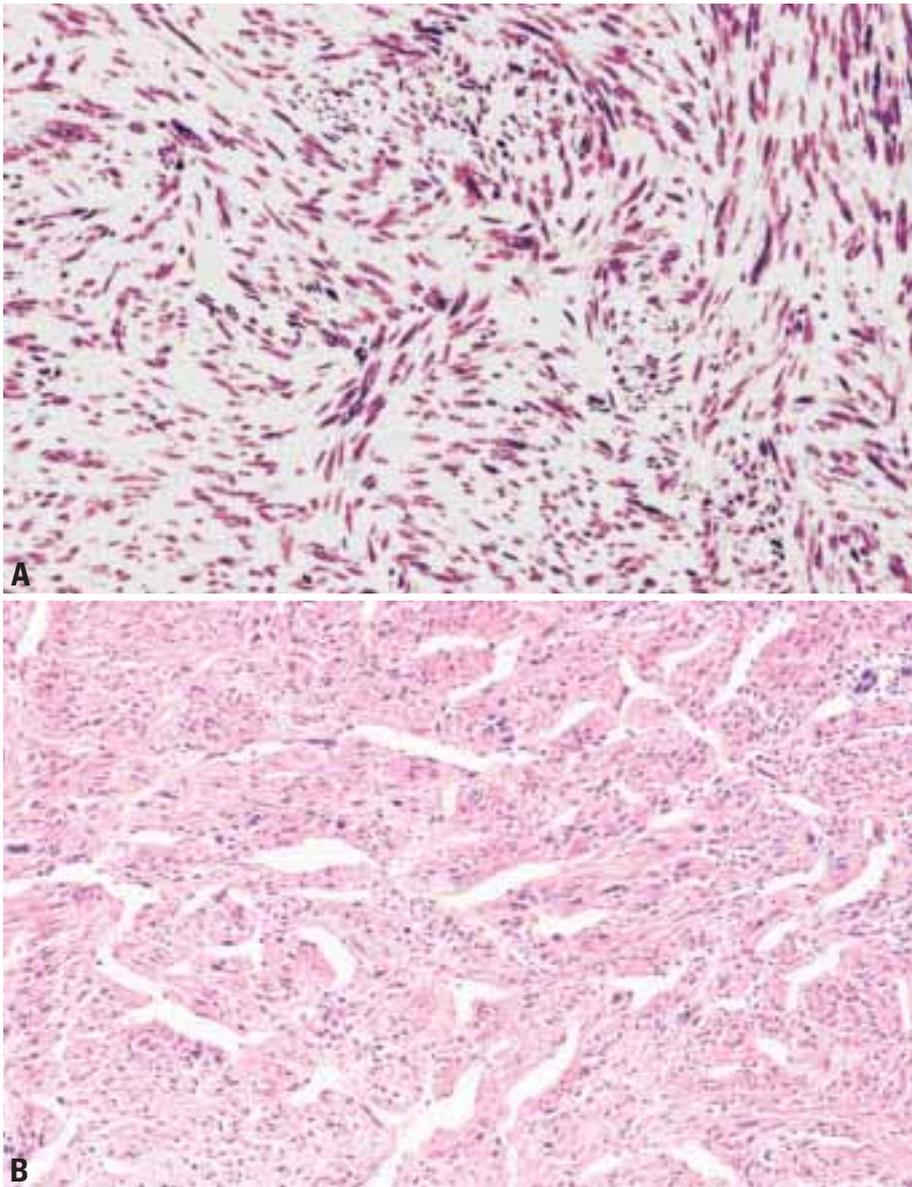
Soft tissue leiomyosarcoma generally presents as a mass lesion. With retroperitoneal tumours, pain may also be present. The symptoms produced by leiomyosarcoma of the inferior vena cava depend on the portion involved. When the tumour is in the upper portion, it obstructs the hepatic veins and produces the Budd-Chiari syndrome, with hepatomegaly, jaundice, and ascites.



**Fig. 4.05** Leiomyosarcoma composed of nodules and bundles of eosinophilic spindle cells.



**Fig. 4.06** Leiomyosarcoma with typical intersecting groups of spindle cells.



**Fig. 4.07** Leiomyosarcoma (A) showing fascicles which intersect at 90° and, in another case (B), showing a pericytoma-like vascular pattern.

