Virchows Arch (1995) 427:353–363
© Springer-Verlag 1995

REVIEW ARTICLE

Thomas Mentzel · Christopher D.M. Fletcher

Lipomatous tumours of soft tissues: an update

Received: 6 June 1995 / Accepted: 28 August 1995

Abstract This review summarizes the clinicopathological features of recently characterized variants of lipomatous tumours of soft tissue, attempts to deal with some difficult conceptual issues relating to adipocytic neoplasms and aims to provide an update on cytogenetic aspects of fatty tumours. Myolipoma is a rare benign neoplasm, occurring most frequently in adults in the deep soft tissue of the abdomen or retroperitoneum, and is composed of irregularly admixed mature adipose and smooth muscle tissues. Chondroid lipoma represents an unusual benign lesion occurring mainly in adult females subcutaneously or in deep soft tissue; it is easily mistaken for myxoid liposarcoma or extraskeletal myxoid chondrosarcoma. Spindle-cell liposarcoma is a variant of well-differentiated liposarcoma quite commonly found in subcutaneous tissue of the shoulder region and upper limbs and is composed of relatively bland-appearing spindle cells mixed with a well-differentiated liposarcomatous component. Recently there has been considerable debate about classification of lipomatous tumours. The term atypical lipoma was proposed for a group of well-differentiated non-metastasizing liposarcomas arising in surgically amenable soft tissues and for deep-seated atypical adipocytic neoplasms that show variation in adipocytic size and atypical stromal cells but lack lipoblasts. However, these neoplasms recur repeatedly and may dedifferentiate and thereby acquire metastatic potential. We use the diagnosis atypical lipoma with caution and propose to use the terms well-differentiated liposarcoma and atypical lipoma interchangeably. The relationship between myxoid and round-cell liposarcoma, which constitutes the morphological spectrum of a single entity, has been clarified but there remain considerable problems in defining likely clinical behaviour. The recent advances in cytogenetic characterization and classification of lipomatous tumours, which is already proving to be of diagnostic importance, are reviewed, and the genetic importance of the distinct chromosomal translocation in myxoid/round cell liposarcoma is briefly discussed.

Key words Adipose tissue · Classification · Lipoma · Liposarcoma · Atypical lipoma · Cytogenetic

T. Mentzel · C.D.M. Fletcher (✉)[1]
Soft Tissue Tumour Unit, Department of Histopathology, St. Thomas's Hospital, London, UK

T. Mentzel
Institute of Pathology, Jena, Germany

Mailing address:[1] Division of Surgical Pathology, Department of Pathology, Brigham & Women's Hospital, Francis Street, Boston, MA 02115, USA

Introduction

Lipomatous tumours are the most common soft tissue tumours and form part of the daily practice of every surgical pathologist. With rare exceptions they may occur at any age and at almost any anatomical location. Although typical lipoma and liposarcoma are straightforward diagnoses, over the last few years several distinct variants of benign and malignant lipomatous tumours have been described, which may cause diagnostic problems. Their recognition is important to avoid diagnostic pitfalls and inappropriate therapy. The diagnosis of well-differentiated liposarcoma has become a subject of considerable debate because of a proposed change in nomenclature. It has been realised in large studies with long follow-up information that pure well-differentiated liposarcoma never metastasizes and therefore the term atypical lipoma has been proposed [2, 17, 29]. Lesions fulfilling the diagnostic criteria for atypical lipoma may dedifferentiate if they recur repeatedly [56], and dedifferentiation may occur rarely also in subcutaneous tissues [36]. A further conceptual problem is the relationship between myxoid and round cell liposarcoma because of overlapping clinicopathological features and shared cytogenetic abnormalities. The spectrum of clinical behaviour in such lesions is wide and reliable prognostication may be difficult.

In order to provide an update on the group of adipocytic tumours of soft tissues, we review recently described entities and variants (see also Table 1), discuss controver-

Table 1 Updated classification of lipomatous tumours of soft tissue

Benign tumours
Subcutaneous lipoma (solitary/multiple)
Deep lipoma
– Intramuscular lipoma
– Intermuscular lipoma
– Synovial lipoma (lipoma arborescens)
– Neural fibrolipoma (fibrolipomatous hamartoma of nerve)
Lipoblastoma/lipoblastomatosis
Angiolipoma
– Cellular angiolipoma
Myolipoma
Chondroid lipoma
Extrarenal angiomyolipoma
Extraadrenal myelolipoma
Spindle cell/pleomorphic lipoma
– Pseudoangiomatous variant
Hibernoma
Lipomatosis
– Diffuse lipomatosis
– Cervical symmetrical lipomatosis
– Pelvic lipomatosis
Malignant tumours
Well-differentiated liposarcoma (atypical lipoma)
– Adipocytic (lipoma-like) liposarcoma
– Sclerosing liposarcoma
– Inflammatory liposarcoma
– Spindle-cell liposarcoma
– Dedifferentiated liposarcoma
Myxoid/round cell liposarcoma
Pleomorphic liposarcoma

sies in classification and review recent advances in cytogenetic studies and their molecular correlation which are of help in the diagnosis and classification of lipomatous lesions and bring new insight into tumour biology.

Recently described entities

Myolipoma

Clinical features

Myolipoma (or lipoleiomyoma [48]) is a recently described, rare neoplasm occurring in adults, most commonly in the abdomen, retroperitoneum and the abdominal wall, and only rarely arising in subcutaneous tissue [37]. Although myolipoma can reach a considerable size (the median size of all 10 reported cases is 17 cm in greatest diameter), these lesions often are found only incidentally because of their deep location. None of the lesions with follow-up information has recurred or metastasized.

Morphological findings

Grossly, the lesions are completely or partially encapsulated with glistening, myxoid, or yellow-white cut surfaces. Histologically, myolipoma is composed of an irregular admixture of mature adipocytic tissue and bundles and sheets of well-differentiated smooth muscle in varying proportions (Fig. 1). Both components are entirely mature and cytologically bland without nuclear atypia (Fig. 2). Small blood vessels are variably prominent and scattered inflammatory cells may be seen, whereas necrosis, cystic change or haemorrhage, and increased mitotic activity are absent. Immunohistochemistry positivity for smooth muscle actin and desmin in most cases and electron microscopy in one case confirmed the coexistence of smooth muscle and adipocytic differentiation.

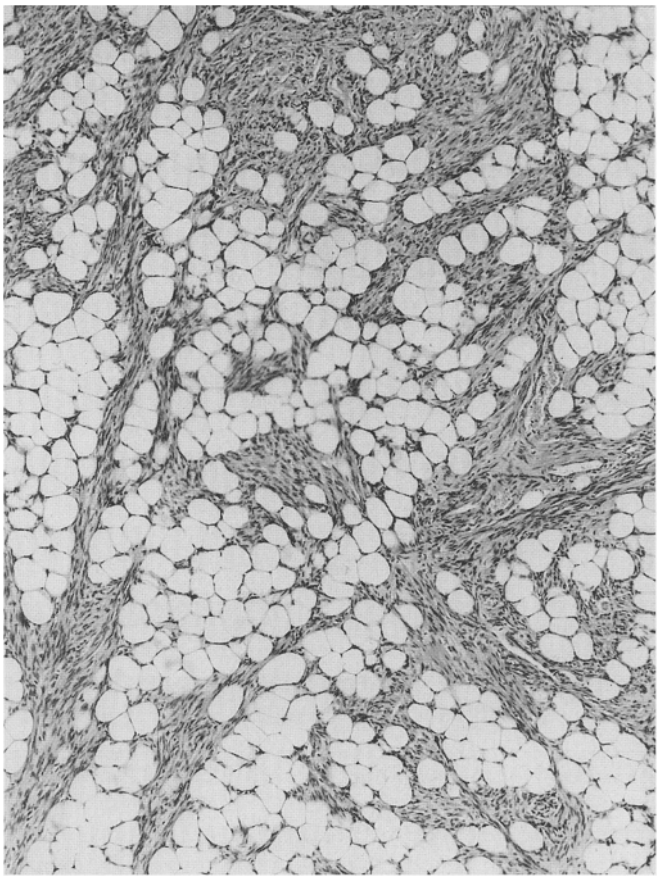

Fig. 1 Myolipoma. Note the even admixture of smooth muscle and fat cells. HE, ×63

The existence of a dual-lineage tumour consisting of smooth muscle and adipocytic elements is of interest, since clonal chromosomal aberrations in lipomas and leiomyomas involve similar regions of chromosome 12 [21] (see below).

