CHAPTER 1

Adipocytic Tumours

Adipocytic tumours represent the largest single group of mesenchymal tumours, due to the high prevalence of lipomas and angiolipomas. Liposarcomas represent the single most common type of soft tissue sarcoma. Its principal histological subtypes (well differentiated, myxoid, and pleomorphic) are entirely separate diseases with different morphology, genetics, and natural history. Most types of adipocytic neoplasm have distinctive karyotypic aberrations which can be of considerable help in diagnosis.

Principal changes and advances since the 1994 WHO classification have been
> the recognition that atypical lipomatous tumour and well differentiated liposarcoma are essentially synonymous and that site-specific variations in behaviour relate only to surgical resectability,
> the inclusion of two newly characterized entities, myolipoma and chondroid lipoma, and
> the renaming of fibrolipomatous hamartoma of nerve as lipomatosis of nerve.

Descriptions of angiomyolipoma and myelolipoma are provided in the Urogenital and Endocrine volumes, respectively.

Lipoma

G.P. Nielsen
N. Mandahl

Definition
Lipoma is a benign tumour composed of mature white adipocytes and is the most common soft tissue mesenchymal neoplasm in adults.

ICD-O code   8850/0

Epidemiology
Conventional lipoma occurs over a wide age range but is most common between the ages of 40 and 60 years and is more frequent in obese individuals {601}. Lipomas are rare in children. Approximately 5% of patients have multiple lipomas.

Sites of involvement
Conventional lipoma can arise within subcutaneous tissue (superficial lipoma) or within deep soft tissues (deep lipoma) or even on the surfaces of bone (parosteal lipoma) {1079,1800}. Deep seated lipomas that arise within or between skeletal muscle fibres are called *intramuscular* or *intermuscular lipomas*, respectively {685,1113}. Intramuscular lipoma arises during mid to late adulthood and involves skeletal muscle in a variety of locations including the trunk, head and neck region, upper and lower extremities {685,1113}. Intermuscular lipoma arises between muscles most frequently in the anterior abdominal wall, and involves a similar age group as the intramuscular lipoma. So-called *lipoma arborescens* (villous lipomatous proliferation of synovial membrane) is characterized by fatty infiltration of the subsynovial connective tissue and may represent a reactive process.

Clinical features
Lipomas usually present as a painless soft tissue mass, except for larger ones that can be painful when they compress peripheral nerves. Superficial lipomas are generally smaller (<5cm) than the deep seated ones (>5cm). Patients with lipoma arborescens are usually adult men that complain of gradual swelling of the affected joint {324,837,875,1343, 1982}. Imaging studies show a homogeneous soft tissue mass that is isodense to the subcutaneous tissue and demonstrates fat saturation. Attenuated fibrous strands can be seen but they are not as prominent as seen in the atypical lipomas. Intramuscular lipomas are more variably circumscribed, and lipoma arborescens shows diffuse fatty infiltration of the synovium.

Aetiology
Unknown. Lipomas are more common in obese individuals.

Macroscopy
Grossly, lipomas are well circumscribed and have a yellow, greasy cut surface. Different types are basically similar in appearance, however bone formation can be seen in osteolipoma and grey glistening nodules may be seen in chondrolipoma. Intramuscular and intermuscular lipoma do not show any specific gross features except that a portion of skeletal muscle is often attached to the periphery of the tumour. In lipoma arborescens the entire synovium assumes a nodular and papillary appearance and has a bright yellow cut surface.

Histopathology
Conventional lipoma is composed of lobules of mature adipocytes. The cells are identical to the surrounding adipose tissue except for slight variation in the size and shape of the cells in lipomas. Lipomas can occasionally have areas of bone formation (osteolipoma), cartilage (chondrolipoma), abundant fibrous tissue (fibrolipoma), or extensive myxoid change (myxolipoma). Intramuscular lipoma may be either well demarcated from the surrounding skeletal muscle or, more often, shows an infiltrative growth pattern with mature adipocytes infiltrating and encasing skeletal muscle fibres that often show evidence of atrophy. In lipoma arbor-escens the subsynovial connective tissue is infiltrated by mature adipocytes; scattered inflammatory cells are also usually present.

Immunophenotype
Mature adipocytes stain for vimentin, S100 protein and leptin {1610}.

Ultrastructure
Lipoma is composed of cells that have a large, single lipid droplet compressing a peripherally situated nucleus.
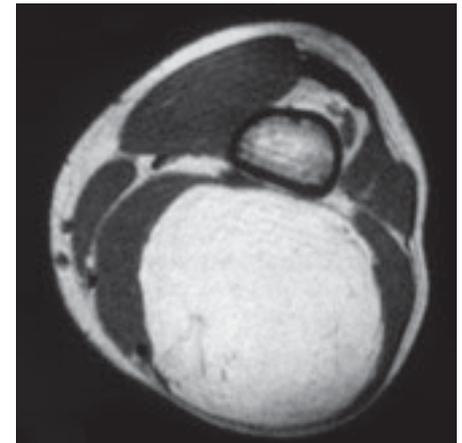

Fig. 1.01 Image of a deep seated conventional lipoma showing a well circumscribed, homogenous tumour with the same characteristics as the adjacent subcutaneous fat.
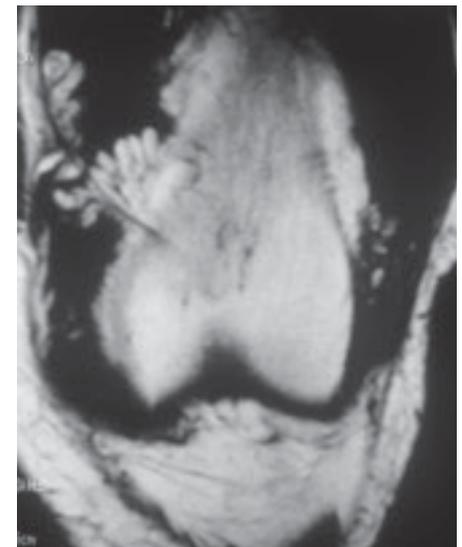