Location in the middle portion may result in blockage of the renal veins and consequent renal dysfunction, whereas involvement of the lower portion may cause leg oedema. The latter may also occur with leiomyosarcomas of the large veins of the lower extremity.

Imaging studies of leiomyosarcoma demonstrate a nonspecific soft tissue mass but are helpful in delineating the relationship to adjacent structures, particularly in the retroperitoneum.

In the instance of leiomyosarcoma of vein origin, venogram may demonstrate an intraluminal component.

#### **Aetiology**

The cause of soft tissue leiomyosarcoma is unknown. The predominant occurrence of retroperitoneal and inferior vena cava leiomyosarcomas in women raises the question of hormonal influence, but this is unclear.

#### **Macroscopy**

Leiomyosarcoma of soft tissue typically forms a fleshy mass, with colours varying from grey to white to tan. A whorled character may be evident to some degree. Larger examples often display haemorrhage, necrosis, or cystic change. The tumour border

frequently appears well circumscribed, although obvious infiltrativeness may also be found. In the retroperitoneum there may be extension into adjacent organs.

#### **Histopathology**

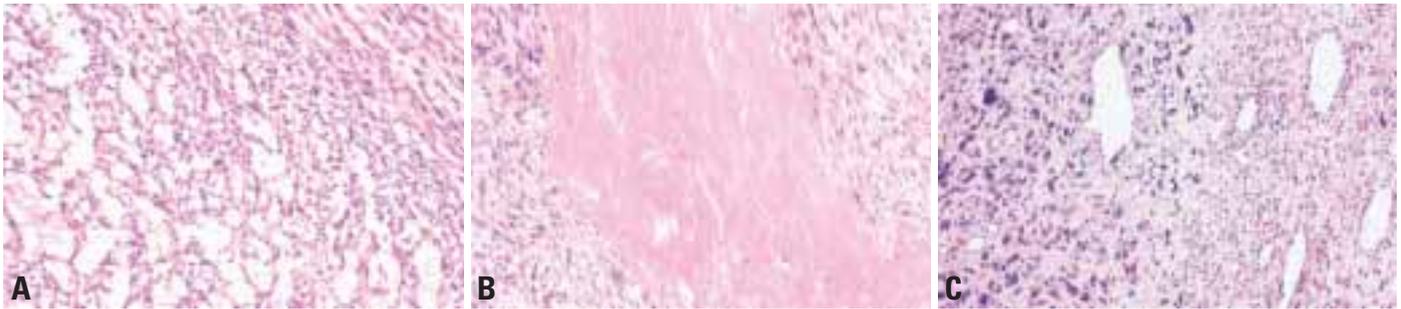
The typical histological pattern of leiomyosarcoma is that of intersecting, sharply marginated groups of spindle cells. This pattern may be less well defined in areas of some tumours, and occasionally there is a focal storiform, palisaded, or haemangiopericytoma-like arrangement. The tumours are usually compactly cellular, but fibrosis or myxoid change may be present; in the latter instance, a retiform or microcystic pattern may result. Hyalinized, hypocellular zones and coagulative tumour necrosis are frequent in larger leiomyosarcomas. Rarely there is abundant chronic or acute inflammation {1421}.

The tumour cell nuclei are characteristically elongated and blunt-ended and may be indented or lobated. Nuclear hyperchromatism and pleomorphism are generally notable, although they may be focal, mild, or occasionally absent. Mitotic figures can usually be found readily, although they may be few or patchy; and atypical mitoses are often seen. The cytoplasm varies from typically eosinophilic to pale, and in the former instance is often distinctly fibrillar. Cytoplasmic vacuolation is frequently apparent, particularly in cells cut transversely. Epithelioid cytomorphology, multinucleated osteoclastlike giant cells {1411}, very prominent chronic inflammatory cells {1421}, and granular cytoplasmic change {1573} are unusual findings that are normally present in only part of a tumour when identified.

Occasional soft tissue leiomyosarcomas contain areas with a nonspecific, poorly differentiated, pleomorphic appearance in addition to typical areas {1594}. These could be regarded as "dedifferentiated leiomyosarcomas" although this term is not in common use. Rarely, an osteosarcomalike or rhabdomyosarcomatous component is associated with leiomyosarcoma (see "malignant mesenchymoma").