Myolipoma is a distinct entity that appears to follow a benign clinical course despite its frequently large size and deep location. The regular distribution of adipose tissue throughout the lesion distinguishes myolipoma from leiomyoma with degenerative fatty change, the lack of thick-walled blood vessels and infiltrating borders as well as the immunonegativity of the smooth muscle com-

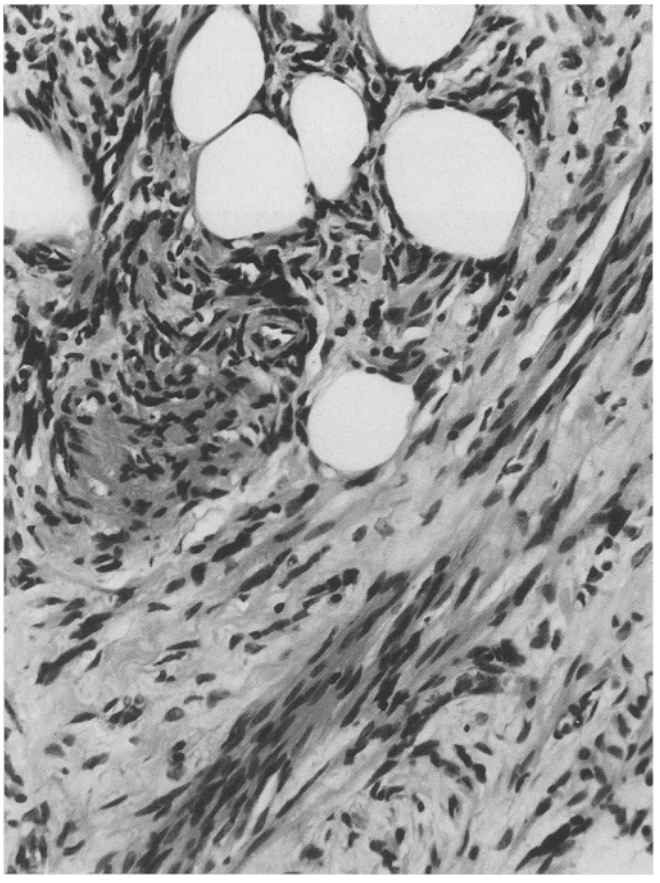

Fig. 2 Myolipoma. The constituent cells are cytologically bland and well-differentiated. HE, ×250

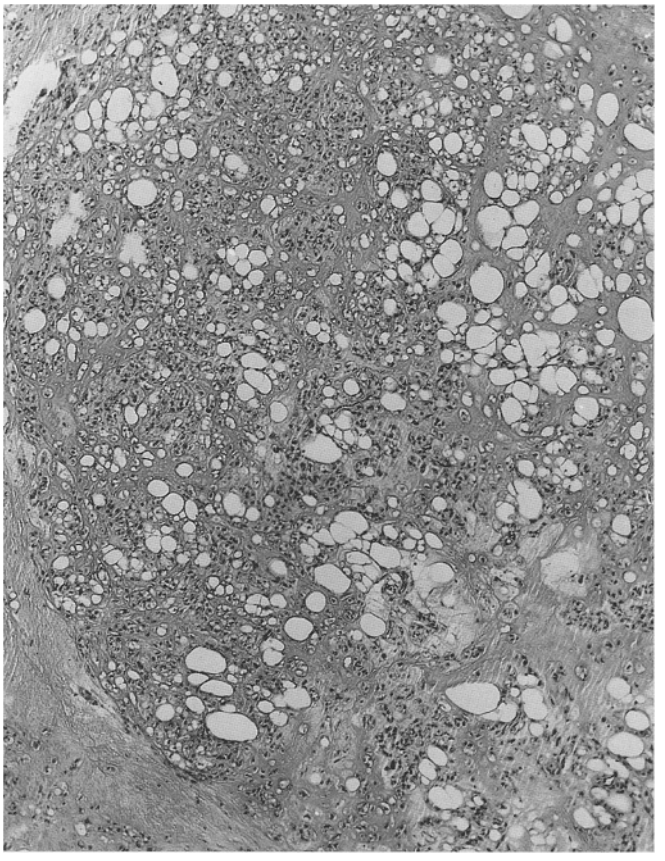

Fig. 3 Chondroid lipoma. Note the admixture of adipocytic and vacuolated cells in a myxohyaline matrix. HE, ×63

ponent for HMB-45 argue against angiomyolipoma, and the bland cytomorphology of both components helps in distinction from liposarcomatous/atypical lipomatous lesions associated with a smooth muscle component [15]. Spindle-cell lipoma does not contain a smooth muscle component and is found mainly subcutaneously on the lower neck or upper back [11, 20]. Although it may seem somewhat arbitrary to separate myolipoma from the heterogeneous group of lesions referred to in the past as benign mesenchymomas, the precise recognition of myolipoma is important, especially in deep-seated, large lesions, to prevent confusion with liposarcoma with heterologous elements (see below).

Chondroid lipoma

Clinical features

Chondroid lipoma is a rare benign fatty tumour, with no reported recurrences or metastases, which is very easily mistaken for myxoid liposarcoma or extraskeletal myxoid chondrosarcoma. It affects mainly adult females, and is found subcutaneously or in deeper soft tissues in the limbs and limb girdles, the trunk, and the head and neck region [38]. The median size of all reported lesions to date is 4 cm.

Morphological findings

Chondroid lipoma presents as a well-demarcated, often-encapsulated mass with a rubbery, yellow cut surface. Histologically, these lobulated tumours are composed of an admixture of mature adipocytes, eosinophilic and vacuolated cells, which contain glycogen and fat droplets, set in a myxohyaline matrix that has a somewhat cartilaginous appearance (Fig. 3). Frequently the eosinophilic and vacuolated tumour cells are arranged in sheets, clusters and cords and contain irregular, hyperchromatic nuclei with inconspicuous nucleoli; some of the vacuolated cells are indistinguishable from lipoblasts (Fig. 4). Most lesions show prominent vascularization, varying from thick-walled to thin-walled blood vessels or cavernous vascular spaces. A plexiform pattern of delicate small vessels is absent.

Whereas reactive and degenerative changes such as haemorrhage, haemosiderin deposition, and hyalinization are frequently seen, cellular pleomorphism and increased mitotic activity are absent. Immunohistochemically, tu-

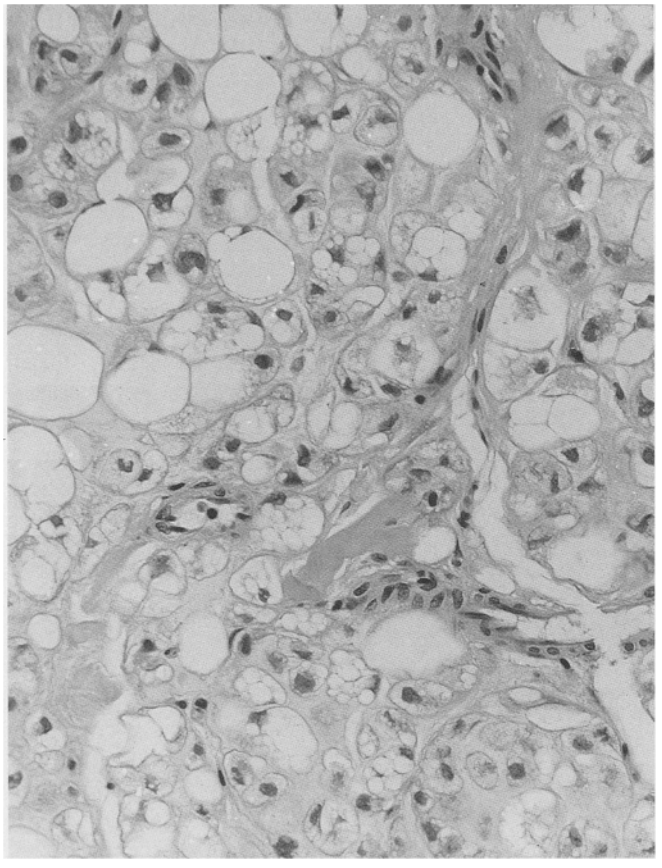

Fig. 4 Chondroid lipoma. Some of the vacuolated cells are identical to lipoblasts, while other smaller cells resemble chondroblasts. HE, ×250