Fig. 1.02 Synovial lipoma (lipoma arborescens) demonstrating a fatty infiltration of the synovium that assumes papillary appearance.
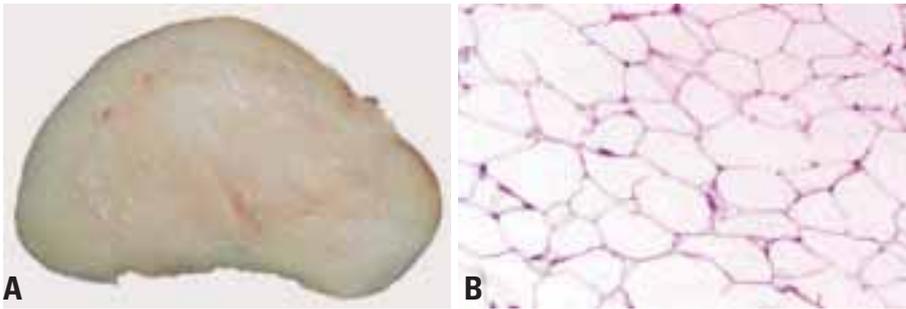
Fig. 1.03 Conventional lipoma. **A** Grossly, the tumour is well circumscribed and has a homogenous yellow cut surface. **B** The mature adipocytes vary only slightly in size and shape and have small eccentric nuclei.
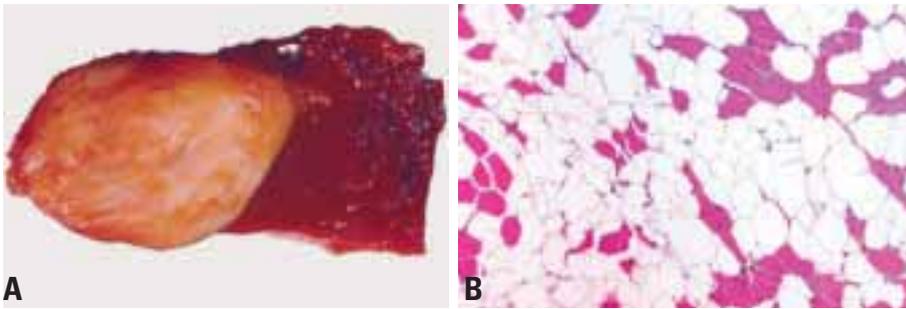

Fig. 1.04 Intramuscular lipoma. **A** This intramuscular lipoma appears well circumscribed from the adjacent skeletal muscle (right). **B** Mature adipocytes infiltrate and encase skeletal muscle fibres.

Pinocytotic vesicles are present and external lamina is seen surrounding the cells {1110}.

Genetics
Cytogenetics
Lipomas have been analysed extensively by chromosome banding. In larger cytogenetically investigated series, chromosome aberrations have been found in 55-75% of the cases {1320,2020,2271}. Among the abnormal tumours, about 75% show seemingly balanced karyotypes and in more than 50% there is a single abnormality in at least one clone {1477}. On average, signs of clonal evolution is found in every sixth tumour. Numerical chromosome changes are rare and randomly distributed, and chromosome numbers deviating from 46 are exceedingly rare. The pattern of cytogenetic aberrations is quite heterogeneous, but three cytogenetically defined subgroups have been distinguished: 1) the major subgroup consisting of tumours with aberrations involving 12q13-15, 2) tumours with aberrations involving 6p21-23, and 3) tumours with loss of material from 13q. Patients with and without aberrations of 12q13-15 show no differences with respect to age distribution and gender. The frequency of abnormal karyotypes seems to be higher among older patients {2020,2271}. Otherwise, no clear, consistent correlations between clinical and cytogenetic data have been identified.

Tumours with 12q13-15 aberrations
About two-thirds of tumours with abnormal karyotypes show aberrations of 12q13-15, which has been found to recombine with a large number of bands in all chromosomes except 16 and Y. The preferred rearrangement, seen in more than 20% of tumours with 12q13-15 aberrations, is t(3;12)(q27-28;q13-15). Other recurrent recombination partner regions, present in 3-7% of these tumours, are 1p36, 1p32-34, 2p22-24, 2q35-37, 5q33, 11q13, 12p11-12, 12q24, 13q12-14, 17q23-25, and 21q21-22. The majority of these aberrations originate through translocations or insertions. One in six of these tumours show more or less complex intrachromosomal rearrangements - including primarily inversions, but also deletions and duplications - leading to recombination between 12q13-15 and other segments of chromosome 12, primarily 12p11-12 and 12q24.

Tumours without 12q13-15 aberrations
Among these tumours, constituting one-third of lipomas with acquired chromosome aberrations, all chromosomes except 20 have been involved, but the only distinct clustering of breakpoints seen is to 6p21-23, 13q11-22, and, less often, 12q22-24, together constituting about half of this group of tumours. Involvement of 6p21-23, mostly in the form of seemingly balanced translocations, has been found in more than 20% of these tumours. The only recurrent translocation partner has been 3q27-28 in two cases. Aberrations affecting the long arm of chromosome 13 are dominated by deletions, which have been found in slightly less than 20% of the cases. Most aberrations are interstitial deletions with breakpoints in 13q12-14 and 13q22, respectively. There is an overlap between 6p21-23 rearrangements and 13q deletions, with some tumours showing both aberrations, but more often these aberrations occur as sole anomalies.

Simultaneous involvement of 6p21-23 and 12q13-15 is uncommon, in contrast to the coexistence of 12q13-15 aberrations and 13q losses. In tumours with combinations of 6p, 12q, and 13q aberrations, 13q is mostly involved in bal-
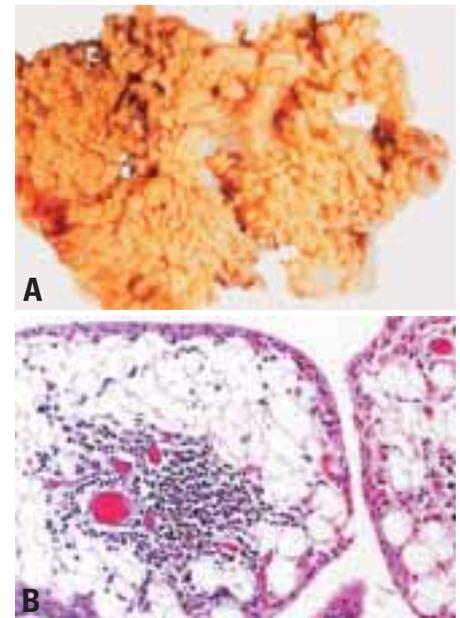