#### **Immunophenotype**

SMA, desmin and h-caldesmon are positive in a great majority of soft tissue leiomyosarcomas. However, none of



**Fig. 4.08** Leiomyosarcoma showing (A) a myxoid, reticular appearance, (B) necrosis and hyalinization, and (C) abrupt transition to more pleomorphic tumour indicative of dedifferentiation.

these is absolutely specific for smooth muscle (or indeed muscle in general), and positivity for two of these markers is more supportive of leiomyosarcoma than positivity for one alone. "Dedifferentiated" areas may be negative for SMA and desmin, but total negativity for both in a tumour would cast great doubt on the diagnosis of leiomyosarcoma. Stains that may be positive, at least focally, include keratin, EMA, CD34, and S100 protein. KIT (CD117) is normally negative, in contrast to gastrointestinal stromal tumours. In general, the diagnosis of soft tissue leiomyosarcoma should not be made on the basis of immunostains in the absence of appropriate morphologic features.

#### Ultrastructure

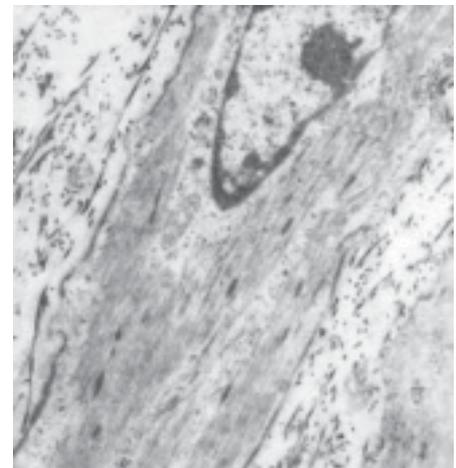
Soft tissue leiomyosarcomas usually demonstrate at least some of the ultrastructural features of normal smooth muscle cells, namely cytoplasmic filaments with densities, cell junctions, pinocytotic vesicles, and basement membrane. However, any, or occasionally, all of these may be focal or absent, and the findings may be nonspecific. It is particularly important to note that filaments with densities are present in myofibroblasts and can occur in other cells. Electron microscopy is not generally needed for the diagnosis of soft tissue leiomyosarcoma, and ultrastructural observations should always be correlated with the light microscopic appearance.

#### Genetics

##### Cytogenetics

Karyotypes from around 100 leiomyosarcomas have been reported [1477]. Most karyotypes are complex and no consistent aberrations have been noted

{2215}. Frequently lost chromosome regions include 3p21-23, 8p21-pter, 13q12-13, 13q32-qter, whereas the 1q21-31 region is often gained [1314]. No striking differences among different subtypes have been identified [1314]. Comparative genomic hybridization (CGH) has confirmed frequent numerical changes, including gain of material from chromosomes 1, 15, 17, 19, 20, 22 and X and loss from 1q, 2, 4q, 9p, 10, 11q, 13q and 16, and has identified regions of amplification, e.g., 1q21, 5p14-pter, 12q13-15, 13q31, 17p11 and 20q13) [2215]. Tumour size-related changes have been observed, such as an association of gain of 16p and 17p with smaller tumours and gain of 6q and 8q with larger tumours [577].



**Fig. 4.09** Leiomyosarcoma. Tumour cells contain prominent longitudinal filament bundles with focal densities. Note also the external lamina.