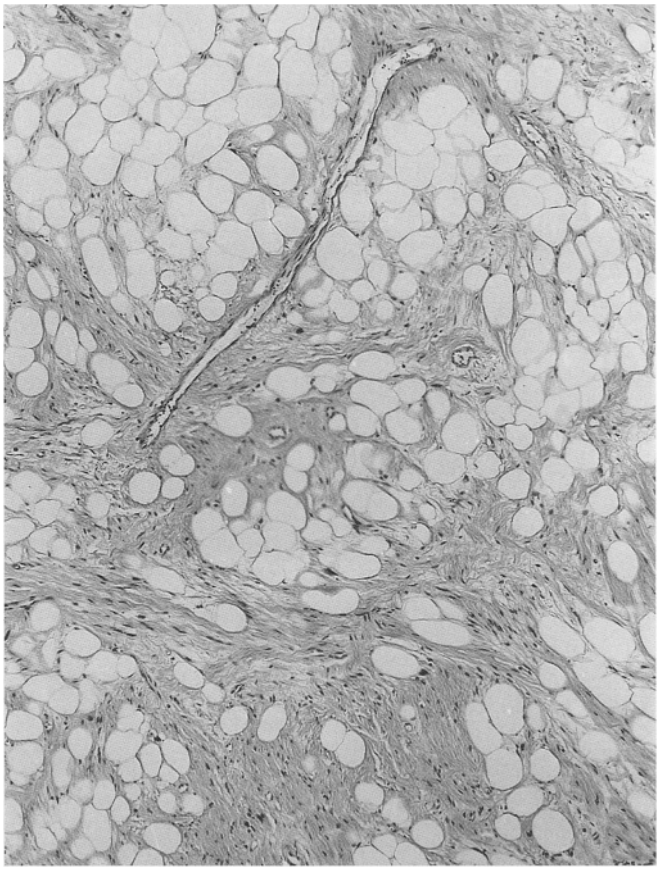

Fig. 5 Spindle-cell liposarcoma. The lesion is composed of variously sized adipocytes and spindle-cell areas. HE, ×63

mour cells stain positively for vimentin and S-100 protein, and focal staining for CD68 in the vacuolated tumour cells has been noted [38].

Chondroid lipoma has to be distinguished from soft tissue chondroma and is easily mistaken for sarcoma, especially myxoid liposarcoma and extraskeletal myxoid chondrosarcoma.

Although some years ago a similar lesion was described as extraskeletal chondroma with lipoblast-like cells [5], it is more likely that it represents a chondroid lipoma. Soft tissue chondroma occurs in the hands and feet and often contains multinucleated giant cells along with variably cellular hyaline cartilage. The multivacuolated cells can be indistinguishable from true lipoblasts, and the areas of myxoid/chondroid matrix surrounding strands of multivacuolated hibernoma-like cells may resemble myxoid liposarcoma as well as myxoid chondrosarcoma. However, the overall architecture of chondroid lipoma, and the lack of plexiform vascularity and relatively uniform lipoblasts distinguish chondroid lipoma from myxoid liposarcoma. Extraskeletal myxoid chondrosarcoma shows distinct lobulation with peripheral tumour cell accumulation, and the characteristic cells are uniformly round or oval; multi-vacuolated forms are absent.

Spindle-cell liposarcoma

Clinical features

Spindle-cell liposarcoma is a recently described, uncommon variant of well-differentiated liposarcoma [10], which occurs in adults and is located quite frequently in subcutaneous tissue, often around the shoulder girdle or upper limbs. Despite location in subcutaneous tissue and well-differentiated morphology, three out of six cases reported in the original series recurred locally, and in one case dedifferentiation occurred, followed by systemic metastases and death of the patient. Subsequent personal unpublished experience has revealed an increasing number of cases in deeper soft tissue of the limbs, abdomen and neck, comparable to other types of well-differentiated liposarcoma.

Morphological findings

Grossly, the tumours are firm in consistency with pale cut surfaces, often containing gelatinous-appearing foci. The lesions show varying cellularity and are composed histologically of relatively bland spindle cells arranged

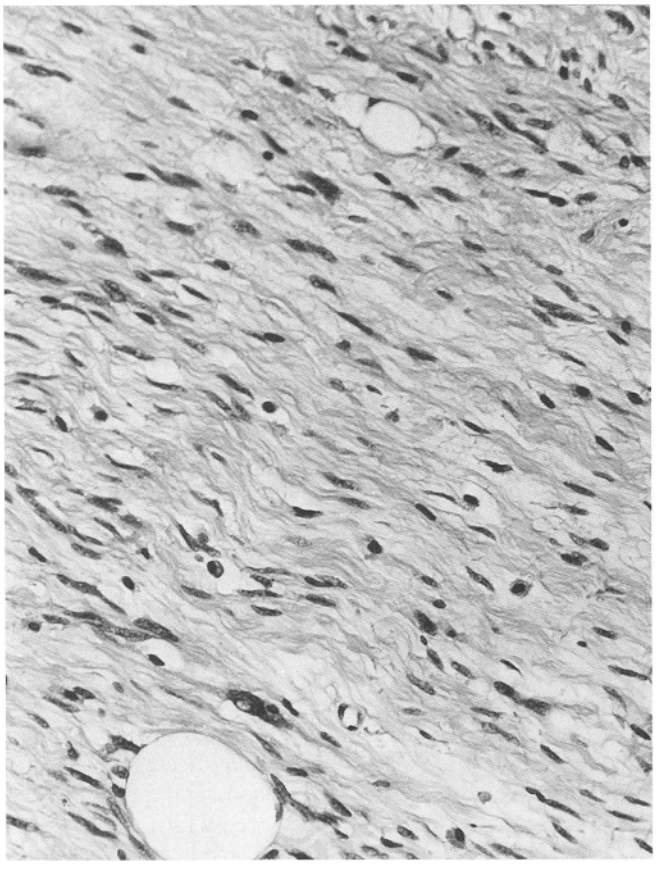

Fig. 6 Spindle-cell liposarcoma. The spindle cells have tapering, somewhat hyperchromatic nuclei. Note the lipoblast (*top*). HE, ×250

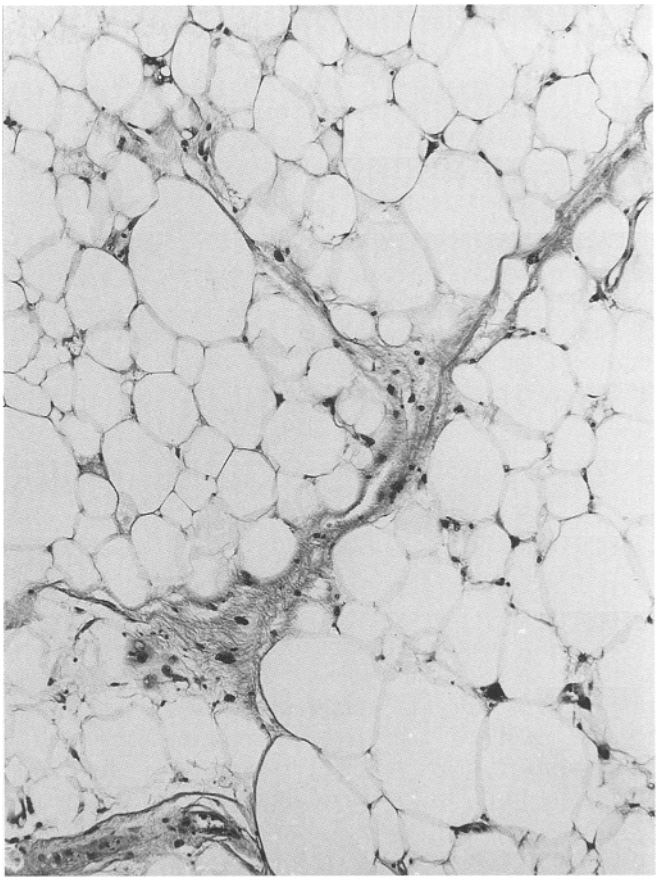

Fig. 7 Spindle cell liposarcoma. In the lipomatous areas, note variation in cell size and the atypical nuclei in both adipocytes and stromal cells. HE, ×100

in short fascicles or whorls or sometimes in a storiform fashion, and a well-differentiated liposarcomatous component (Fig. 5). The fusiform cells have poorly demarcated, palely eosinophilic cytoplasm and hyperchromatic nuclei (Fig. 6). Nuclear atypia in the spindle-cell component is only mild, and mitoses are scarce. Myxoid change and hyalinization of the intercellular matrix and a patternless capillary network are quite often seen. The adipocytic component shows striking variation in cell size and shape, hyperchromatic and atypical adipocytic nuclei and scattered lipoblasts, as well as atypical stromal cells (Fig. 7). Whereas the adipocytic component often stains positively for S-100 protein, the spindle cells are negative but demonstrate immunopositivity for vimentin. Single cells may be positive for CD34 and desmin in some cases.