Fig. 1.05 **A** Synovial lipoma (lipoma arborescens). The entire synovium is bright yellow and has a nodular or papillary appearance. **B** Synovial lipoma (lipoma arborescens). The subsynovial connective tissue has been replaced by mature adipocytes. Note also scattered chronic inflammatory cells.
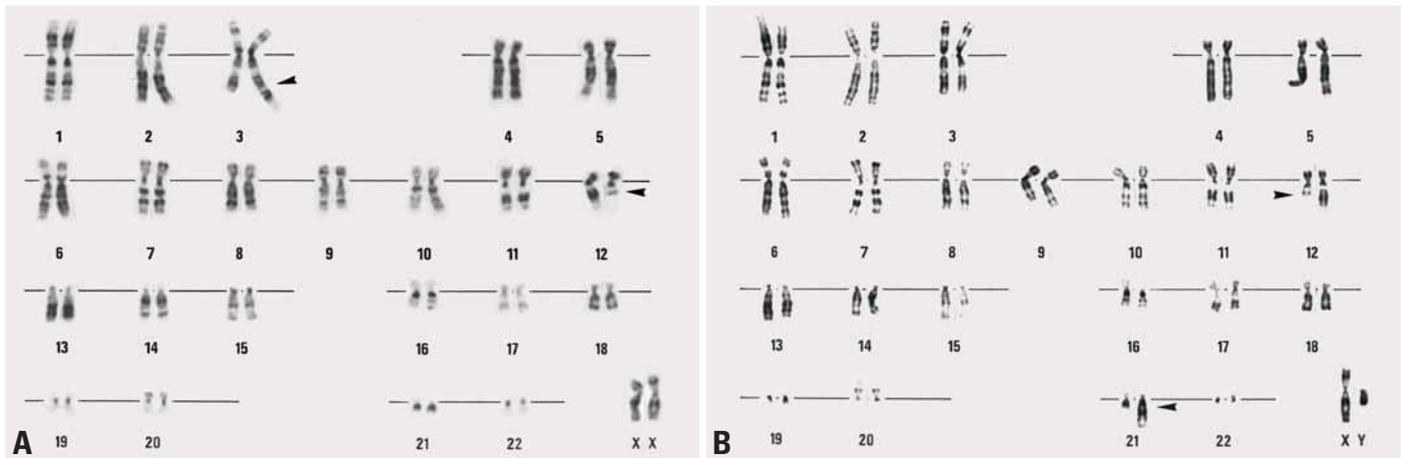
Fig. 1.06 A Karyotype from a lipoma showing the most common structural rearrangement, a translocation t(3;12)(q27;q15). **B** Lipoma with t(12;21)(q15;q22) as the sole chromosomal aberration. Arrowheads indicate breakpoints.

anced translocations when recombining with 6p21-23 or 12q13-15, whereas deletions in 13q are predominating when aberrations of 6p21-23 or 12q13-15 are present but recombine with other chromosome segments.

Among tumours without rearrangements of 12q13-15 or 6p21-23 or loss of 13q sequences, one-fifth of the breakpoints coincide with those recurrently recombining with 12q13-15.

Molecular genetics

The *HMGIC* (a.k.a. *HMGA2*) gene, encoding a family member of the high mobility group of proteins, located in 12q15 is affected in at least some lipomas with rearrangements of 12q13-15 {90,1890}. In tumours with t(3;12)(q27-28;q13-15), the consequence at the molecular level is the formation of a fusion gene involving *HMGIC* and *LPP* in 3q27-28, a member of the LIM protein gene family {1696}. In addition, this fusion gene has been observed in a few cases with complex karyotypic changes including 12q13-15 but not 3q27-28 and in cases with normal karyotypes, indicating that cytogenetic analysis underesti-

mates the frequency of tumours with recombination between these two chromosome segments {1696}. In all cases, the chimeric *HMGIC/LPP* transcript is expressed, whereas the reciprocal *LPP/HMGIC* transcript is expressed only occasionally. Alternative fusion transcripts, encoding the three DNA binding AT-hook domains of HMGIC and two or three LIM domains of LPP have been reported, thus excluding the 3′ acidic, protein-binding domain and the N-terminal leucine-zipper motif, respectively. The preferred breakpoints are in the large intron 3 of *HMGIC* and *LPP* intron 8. The chimeric transcript is not unique for lipomas of the soft tissues but has also been detected in parosteal lipoma and pulmonary chondroid hamartoma {1698,1803}.

Rearrangement of *HMGIC* has been detected also in tumours with changes involving 12q13-15 and other chromosome segments. In a single case of lipoma with t(12;13)(q13-15;q12), an *HMGIC/LHFP* fusion transcript has been reported {1697}. Also in this case, the breakpoint was in *HMGIC* intron 3. In lipomas with recombination between

12q13-15 and 12p11, due to inversion, fusion of putative but yet unidentified gene sequences in 12p11 with *HMGIC* was found {1081}, and ectopic sequences mapping to chromosome 15 have been implicated {90}. Possibly, the related *HMGIY* (*HMGA1B*) gene is the target, directly or indirectly, in lipomas with 6p21-23 aberrations; split FISH signals, using probes covering *HMGIY*, have been reported in cases with translocations involving 6p {1082,2083}. Transcriptional activation of *HMGIC* or *HMGIY* is indicated by immunohistochemical studies, and correlates well with cytogenetic findings of breakpoints in the regions where these two gene loci are located {2083}.

Prognostic factors

The subclassification of conventional lipoma does not have any prognostic significance except for the infiltrating intramuscular lipoma that has a higher local recurrence rate, therefore total removal of the involved muscle or a compartmental resection has been suggested for these infiltrating tumours in order to minimize local recurrence {206}.

Lipomatosis

G.P Nielsen
A.E. Rosenberg

Definition
Lipomatosis is a diffuse overgrowth of mature adipose tissue. It occurs in a variety of clinical settings and can affect different anatomic regions of the body.

ICD-O code   8850/0

Synonyms
Madelung disease, Launois-Bensaude syndrome.

Fig. 1.07 Lipomatosis presenting as diffuse enlargement of the lower leg in an infant

Fig. 1.08 Patient showing typically symmetrical, massive expansion of the neck.