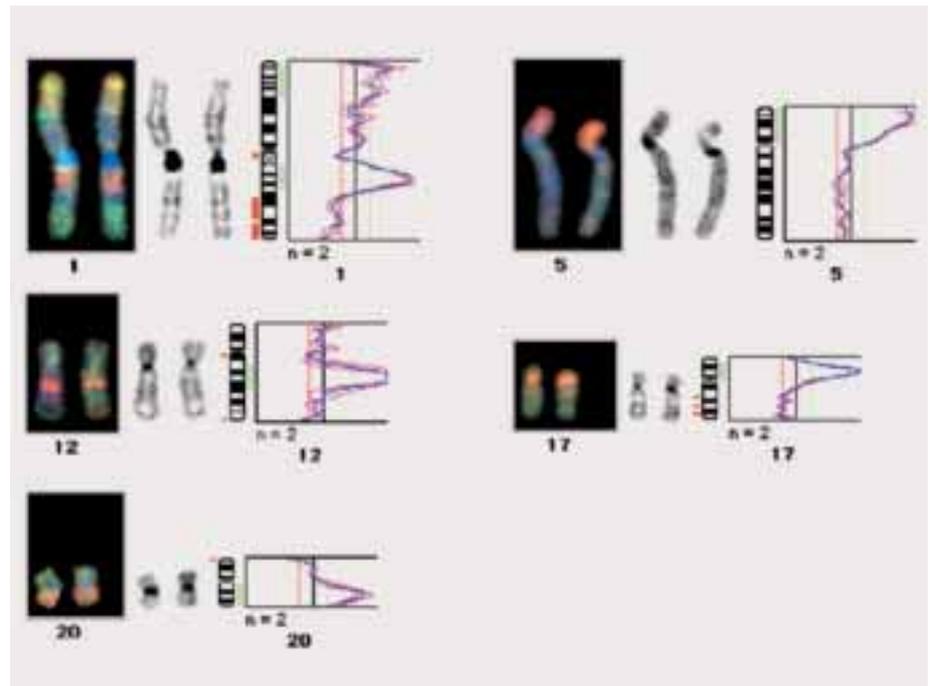
**Fig. 4.10** 24-colour karyotype and corresponding reverse DAPI-banded image from a soft tissue leiomyosarcoma showing multiple copies of chromosomes and many rearranged chromosomes.

### Molecular genetics

The *RB1* gene has been implicated, which is consistent with loss of chromosome 13 material [2042]. Analysis of the genes and proteins in the Rb-cyclinD pathway (*RB1*, *CDKN2A*, *CCND1*, and *CCND3*) has revealed frequent abnormalities in leiomyosarcomas [488]. Involvement of *TP53* and *MDM2* appears less frequent than in other sarcoma types [488,692], although such abnormalities have been suggested to correlate with a poorer prognosis in leiomyosarcomas [1668]. Amplification at a number of loci suggest candidate genes in these regions including *MDM2*, *GLI*, *CDK4* and *SAS* at 12q13-15, the *FLF* and *PRUNE* genes at 1q21, and the critical region involved in Smith-Magenis syndrome at 17p11.2 [579,692,708,709,712,1627].

### Prognostic factors

Soft tissue leiomyosarcomas are capable of both local recurrence and distant metastasis. Regional (or other) lymph node metastasis is rare. The most important prognostic factors by far are tumour location and size, which are strongly interrelated. Retroperitoneal leiomyosarcomas are fatal in the great majority of cases; they are typically large (over 10 cm), often difficult or impossible to excise with clear margins, and prone to both local recurrence and metastasis. Leiomyosarcomas of large vessels also tend to have a poor prognosis, although local control rates are higher except for those in the upper inferior vena cava, and very small examples (1-2 cm) may be less prone to metastasize. Nonretroperitoneal soft tissue leiomyosarcomas are generally smaller than those in the retroperitoneum, more amenable to local control, and more favourable in outlook overall. In some studies, intramuscular



**Fig. 4.11** Amplification in leiomyosarcomas identified by CGH analysis. CGH images, reverse DAPI-banded chromosomes and corresponding profiles of the red to green fluorescence intensities are shown and indicate amplification at 1q21-q25, 5p, 12q13-q21, 17q11.2-q12 and 20q, respectively.

rather than subcutaneous location [903] and larger tumour size [642, 1479] were related to increased metastasis and poorer patient survival within this group. Histological grading as well as osseous and vascular involvement are reliable prognostic indicators.

Local recurrences and metastases of soft tissue leiomyosarcoma usually become manifest within the first few years after diagnosis but may appear as much as 10 years later. For retroperitoneal leiomyosarcomas, the most common sites of metastases are the lungs and liver, whereas the lungs are the dominant location when the primary tumour is nonretroperitoneal. Metastases also occur with some frequency in skin, soft tissue, and bone.

### Smooth muscle tumours in immunocompromised patients

Smooth muscle tumours in immunocompromised individuals, to this point described only in single case reports and small series, form a distinctive subgroup. These usually involve parenchymal organs rather than soft tissue, occur predominantly in children and young adults who are HIV positive [323,1368,1811, 2179] or post-transplant, and are associated with Epstein-Barr virus. The tumours may be multifocal, and at least in some instances this appears to represent true multicentricity rather than metastasis [1811,1985]. Histologically, they range from bland to mitotically active, may have a variable lymphocytic infiltrate of uncertain significance and may show a perivascular growth pattern.