The main differential diagnoses of spindle-cell liposarcoma include spindle-cell lipoma (characterized by bland, sometimes palisaded spindle cells and brightly eosinophilic refractile collagen bundles), neurofibroma (less cellular, no mitoses, wavy bland nuclei, minimal nuclear pleomorphism, and S-100 positive), dermatofibrosarcoma protuberans (distinctive storiform growth pattern and honeycomb pattern of infiltration, no lipoblasts, diffusely CD34 positive), well-differentiated sclerosing liposarcoma (less cellular, dense fibrillary collagen, bizarre stromal cells), and low-grade MPNST (typically comma-shaped nuclei, perivascular tumour cell condensation, no lipoblasts, more consistent S-100 positivity). The adipocytic component in spindle-cell liposarcoma helps in distinction from low-grade myxofibrosarcoma and low-grade fibromyxoid sarcoma as described by Evans [16]. Spindle-cell liposarcoma is a distinctive entity and appears quite different from the poorly defined, so-called fibroblastic liposarcoma [19].

Conceptual problems in classification of liposarcoma

Liposarcoma is the single most common soft tissue sarcoma, accounting for 20% of cases [31]. Peak age incidence is between the 5th and 7th decades in the case of well-differentiated and pleomorphic liposarcoma and approximately 10–15 years sooner for myxoid/round cell liposarcoma [12, 28]. Liposarcoma is exceedingly rare in children under 10 years of age, with only four well-documented cases in the English literature [40]. Because of striking differences in clinical and morphological features, supported by cytogenetic studies, as well as different prognosis, classification of liposarcoma into subtypes

is necessary. Enzinger and Winslow [12] described four main subtypes, well-differentiated, myxoid, round-cell, and pleomorphic liposarcoma, and in the new WHO classification dedifferentiated liposarcoma, a fifth subtype, is added [55]. It seems, however (and cytogenetic studies support this), that liposarcoma occurs in three principal forms:

1. Well-differentiated liposarcoma with adipocytic (lipoma-like), sclerosing, spindle-cell, inflammatory, and dedifferentiated variants.
2. Myxoid liposarcoma, which forms a continuous spectrum with the round cell type.
3. Pleomorphic liposarcoma.

It is rare for combined types to be found.

The atypical lipoma controversy

Well-differentiated liposarcoma occurs with approximately equal frequency in the limbs and retroperitoneum. Grossly, well-differentiated liposarcoma tends to be well-circumscribed and lobulated with lipoma-like, and often firmer, yellow-grey areas on the cut surface. Histologically, well-differentiated liposarcoma is seen mainly in its adipocytic (lipoma-like) form and less often in its sclerosing form, which is commonest in the retroperitoneum and spermatic cord. Adipocytic (lipoma-like) liposarcoma is composed of mature-appearing adipocytes showing considerable variation in cell size and, at least focally, atypical, hyperchromatic nuclei. The latter are most frequently seen within the fibrous stroma, which occasionally contains bizarre, multinucleated stromal cells; bizarre cells may also be seen in perivascular fibrous tissue or in vessel walls. Typical lipoblasts are sometimes hard to find or completely absent; they can be seen most frequently around the fibrous septa, mainly in multivacuolated forms. Occasionally, metaplastic bone [28], cartilage, or smooth muscle differentiation within well-differentiated liposarcoma [15] are noted. Well-differentiated sclerosing liposarcoma is characterized by dense fibrillary collagen containing characteristically bizarre, often multinucleated, hyperchromatic stromal cells and infrequent lipoblasts.

Dedifferentiated liposarcoma, delineated as an entity by Evans [14], is defined by its abrupt transition from well-differentiated liposarcoma, either adipocytic, sclerosing, or spindle-cell type, to high-grade, non-lipogenic sarcoma (Fig. 8). This phenomenon occurs more often de novo than in recurrent well-differentiated liposarcoma [27, 36]. Dedifferentiated liposarcoma is most frequently seen in the retroperitoneum; however, the anatomical distribution is wide, and it also occurs in deep soft tissues of the extremities and occasionally in subcutaneous tissue [10, 36]. The dedifferentiated component histologically most often resembles storiform "MFH", pleomorphic "MFH", myxofibrosarcoma or myxoid embryonal rhabdomyosarcoma. Recently, the occurrence of heterologous elements in the dedifferentiated component, such as rhabdo- and leiomyosarcomatous, as well as osteo-and angiosarcomatous, elements has been reported [18, 52]. In rare instances a micronodular pattern of dedifferentiation may occur, raising important questions about the pathogenetic and molecular genetic mechanisms underlying this process [36].

Contrary to popular belief and despite the pleomorphic pattern in dedifferentiated areas, dedifferentiated liposarcoma has a better prognosis than other pleomorphic sarcomas, since less than 25% of de novo dedifferentiated liposarcomas have metastasized [14, 25, 27, 36]. If dedifferentiated liposarcoma occurs in the retroperitoneum it may kill the patient by local destructive growth rather than by distant metastases, as is also the case with

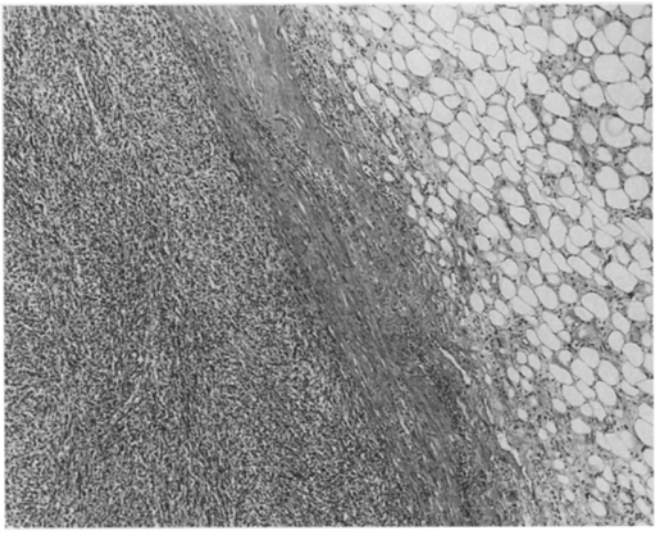

Fig. 8 Dedifferentiated liposarcoma. Note the transition from well-differentiated lipogenic tumour to high-grade spindle-cell sarcoma. HE, ×63

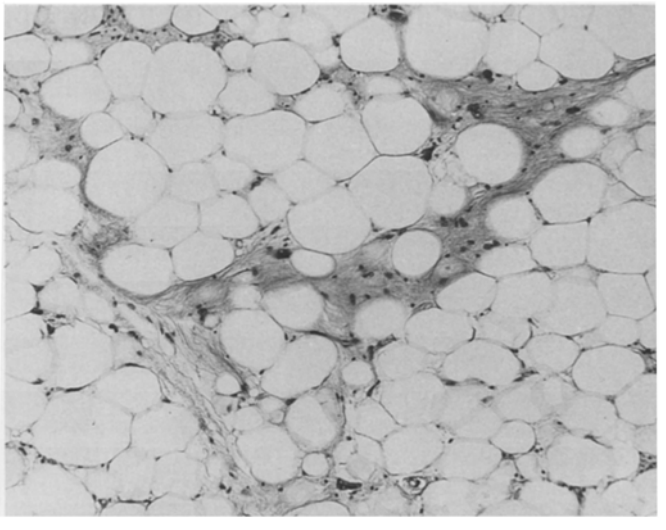

Fig. 9 Atypical lipoma. Note the bizarre stromal cells in the fibrous septa and the variously-sized adipocytes. HE, ×100

well-differentiated liposarcomas at this location. It seems that the extent of dedifferentiation in these lesions does not affect the prognosis significantly [27]. The observation that dedifferentiated liposarcomas may show an entirely well-differentiated appearance in subsequent recurrence adds support to the classification of these lesions as a variant of well-differentiated liposarcoma.