Epidemiology
Diffuse lipomatosis usually occurs in individuals under 2 years of age but it may also arise in adults {1574}. Pelvic lipomatosis most frequently affects black males who range in age from 9 to 80 {839,944,1135}. Symmetric lipomatosis develops in middle aged men of Mediterranean origin. Many patients have a history of liver disease or excessive alcohol consumption. Steroid lipomatosis manifests in patients on hormonal therapy or have increased endogenous production of adrenocortical steroids. HIV lipodystrophy is frequently seen in AIDS patients treated with protease inhibitors but is also seen in patients receiving other forms of anti-retroviral therapy {234,1175}.

Sites of involvement
Diffuse lipomatosis involves the trunk, large portion of an extremity, head and neck, abdomen, pelvis or intestinal tract. It may be associated with macrodactyly or gigantism of a digit {836,1365,1616}. Symmetric lipomatosis manifests as symmetric deposition of fat in the upper part of the body particularly the neck. In pelvic lipomatosis there is diffuse overgrowth of fat in the perivesical and perirectal areas. Steroid lipomatosis is characterized by the accumulation of fat in the face, sternal region or the upper middle back (buffalo hump). HIV-lipodystrophy typically shows the accumulation of visceral fat, breast adiposity, cervical fat pads, hyperlipidemia, insulin resistance as well as fat wasting in the face and limbs {400,1461}.

Clinical features
In most forms of lipomatosis the patients present with massive accumulation of fat in the affected areas that may mimic a neoplasm. Additionally patients with symmetric lipomatosis can have neuropathy and central nervous system involvement {1541,1712}. Accumulation of fat in the lower neck areas in these patients can also cause laryngeal obstruction, and compression of the vena cava. Patients with pelvic lipomatosis frequently complain of urinary frequency, perineal pain, constipation, and abdominal and back pain. Bowel obstruction and hydronephrosis may eventually develop. Imaging studies in all forms of lipomatosis show accumulation of fat and are only helpful in determining the extent of its accumulation and excluding other processes.

Aetiology
The basic mechanism underlying lipomatosis is not well understood. In symmetric lipomatosis point mutations in mitochondrial genes have been implicated in its pathogenesis {1140}. The similarity between HIV lipodystrophy and benign symmetric lipomatosis suggests a similar pathogenesis in that mitochondrial DNA damage may be induced by the drugs being used to treat HIV {153,400}.

Macroscopy
The gross appearance of lipomatosis is the same for all of the different subtypes. The lesions consist of poorly circumscribed aggregates of soft yellow fat that is identical in appearance to normal fat. The only differences are the site of involvement and the distribution of the fat.

Histopathology
All of the different types of lipomatosis have identical morphologic features, consisting of lobules and sheets of mature adipocytes that may infiltrate
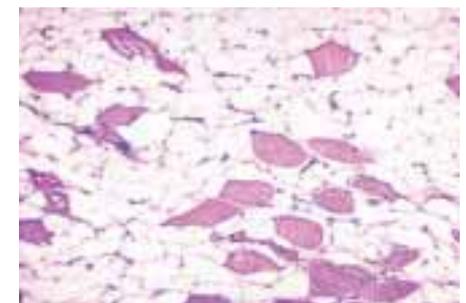

Fig. 1.09 Diffuse lipomatosis showing extensive skeletal muscle infiltration of mature adipocytes.

other structures such as skeletal muscle.
Immunophenotype
The adipose tissue stains for vimentin and S-100, similar to normal fat.

Ultrastructure
The adipocytes have the features of white fat.

Genetics
An association with several genetic disorders has been reported, and an autosomal dominant inheritance is suggested {1377}.

Prognostic factors
All idiopathic forms of lipomatoses have a tendency to recur locally after surgery.

The treatment is palliative surgical removal of excess fat. Massive accumulation of fat in the neck region may cause death due to laryngeal obstruction. The fat in steroid lipomatosis regresses after steroid levels have been lowered. Experimental drugs such as recombinant growth hormones have been used to treat HIV-lipodystrophy.

Lipomatosis of nerve

G.P. Nielsen

Definition
Lipomatosis of nerve is characterized by infiltration of the epineurium by adipose and fibrous tissue. The tissue grows between and around nerve bundles thereby causing enlargment of the affected nerve.

ICD-O code   8850/0

Synonyms and historical annotations
Fibrolipomatous hamartoma, lipofibroma, fibrolipomatosis, intraneural lipoma of the median nerve, perineural lipoma, median nerve lipoma, macrodystrophia lipomatosa, neural fibrolipoma.

Epidemiology
Lipomatosis of nerve is frequently first noted at birth or in early childhood, but

patients may not present for treatment until early or mid adulthood. In the largest reported series the patients ranged in age from 11 to 39 years. Because the constituent tissues are normal components of the epineurium, some have considered this lesion to be a hamartoma of the nerve sheath {445, 2103}. In some cases it is associated with macrodactyly of the digits inervated by the affected nerve.

Associated macrodactyly was present in approximately 1/3 of patients, including 5 females and 2 males {1952}. Females predominate when lipofibroma is accompanied by macrodactyly, whereas males are more commonly affected when macrodactyly is absent.

Sites of involvement
The median nerve and its digital branches are most commonly affected followed by the ulnar nerve {189,1952}. The process has also been reported to involve unusual sites such as the cranial nerves and the brachial plexus {176,1726}.

Clinical features
Patients present with a gradually enlarging mass in the affected area that may be asymptomatic or associated with motor or sensory deficits. Patients with macrodactyly have symmetrical or asymmetrical enlargement of the affected finger(s) with enlargement of the involved bones. Imaging studies show fusiform enlargement of the nerve with fatty infiltration

Fig. 1.10 Lipomatosis of nerve. **A** A clinical picture showing macrodactyly of the second and third fingers. **B** An intraoperative view of lipomatosis of nerve showing a transition between the normal nerve (left) and the affected area (right). **C** Cross section reveals nerve bundles entrapped within fibroadipose tissue.

{474} and MRI findings are virtually pathognomonic {1336}.

Aetiology
The aetiology is unknown. Lipomatosis of nerve is not associated with any syndrome nor is there any known hereditary predisposition.

Macroscopy
Grossly there is fusiform enlargement of the nerve by yellow fibrofatty tissue, which is generally confined within the epineurial sheath.

Histopathology
The epineurial and perineurial compartments of the enlarged nerve are infiltrated by mature adipose tissue admixed with fibrous tissue which dissects between and separates individual nerve bundles {1952}. Concentric perineurial fibrous tissue is a prominent feature. The affected nerve may also show other changes such as perineural septation, microfascicle formation and pseudo-onion bulb formation mimicking an intraneural perineurioma {1882}. Metaplastic bone formation is rarely present {551}.

Immunophenotype
Immunohistochemical studies are not helpful in diagnosing this lesion as all of its components are seen in normal nerves.

Ultrastructure
There are no characteristic ultrastructural findings. The nerve bundles demonstrate onion bulblike formations with one or two nerve fibres and peripheral perineural cells {99}.

Prognostic factors
Lipomatosis of nerve is a benign lesion with no effective therapy. Surgical excision usually causes severe damage of the involved nerve. Division of the transverse carpal ligament may relieve neurological symptoms.
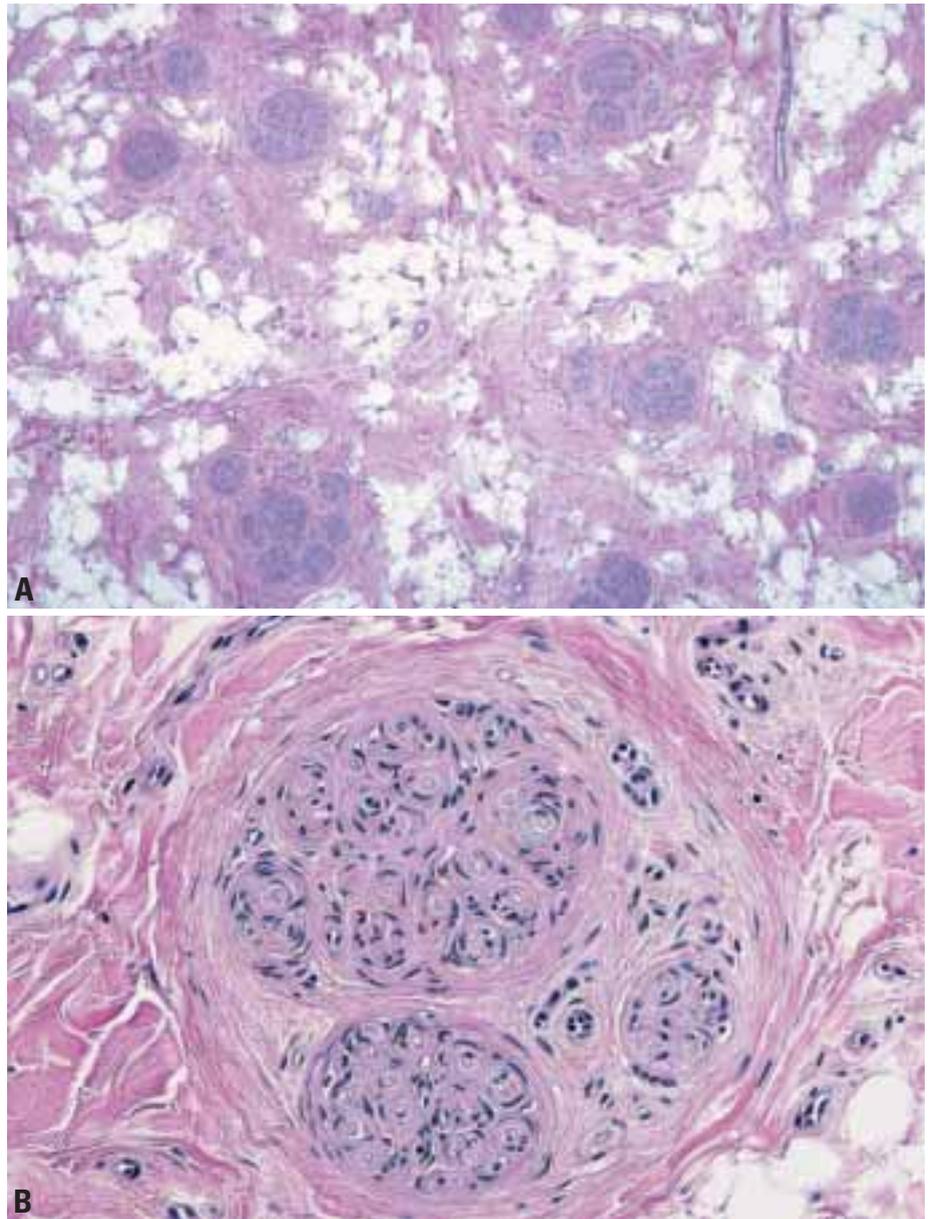
Fig. 1.11 A Epineural infiltration of fibroadipose tissue separating nerve bundles. **B** The nerves show pseudoonion bulb formation and perineural fibrosis.

Lipoblastoma / Lipoblastomatosis

R. Sciot
N. Mandahl

Definition
A lobulated, localized (lipoblastoma) or diffuse (lipoblastomatosis) tumour, resembling fetal adipose tissue.

ICD-O code   8881/0

Synonyms
Foetal lipoma, embryonic lipoma, infantile lipoma.

Epidemiology
Both tumours are most commonly found in the first three years of life. They may occasionally be present at birth or in older children. There is a male predilection {348,391,1410,2196}.

Sites of involvement
The extremities are most commonly involved, but locations in the mediastinum, retroperitoneum, trunk, head & neck, and various organs (lung, heart, parotid gland) have been described {273,500,525,1002,1010,1177,1192, 1352,1654,1713,1720,1762,2134,2149}.

Clinical features
Most patients present with a slowly growing soft tissue nodule/mass, well circumscribed and confined to the subcutis in case of lipoblastoma, infiltrating the deeper muscle in case of lipoblastomatosis. Depending on the location, the tumour may compress adjacent structures, such as the trachea. Imaging reveals a mass with adipose tissue density, but does not allow distinction from lipoma and liposarcoma {1777}.

Macroscopy
Notwithstanding exceptions, lipoblastomas are relatively small lesions (2-5 cm), showing fatty looking tissue with gelatinous areas.