In recent years it has become obvious in clinicopathological and prognostic studies that well-differentiated liposarcoma in its histologically pure form does not metastasize and that wide excision of such lesions arising in surgically amenable soft tissue is almost always curative. It was Harry Evans and his group who first introduced the term 'atypical lipoma' as an alternative, more appropriate term for well-differentiated liposarcomas located subcutaneously and inter- and intramuscularly in the extremities, because lesions of this kind were capable of local recurrence, but did not behave in a locally destructive fashion or metastasize [17]. Other authors proposed that atypical lipoma could be characterized by univacuolated fat cells, varying in size and shape and with nuclear atypia and moderate pleomorphism but without lipoblasts, and that the term well-differentiated liposarcoma should be retained for adipocytic neoplasms containing atypical multivacuolated lipoblasts and for lipomatous tumours characterized by pronounced nuclear pleomorphism and containing numerous spindle-shaped cells and multinucleated cells [29]. Later the term atypical lipomas was also used for atypical adipocytic tumours arising in deep soft tissue, especially retroperitoneum, which showed considerable variation in adipocytic size and contained multinucleated or fusiform cells but lacked lipoblasts [14] (Fig. 9), and it was suggested that the term well-differentiated liposarcoma should be abandoned entirely.

The designation of these tumours as atypical lipomas could emphasize a role for more conservative therapy; however,several comments are pertinent to an understanding of the true nature of these neoplasms. First, it is well known that these lesions often recur locally if not widely excised, regardless of their location [2, 12–14, 17, 28, 29], and that local recurrence increases the possibility of dedifferentiation and progression to a more aggressive neoplasm capable of metastasis. It has been shown clearly that dedifferentiation in lipomatous lesions is a time-dependent phenomenon rather than a site-dependent phenomenon [5] and can also occur in the extremities and subcutaneously [36]. Secondly, it has to be emphasized that these lesions (like all mesenchymal neoplasms) should always be thoroughly sampled to exclude areas of any higher grade before recording the optimistic diagnosis of atypical lipoma. In day-to-day practice we use the terms interchangeably (well-differentiated liposarcoma/atypical lipoma), depending on circumstances and on the degree of clinicopathological liaison with the surgeons, because misinterpretation of the nature of these lesions may lead to either excessive or inadequate treatment.

In contrast, spindle-cell/pleomorphic lipomas [11, 20] are part of a spectrum of entirely benign lesions, which have to be distinguished from atypical lipoma. Most recently published cytogenetic differences support the separation of spindle-cell/pleomorphic lipoma from atypical lipoma [35]. They develop in mid- to adult life, show a striking male predominance and are found subcutaneously, mainly on the lower neck or upper back. Spindle-cell/pleomorphic lipomas recur very rarely and never progress to lesions with metastatic potential.

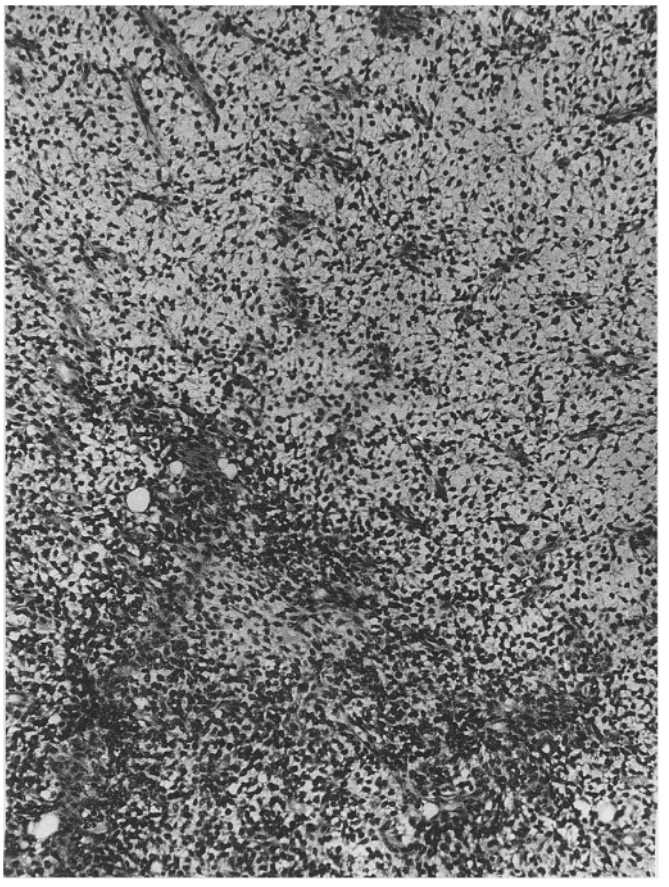

Fig. 10 Myxoid and round cell liposarcoma. Note the transition to more cellular (high-grade) areas. HE, ×100

Myxoid/round-cell liposarcoma

Myxoid and round-cell liposarcoma were classified in the past as two independent subtypes of liposarcoma; however, it has long been stated that combined myxoid/round-cell lesions occur and that the two subtypes have clinically overlapping features [12, 28]. Again it was Harry Evans who proposed abandoning the term round-cell liposarcoma and calling the entity instead myxoid liposarcoma with hypercellular zones [13, 14], and others subsequently agreed that round-cell liposarcoma is a high-grade malignant lesion in the morphological spectrum of myxoid liposarcoma [2]. Since reports of ultrastructurally shared features [3], recent cytogenetic and molecular studies have lent further credence to the idea that myxoid and round-cell liposarcoma constitute one single defined tumour entity characterized by a reciprocal (12;16) chromosome