Histopathology
Lipoblastoma shows a lobulated appearance with an admixture of mature and immature adipocytes, the latter corresponding to lipoblasts in various stages of development. Depending on the age of the patient, lipoblasts may be very scarce. Connective tissue septa separate the lobules. The lobulation is less prominent in lipoblastomatosis, in which entrapped muscle fibres frequently occur. The matrix can be quite myxoid, with a plexiform vascular pattern, thus mimicking myxoid liposarcoma. The latter tumour, which is exceptionally rare under the age of 10, usually shows nuclear atypia and does not show the pronounced lobulated pattern of lipoblastoma {223}. However, in rare cases molecular genetic analysis may be required for definitive distinction. Occasionally, lipoblastoma(tosis) may show extramedullary haematopoiesis or cells resembling brown fat. Cellular maturation has been described, leading to a lipoma-like picture. When fascicles of primitive mesenchymal cells are present in the septa, lipoblastoma resembles infantile lipofibromatosis or infantile fibromatosis {658}. The lobulated aspect, the at least focal myxoid stroma and plexiform capillaries, as well as the overwhelming fat component with lipoblasts, help to separate lipoblatoma(tosis) from these lesions.

Ultrastructure
Lipoblastoma(tosis) strongly resembles normal developing fat, with a spectrum ranging from primitive mesenchymal cells to multivacuolated lipoblasts and mature lipocytes {223}.

Genetics
Typically, lipoblastomas have simple, pseudodiploid karyotypes with structural chromosome aberrations. The characteristic cytogenetic feature is rearrangement of 8q11-13, which has been found in the vast majority of cases. The only chromosome segments that, so far, have been found to be involved in recurrent recombinations with 8q11-13 are 3q12-13, 7p22, and 8q24, but several other chromosome segments have been the translocation partners in single cases. Numerical changes are rare, but gain of chromosome 8 has been found in cases with or without simultaneous rearrangement of 8q11-13.

To date, two different fusion genes have been reported to result from the chromosomal rearrangements, *HAS2/PLAG1* in three cases and *COL1A2/PLAG1* in a single case {945}. The *PLAG1* gene is located in 8q12, *HAS2* in 8q24 and *COL1A2* in 7q22. The genomic breakpoint of *PLAG1* seems to be in intron1, resulting in loss of exon 1. The entire *HAS2* 5′ untranslated region is involved in the fusion gene, which is probably under control of the *HAS2* promoter, leading to transcriptional up-regulation of *PLAG1* and production of a full-length PLAG1 protein. The *COL1A2-PLAG1* fusion gene encodes a chimeric protein containing the first amino acids of COL1A2 and full-length PLAG1. These fusion genes seem to act through a promoter-swapping mechanism {105,945}. An alternative mechanism associated with lipoblastoma tumourigenesis may act through excess copies of chromosome 8 {792}. Since +8 may be present
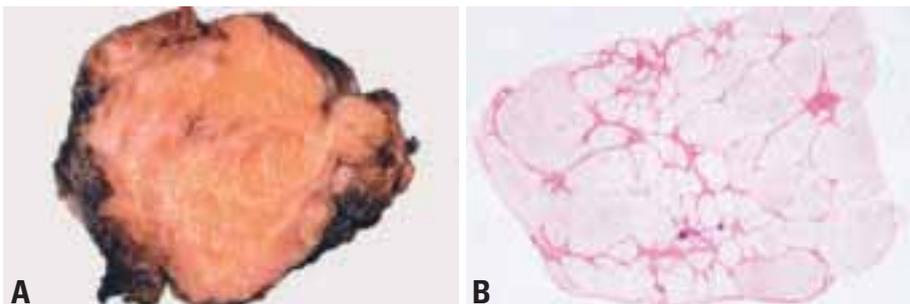
Fig. 1.12 Lipoblastoma. **A** Grossly, the tumour shows vague lobularity and fibrous / gelatinous areas. **B** Low power view. Note the prominent lobulation.
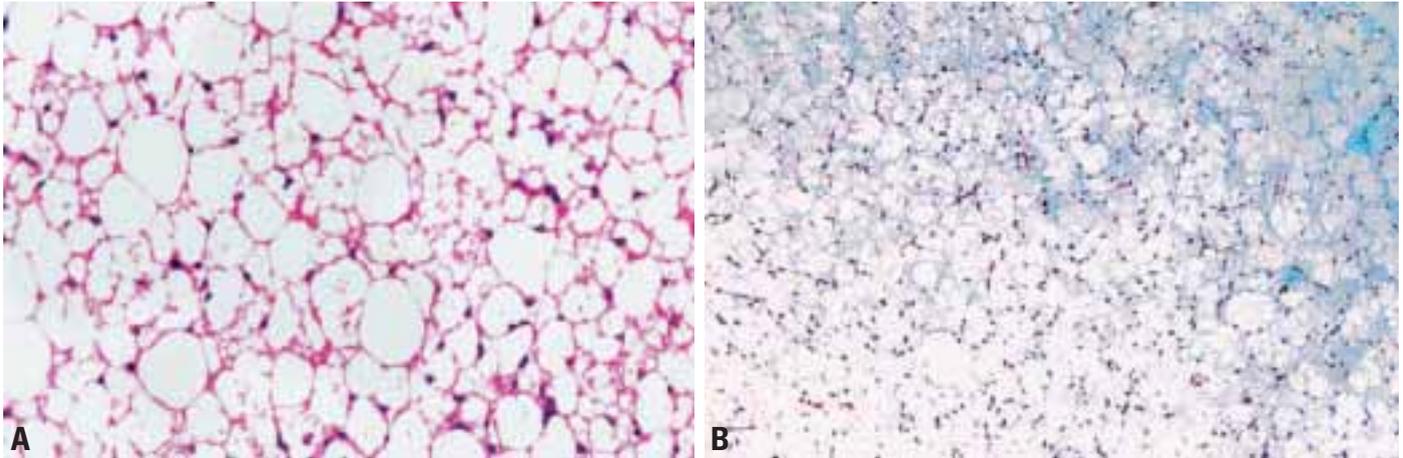
Fig. 1.13 A Admixture of multivacuolated lipoblasts and mature adipocytes. **B** 315 Delicate plexiform vascular pattern and myxoid changes in lipoblastoma.

in tumours both with and without changes of 8q12, the effect of *PLAG1* rearrangement might be reinforced by gain of chromosome 8 in some cases. Whether the extra copies of the *PLAG1* gene are normal or have point mutations is not known. By in situ hybridization it has been shown that split *PLAG1* signals are present in both classical, myxoid, and lipoma-like lipoblastomas as well as in a variety of mesenchymal cell components, indicating the mutation to occur in a progenitor cell that then differentiates {792}.

Prognostic factors
Lipoblastoma(tosis) is fully benign and malignant transformation or metastasis does not occur. Recurrences are described in 9% to 22% of cases, mainly in lipoblastomatosis. Therefore wide total excision of diffuse lesions is advised {348,391,1410,2196}.

Angiolipoma

R. Sciot
N. Mandahl

Definition
A subcutaneous nodule consisting of mature fat cells, intermingled with small and thin-walled vessels, a number of which contain fibrin thrombi.

ICD-O code   8861/0

Epidemiology
Angiolipomas are relatively common and usually appear in the late teens or early twenties. Children and patients older than 50 years are rarely involved. There is a male predominance and an increased familial incidence has been described (5% of all cases) {230,357, 942,977,1062,1232}. The mode of inheritance is not clear.

Sites of involvement
The forearm is the most common site, followed by the trunk and upper arm. Spinal angiolipomas and intramuscular haemangiomas, previously also called 'infiltrating angiolipomas', are different lesions {878,2148}.

Clinical features
Angiolipomas most frequently present as multiple subcutaneous small nodules, usually tender to painful. There is no correlation between the intensity/occurrence of pain and the degree of vascularity {527}.

Macroscopy
Angiolipomas appear as encapsulated yellowish to reddish nodules, most often less than 2 cm in diameter.

Histopathology
Angiolipomas typically consist of two mesenchymal elements: mature adipocytes and branching capillary sized vessels, which usually contain fibrin thrombi. The vascularity is more prominent in the subcapsular area {527}. The relative proportion of adipocytes and vessels varies and some lesions are almost completely composed of vascular channels. These 'cellular' angiolipomas should be distinguished from angiosarcoma and Kaposi sarcoma {983}. Interstitial mast cells may be prominent and in older lesions, increased fibrosis is present.

Genetics
With a single exception, all cytogenetically investigated tumours have had a normal karyotype {1905}.

Prognostic factors
Angiolipomas are always benign and show no tendency to recur. Malignant transformation does not occur.
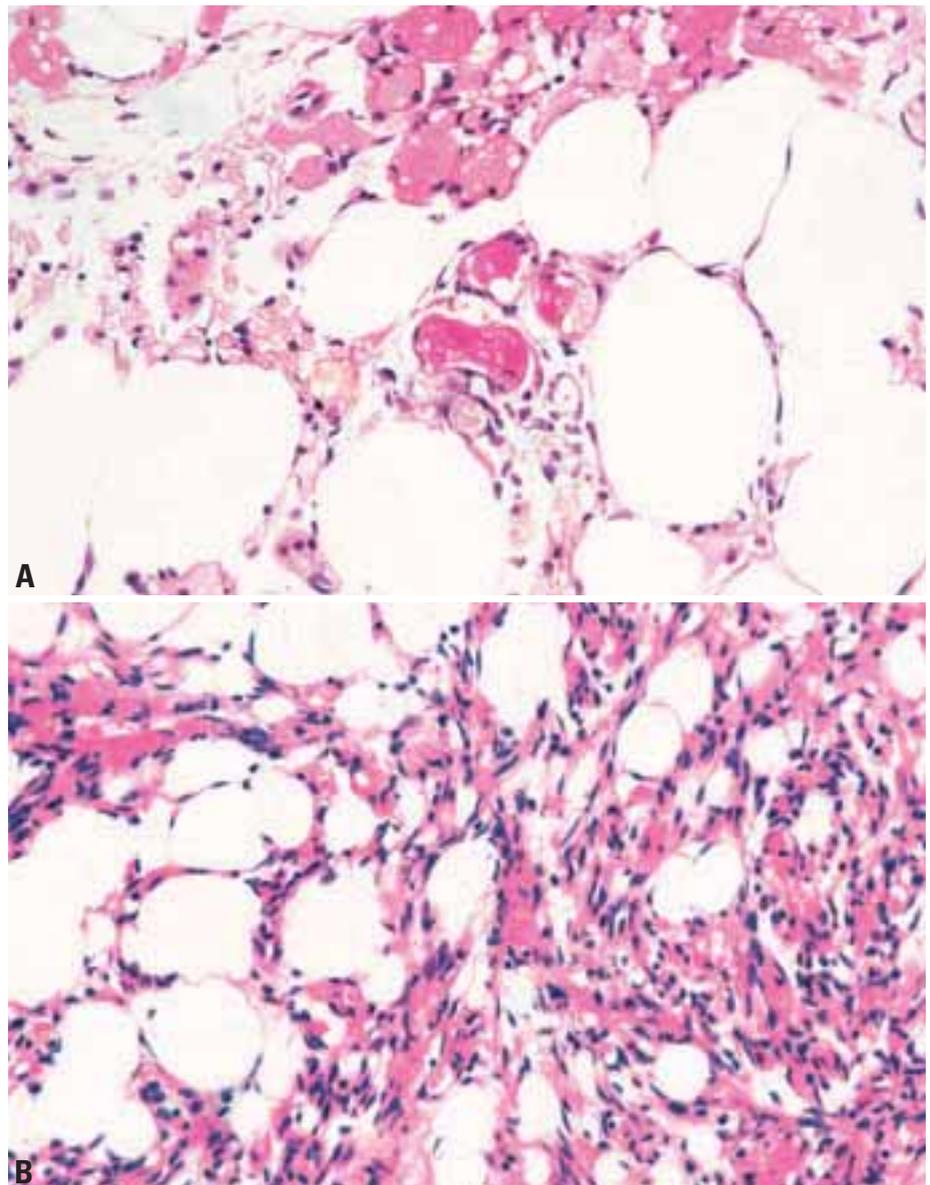
Fig. 1.14 Angiolipoma. **A** The tumour consists of mature adipocytes and capillaries, some of which contain microthrombi. **B** Cellular angiolipoma, in which the vessels predominate.

Myolipoma of soft tissue

J.M. Meis-Kindblom
L.G. Kindblom

Definition
Myolipoma of soft tissue is a benign tumour exhibiting features of mature smooth muscle and mature adipose tissue.

ICD-O code   8890/0

Synonym
Extrauterine lipoleiomyoma.

Epidemiology
Myolipoma of soft tissue is an extremely rare lesion occurring in adults, with a male to female ratio of 1:2 {1393}.

Sites of involvement
The majority of cases are deeply located and involve the abdominal cavity, retroperitoneum, and inguinal areas. The trunk wall and extremities may also be involved; such cases are subcutaneous and may grow deeply to involve the superficial muscular fascia {1393}.