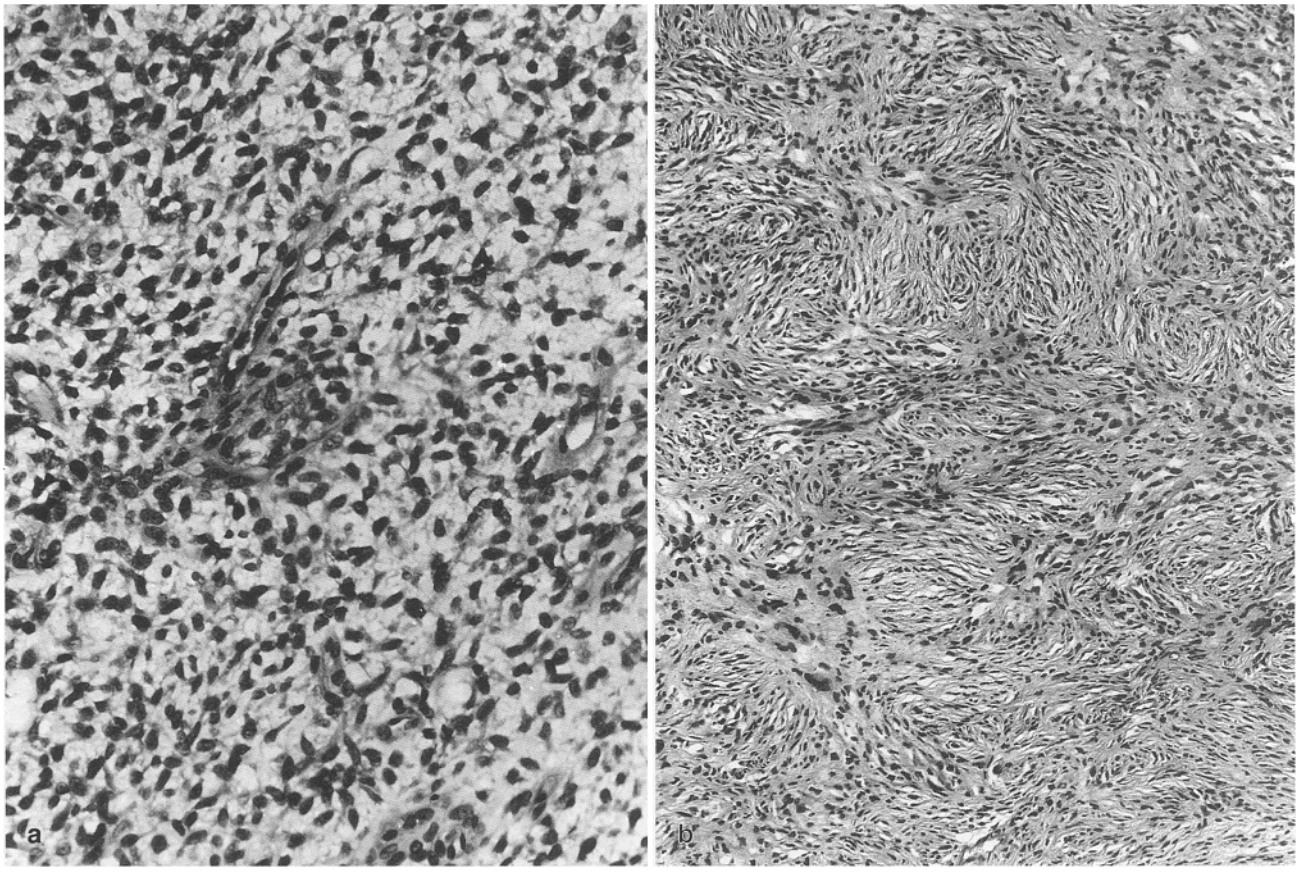

Fig. 11 **a, b** Dedifferentiated myxoid liposarcoma. In some areas this tumour showed features of hypercellular myxoid liposarcoma (**a**) but, elsewhere it showed transition to non-lipogenic 'MFH-like' tumour (**b**). HE, **a** ×250, **b** ×100

translocation and show a continuous spectrum from pure myxoid liposarcoma (low-grade malignancy) to round-cell liposarcoma (high-grade malignancy) [30, 51]. Myxoid/round-cell liposarcoma accounts for around 30–35% of all liposarcomas. With regard to anatomical location, however, it comprises the majority of liposarcomas arising in deep soft tissues of the extremities [4, 44]. A small proportion of myxoid/round-cell liposarcomas occurs in the subcutaneous tissue of the extremities.

Grossly, typical myxoid liposarcoma shows a glistening cut surface. The occurrence of grey-white or grey-brown, and firmer areas or necrosis usually implies transition to the more cellular, round-cell form. Histologically, myxoid liposarcoma is characterized by monomorphic undifferentiated fusiform or stellate cells and mainly small, univacuolated, signet-ring lipoblasts set in a myxoid matrix. These last often show a so-called pooling phenomenon by forming large spaces containing stromal mucin. A virtually constant and diagnostic finding is a prominent, delicate, plexiform meshwork of thin-walled capillaries. Mitotic figures are rare and often difficult to find, even in round-cell areas.

Myxoid liposarcoma in its pure form is a low-grade liposarcoma and does not metastasize per se. Of great prognostic importance therefore is the demonstration of more cellular areas in myxoid liposarcoma, composed of primitive round or oval cells with round, larger, and more hyperchromatic nuclei, often forming variably sized aggregates (Fig. 10). Although, even now, strict criteria defining the prognostic significance of the round cell extent in myxoid liposarcoma have not been established, we believe that even tiny round cell areas should be reported and their potential importance mentioned. Lesions with 10% or more round-cell areas should be graded as high-grade liposarcoma with a high metastatic risk. This gradual progression of myxoid to round-cell liposarcoma is the commonest form of tumour progression seen in myxoid liposarcoma. However, we have also seen rare examples of myxoid liposarcoma with areas of high-grade, non-lipogenic sarcoma, similar to dedifferentiation in well-differentiated liposarcoma (Fig. 11). Occasionally, myxoid/round cell liposarcoma may merge with areas resembling well-differentiated adipocytic or sclerosing liposarcoma. Other histological variations include prominent hibernoma-like cells and scattered pleomorphic stromal cells. Rarely, cases of myxoid/round cell liposarcoma containing numerous large spindle cells were noted [28].

Cytogenetics of lipomatous tumours

Benign and malignant lipomatous tumours have been studied extensively by cytogenetics in recent years, and

Table 2 Review of principal chromosomal aberrations in lipomatous tumours

Subcutaneous lipoma	– Translocations involving 12q13–15 – Interstitial deletions of 13q – Rearrangements involving 6p21–23 – Rearrangements involving 1p36.1–36.3 – Translocations involving 11q13
Spindle-cell lipoma	– Loss of 16q13–qter
Lipoblastoma	– Rearrangements involving 8q11–13
Hibernoma	– Rearrangements involving 11q13,10q22
Atypical lipoma/ well differentiated liposarcoma	– Ring chromosomes and long marker chromosomes from 12q13–15
Myxoid/round-cell liposarcoma	– t(12;16)(q13.3;p11.2)
Pleomorphic liposarcoma	– Complex rearrangements

it has been shown that there are consistent chromosomal abnormalities in both benign and malignant lesions (for a review see Table 2). Characteristic structural rearrangements have been demonstrated and correlated with histological subtypes. Additionally, some of the molecular changes resulting from such chromosomal rearrangements have been studied, yielding new insight into the biology of lipomatous lesions.

Lipoma

Lipomas have shown a wide range of chromosomal abnormalities, supporting the idea that there are different genetic pathways for benign lipomatous proliferation. Whereas most if not all multiple lipomas (most likely angiolipomas) are karyotypically normal [26, 34], in approximately 50% of solitary subcutaneous lipomas clonal abnormalities have been noted. Translocations between chromosome 12 at bands q13–15, with various chromosomes (chromosomes 1, 2, 3 and 21 being the commonest translocation partners) with different breakpoints reported, constitute the most frequent karyotypic aberrations in lipoma (affecting about 30% of all lipomas analysed) [26, 32, 34, 49, 54]. The chromosome segment 12q13–15 is also involved in other different benign and malignant soft tissue tumours, including myxoid liposarcoma (see below). However, it has been clearly shown that the breakpoints in lipoma (12q15) and myxoid liposarcoma (12q 13.3) are at different locations [42]. The main reproducible cytogenetic changes in lipomas without rearrangement of chromosome 12 comprise abnormalities on chromosome 13 (interstitial deletion of 13q) [34, 49] in about 13% of the cases, aberrations of chromosome 6 involving the 6p21–23 region in approximately 8% of the cases [34, 45, 49], translocations involving chromosome 11 at band q13 [49], and the rearrangements of 1p36.1-36.3 [34, 49]. Interestingly, complex chromosome changes have also been reported in a minor group of benign lipomas, which is puzzling in view of their benign nature [34, 49].

Spindle-cell/pleomorphic lipoma

Spindle-cell/pleomorphic lipoma forms a spectrum of relatively uncommon, benign lesions that develop in middle to late adult life, predominantly in subcutaneous tissue on the neck, shoulder or upper back of mainly male patients [11, 20]. Histologically, spindle-cell/pleomorphic lipoma sometimes may be confused with atypical lipoma/well-differentiated liposarcoma. More recently, consistent cytogenetic changes in both forms were noted, characterized by reproducible loss of long arm material from chromosome 16q [35]. None of the typical and atypical lipomas analysed demonstrated loss of chromosome16q material. These results not only add support to the delineation of spindle-cell/pleomorphic lipoma as a discrete entity, but also distinguish these lesions from ordinary lipoma, and especially from atypical lipoma/well-differentiated liposarcoma.

Lipoblastoma

Lipoblastoma in its circumscribed or diffuse form (lipoblastomatosis) is a rare benign tumour affecting almost-exclusively infants and young children, mainly before the age of 8 years [6, 40]. In its immature, more myxoid form, lipoblastoma/lipoblastomatosis can be strikingly similar to myxoid liposarcoma morphologically, and histological distinction may be arbitrary, especially if older children and adolescents are affected [40]. Most recently it has been shown that all lipoblastomas analysed share rearrangements of chromosome 8q11–13 but lack the characteristic 12;16 translocation seen in myxoid liposarcoma [9, 21], which underlines the diagnostic role of cytogenetic analysis in these morphologically similar tumours with quite different biological potential.

Hibernoma

Hibernoma is a rare benign tumour of brown fat occurring most commonly in the interscapular region of adults. Although only a small number of cases have been studied cytogenetically to date, the described chromosomal rearrangements included shared abnormalities affecting 11q13 and 10q22 in these tumours [39, 41].

Atypical lipoma/well-differentiated liposarcoma

Atypical lipoma/well-differentiated liposarcoma (see earlier text) is strongly associated cytogenetically with ring chromosomes composed of the q13-q15 regions of chromosome 12, long marker chromosomes derived from the long arm of chromosome 12 and/or telomeric associations [8, 26, 51]. Whereas all atypical lipomas/well-differentiated liposarcomas with chromosome aberrations demonstrated ring chromosomes, these were also found in a minority of ordinary lipomas [34]; how-

ever, it is possible that these latter lesions could also represent atypical lipomas, but with very subtle or unsampled areas of histological atypia.

Demonstration of the same cytogenetic abnormalities in atypical lipomas without lipoblasts as in classical well-differentiated liposarcoma underlines the fact that these are essentially identical lesions (see above).

Myxoid/round-cell liposarcoma

Myxoid/round-cell liposarcoma provides a fascinating example of a constant and reproducible cytogenetic finding in soft tissue sarcomas, which brings new insight into the relationship between morphologically different entities. Both forms, myxoid and round-cell liposarcoma, are characterized by a specific reciprocal chromosome translocation t(12;16)(q13;p11) as the primary chromosomal aberration [30, 51, 53]. Up to now this recurrent cytogenetic abnormality has not been found in other tumours and is therefore a differential marker from those for any other myxoid sarcomas [47].The breakpoints were localized at 12q13.3 and 16p11.2 and are different from the breakpoints in lipoma, showing chromosomal rearrangement at 12q13–15 [42]. This translocation gives rise to a rearrangement of genes that are involved in normal control of fat differentiation and proliferation. These genes encode a so-called CHOP protein (C/EBP-HOmologous Protein) located at12q13.1, which is fused to the 5' end of the TLS gene (Translocated in LipoSarcoma; also known as FUS) on chromosome 16 [1]. This abnormal fused gene is a chimeric protein, which has a different function from the normal CHOP protein and acts as a potent oncogene [57]. Other sarcomas with different 12q aberrations tested for comparison did not show rearrangement of the CHOP gene [43]. Additionally, secondary chromosomal changes have been reported in about half the cases analysed [23, 33]. It is unclear however, whether these non-random secondary chromosome aberrations, such as trisomy 8 and trisomy 5 [33, 50], or the involvement of chromosome 1, are related to tumour progression.

Pleomorphic liposarcoma

Pleomorphic liposarcoma is a rare form of liposarcoma with a poor prognosis. The limited cytogenetic data on this variant show marked heterogeneity, with generally large chromosome numbers and variable and complex chromosomal abnormalities without consistent and specific abnormalities [51].

Conclusions

Aside from the well-characterized and long-established types of lipomatous tumours, additonal and sometimes controversial entities continue to be defined and debated. Myolipoma, a benign neoplasm composed of mature adipose and smooth muscle tissues, chondroid lipoma, a benign lesion mimicking myxoid liposarcoma or extraskeletal myxoid chondrosarcoma, and spindle-cell liposarcoma, a variant of well-differentiated liposarcoma, which is composed of relatively bland spindle cells and a liposarcomatous component, represent recently delineated entities in the spectrum of lipomatous tumours of soft tissue. Atypical lipoma and well-differentiated liposarcoma are essentially identical lesions, and the term atypical lipoma should be used with caution, unless there is close liaison between surgeon and pathologist, thus ensuring appropriate treatment. Myxoid/round cell liposarcoma constitutes a morphological spectrum of a single entity. Cytogenetic analysis of lipomatous tumours is utilized increasingly in their precise characterization and classification and may provide helpful clues to understanding of the molecular basis of neoplasia in this group of lesions.

References

1. Aman P, Ron D, Mandahl N, Fioretos T, Heim S, Arheden K, Willen H, Rydholm A, Mitelman F (1992) Rearrangement of the transcription factor gene CHOP in myxoid liposarcomas with t(12;16)(q13;p11). Genes Chromosom Cancer 5: 278–285
2. Azumi N, Curtis J, Kempson RL, Hendrickson MR (1987) Atypical and malignant neoplasms showing lipomatous differentiation. A study of 111 cases. Am J Surg Pathol 11: 161–183
3. Bolen JW, Thorning D (1984) Liposarcomas. A histogenetic approach to the classification of adipose tissue neoplasms. Am J Surg Pathol 8: 3–17
4. Chang HR, Gaynor J, Tan C, Hajdu SI, Brennan MF (1990) Multifactorial analysis of survival in primary extremity liposarcoma. World J Surg 14: 610-618
5. Chan JKC, Lee KC, Saw D (1986) Extraskeletal chondroma with lipoblast-like cells. Hum Pathol 17: 1285–1287
6. Chung EB, Enzinger FM (1973) Benign lipoblastomatosis. An analysis of 35 cases. Cancer 32: 482–492
7. Dal Cin P, van Damme B, Hoogmartens M, van den Berghe H (1992) Chromosome changes in a case of hibernoma. Genes Chromosom Cancer 5: 178–180
8. Dal Cin P, Kools P, Sciot R, Wever ID, van Damme B, van de Ven W, van den Berghe H (1993) Cytogenetic and fluorescence in situ hybridization investigation of ring chromosomes characterizing a specific pathologic subgroup of adipose tissue tumors. Cancer Genet Cytogenet 68: 85–90
9. Dal Cin P, Sciot R, de Wever I, van Damme B, van den Berghe H (1994) New discriminative chromosomal marker in adipose tissue tumors. The chromosome 8q11-q13 region in lipoblastoma. Cancer Genet Cytogenet 78: 232–235
10. Dei Tos AP, Mentzel T, Newman PL, Fletcher CDM. (1994) Spindle cell liposarcoma: a hitherto unrecognised variant of well-differentiated liposarcoma: analysis of six cases. Am J Surg Pathol 18: 913–921
11. Enzinger FM, Harvey DA (1975) Spindle cell lipoma. Cancer 36: 1852–1859
12. Enzinger FM, Winslow DJ (1962) Liposarcoma. A study of 103 cases. Virchows Arch [A] 335: 367–388
13. Evans HL (1979) Liposarcoma. A study of 55 cases with a reassessment of its classification. Am J Surg Pathol 3: 507–523
14. Evans HL (1988) Liposarcomas and atypical lipomatous tumors: a study of 66 cases followed for a minimum of 10 years. Surg Pathol 1: 41–54
15. Evans HL (1990) Smooth muscle in atypical lipomatous tumors. A report of three cases. Am J Surg Pathol 14: 714–718
16. Evans HL (1993) Low grade fibromxyoid sarcoma. A report of 12 cases. Am J Surg Pathol 17: 595–600

17. Evans HL, Soule EH, Winkelmann RK (1979) Atypical lipoma, atypical intramuscular lipoma, and well differentiated retroperitoneal liposarcoma. A reappraisal of 30 cases formerly classified as well-differentiated liposarcoma. Cancer 43: 574–584
18. Evans HL, Khurana KK, Kemp BL, Ayala AG (1994) Heterologous elements in the dedifferentiated component of dedifferentiated liposarcoma. Am J Surg Pathol 18: 1150–1157
19. Fletcher CDM (1995) Author's reply. Am J Surg Pathol 19: 606–608
20. Fletcher JA (1995) Cytogenetics in soft tissue tumors. In: Enzinger FM, Weiss SW (eds) Soft tissue tumors, 3rd edn. Mosby, St Louis, pp 105–118
21. Fletcher CDM, Martin-Bates E (1987) Spindle cell lipoma: a clinicopathological study with some original observations. Histopathology 11: 803–817
22. Fletcher JA, Kozakewich HP, Schoenberg ML, Morton CC (1993) Cytogenetic findings in pediatric adipose tumors: consistent rearrangement of chromosome 8 in lipoblastoma. Genes Chromosom Cancer 6: 24–29
23. Gibas Z, Miettinen M, Limon J, Nedoszytko B, Mrozek K, Roszkiewicz A, Rhys J, Niezabitowski A, Debiec-Rychter M (1995) Cytogenetic and immunohistochemical profile of myxoid liposarcoma. Am J Clin Pathol 103: 20–26
24. Hashimoto H, Enjoji M (1982) Liposarcoma. A clinicopathologic subtyping of 52 cases. Acta Pathol Jpn 32: 933–948
25. Hashimoto H, Daimaru Y, Tsuneyoshi M, Enjoji M (1990) Soft tissue sarcoma with additional anaplastic components. A clinicopathologic and immunohistochemical study of 27 cases. Cancer 66: 1578–1589
26. Heim S, Mandahl N, Rydholm A, Willen H, Mitelman F (1988) Different karyotypic features characterize different clinicopathologic subgroups of benign lipogenic tumors. Int J Cancer 42: 863–867
27. Henricks WH, Chu YC, Goldblum JR, Weiss SW (1995) Dedifferentiated liposarcoma: a clinicopathologic analysis of 160 cases (abstract). Lab Invest 72: 6A
28. Kindblom LG, Angervall L, Svendsen P (1975) Liposarcoma. A clinicopathologic, radiographic and prognostic study. APMIS [Suppl] 253: 5–71
29. Kindblom LG, Angervall L, Fassina AS (1982) Atypical lipoma. APMIS 90: 27–36
30. Knight JC, Renwick PJ, Dal Cin P, van den Berghe H, Fletcher CDM (1995) Translocation t(12;16)(q13;p11) in myxoid liposarcoma and round cell liposarcoma: molecular and cytogenetic analysis. Cancer Res 55: 24–27
31. Mack TM (1995) Sarcomas and other malignancies of soft tissue, retroperitoneum, peritoneum, pleura, heart, mediastinum, and spleen. Cancer 75: 211–244
32. Mandahl N, Heim S, Johansson B, Bennet K, Mertens F, Olsson G, Rooser B, Rydholm A, Willen H, Mitelman F (1987) Lipomas have characteristic structural chromosomal rearrangements of 12q13-q14. Int J Cancer 39: 685–688
33. Mandahl N, Mertens F, Aman P, Rydholm A, Brosjo O, Willen H, Mitelman F. (1994) Nonrandom secondary chromosome aberrations in liposarcomas with t(12;16). Int J Oncol; 4: 307-310
34. Mandahl N, Hoglund M, Mertens F, Rydholm A, Willen H, Brosjo O, Mitelman F (1994) Cytogenetic aberrations in 188 benign and borderline adipose tissue tumors. Genes Chromosom Cancer 9: 207–215
35. Mandahl N, Mertens F, Willen H, Rydholm A, Brosjo O, Mitelman F (1994) A new cytogenetic subgroup in lipomas: loss of chromosome 16 material in spindle cell and pleomorphic lipomas. J Cancer Res Clin Oncol 120: 707–711
36. McCormick D, Mentzel T, Beham A, Fletcher CDM (1994) Dedifferentiated liposarcoma. Clinicopathologic analysis of 32 cases suggesting a better prognostic subgroup among pleomorphic sarcomas. Am J Surg Pathol 18: 1213–1223
37. Meis JM, Enzinger FM (1991) Myolipoma of soft tissue. Am J Surg Pathol 15: 121–125
38. Meis JM, Enzinger FM (1993) Chondroid lipoma. A unique tumor simulating liposarcoma and myxoid chondrosarcoma. Am J Surg Pathol; 17: 1103–1112
39. Meloni AM, Spanier SS, Bush CH, Stone JF, Sandberg AA (1994) Involvement of 10q22 and 11q13 in hibernoma. Cancer Genet Cytogenet 72: 59–64
40. Mentzel T, Calonje E, Fletcher CDM. (1993) Lipoblastoma and lipoblastomatosis: a clinicopathological study of 14 cases. Histopathology 23: 527–533
41. Mertens F, Rydholm A, Brosjo O, Willen H, Mitelman F, Mandahl N (1994) Hibernomas are characterized by rearrangements of chromosome bands 11q 13-21. Int J Cancer; 58: 503–505
42. Mrozek K, Karakousis CP, Bloomfield CD. (1993) Chromosome 12 breakpoints are cytogenetically different in benign and malignant lipogenic tumors: localization of breakpoints in lipoma to 12q15 and in myxoid liposarcoma to 12q13.3. Cancer Res 53: 1670–1675
43. Nilbert M, Mandahl N, Aman P, Rydholm A, Mitelman F (1994) No rearrangements of the CHOP gene in malignant fibrous histiocytoma. Cancer Genet Cytogenet 72: 155–156
44. Orson GG, Sim FH, Reiman HM, Taylor WF. (1987) Liposarcoma of the musculoskeletal system. Cancer 60: 1362–1370
45. Sait SNJ, Dal Cin P, Sandberg AA, Leong S, Karakousis C, Rao U, Harris K (1989) Involvement of 6p in benign lipomas. A new cytogenetic entity? Cancer Genet Cytogenet 37: 281–283
46. Sandberg AA, Bridge JA (1994) Tumors of fat. The cytogenetics of bone and soft tissue tumors. Landes, Austin, pp 147–217
47. Sciot R, Dal Cin P, Fletcher CDM, Samson I, Smith M, De Vos R, Van Damme B, Van den Berghe H (1995) T(9;22)(q22-31;q11-12) is a consistent marker of extraskeletal myxoid chondrosarcoma: evaluation of 3 cases. Mod Pathol 8:765–768
48. Scurry JP, Carey MP, Targett CS, Dowling JP. (1991) Soft tissue lipoleiomyoma. Pathology 23: 360–362
49. Sreekantaiah C, Leong SPL, Karokousis CP, McGee DL, Rappaport WD, Villar HV, Neal D, Fleming S, Wankel A, Herrington PN, Caromona R, Sandberg AA (1991) Cytogenetic profile of 109 lipomas. Cancer Res 51: 422–433
50. Sreekantaiah C, Karakousis CP, Leong SPL, Sandberg AA (1991) Trisomy 8 as a nonrandom secondary change in myxoid liposarcoma. Cancer Genet Cytogenet 15: 195–205
51. Sreekantaiah C, Karakousis CP, Leong SPL, Sandberg AA (1992) Cytogenetic findings in liposarcoma correlate with histopathologic subtypes. Cancer 69: 2484–2495
52. Tallini G, Erlandson RA, Brennan MF, Woodruff JM (1993) Divergent myosarcomatous differentiation in retroperitoneal liposarcoma. Am J Surg Pathol 17: 546–556
53. Turc-Carel C, Limon J, Dal Cin P, Rao U, Karakousis C, Sandberg AA (1986) Cytogenetic studies of adipose tissue tumors. II. Recurrent reciprocal translocation t(12;16)(q13;p11) in myxoid liposarcoma. Cancer Genet Cytogenet 23: 291–299
54. Turc-Carel C, Dal Cin P, Boghosian L, Leong SPL, Sandberg AA (1988) Breakpoints in benign lipoma may be at 12q13 or 12q14. Cancer Genet Cytogenet 26: 131–135
55. Weiss SW (ed) (1994) Histological typing of soft tissue tumours. World Health Organization International Histological Classification of Tumours. Springer, Berlin Heidelberg New York
56. Weiss SW, Rao VK (1992) Well-differentiated liposarcoma (atypical lipoma) of deep soft tissue of the extremites, retroperitoneum and miscellaneous sites. A follow-up study of 92 cases with analysis of the incidence of "dedifferentiation". Am J Surg Pathol 16: 1051–1058
57. Zinszner H, Albalat R, Ron D (1994) A novel effector domain from the RNA-binding protein TLS or EWS is required for oncogenic transformation by CHOP. Genes Dev 8: 2513–2526