Clinical features
Most lesions present as a palpable mass; the remainder are incidental findings.

Macroscopy
Deep-seated myolipomas of soft tissue range between 10 and 25 cm in size; the average size is 15 cm. Smaller lesions are seen in the subcutis. A completely or partially encapsulated lipomatous tumour intermingles with strands and nodules of firm white-tan, fibrillary to whorled areas corresponding to smooth muscle.

Histopathology
The smooth muscle component usually dominates with a muscle to fat ratio of 2:1. Smooth muscle tends to be evenly distributed and arranged in short fascicles, resulting in a sieve-like pattern as it traverses the fat. Individual smooth muscle fibres have deeply acidophilic fibrillary cytoplasm that becomes fuchsinophilic with the Masson trichrome stain. Nuclear chromatin is evenly dispersed, nucleoli are inconspicuous and no appreciable mitotic activity is seen. Equally important is the absence of any atypia in the mature lipomatous component of myolipoma. Floret cells and lipoblasts are not seen, nor are medium calibre thick-walled blood vessels as

Fig. 1.15 An encapsulated myolipoma of the pelvis with clear fatty and smooth muscle components.

seen in angiomyolipoma. Sclerosis and focal inflammation may be present in the fat.

Immunophenotype
Diffusely and strongly positive smooth muscle actin and desmin immunostaining confirm the presence of smooth muscle in myolipoma.

Prognostic factors
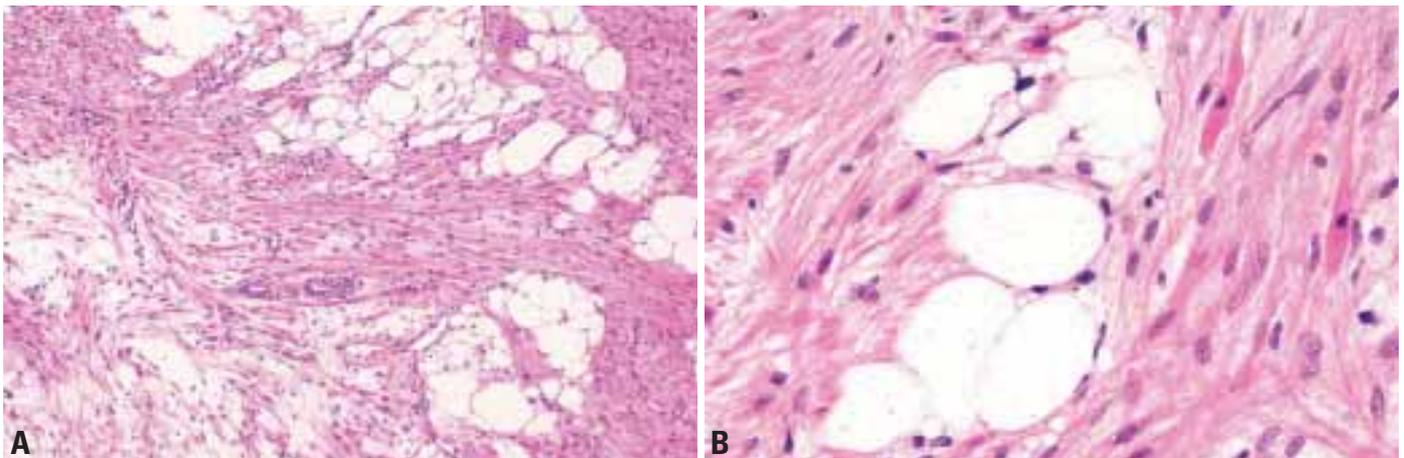Myolipoma does not recur. Complete surgical resection is curative.

Fig. 1.16 A,B Mature adipose tissue and mature smooth muscle arranged in short fascicles are seen in a myolipoma of the distal extremity.

Chondroid lipoma

L.G. Kindblom
J.M. Meis-Kindblom
N. Mandahl

Definition
Chondroid lipoma is a unique and recently recognized benign adipose tissue tumour containing lipoblasts, mature fat, and a chondroid matrix. It bears a strikingly close resemblance to myxoid liposarcoma and extraskeletal myxoid chondrosarcoma.

ICD-O code   8862/0

Epidemiology
Chondroid lipoma is rare and affects primarily adults with a male:female ratio of 1:4 {1396} without racial predilection.

Sites of involvement
This tumour occurs most commonly in the proximal extremities and limb girdles. However, the trunk and head and neck areas may also be affected. Chondroid lipoma is often deep-seated, involving skeletal muscle or deep fibrous connective tissues. Those cases involving the subcutis tend to impinge on the superficial muscular fascia.

Clinical features
The majority of patients present with a painless mass of variable duration. There is a recent history of enlargement in roughly one-half of cases.
Reports of imaging studies of this lesion are exceedingly sparse {1277,2320}.

Macroscopy
Most chondroid lipomas are 2–7 cm in size, although cases with haemorrhage may be significantly larger {1396}. Tumours are typically well circumscribed and yellowish, suggesting fatty differentiation.

Histopathology
Chondroid lipoma is often encapsulated and occasionally multilobular. Its histologic hallmarks are nests and cords of abundant uni- and multivacuolated lipoblasts embedded in a prominent myxoid to hyalinized chondroid matrix admixed with a variable amount of mature adipose tissue. The lipoblast nuclei are small and uniform, ranging from oval, reniform to multilobated in shape, with evenly dispersed chromatin and small nucleoli. The cytoplasm is finely vacuolated, containing small lipid droplets and PAS positive glycogen. Cells may have granular eosinophilic cytoplasm. Chondroid lipoma is highly vascular and not infrequently contains haemorrhage and fibrosis.
Toluidine blue and alcian blue stains at controlled pHs confirm the typical presence of chondroitin sulfates in the matrix {1116}.

Immunophenotype
Lipoblasts are weakly S100 protein positive whereas stronger staining is seen with increasing adipocytic maturation {1116}. Vimentin is uniformly positive in all cells; cytokeratins are detected in rare cases, corresponding ultrastructurally to tonofilaments. EMA is uniformly negative. Proliferative index with MIB1 is <1%.

Ultrastructure
Primitive cells sharing features of embryonal fat and embryonal cartilage are seen, as well as lipoblasts, preadipocytes and mature fat. Cytoplasmic knobby protrusions are often seen. The matrix has features resembling cartilage, including thin filaments, thin collagen fibres and numerous proteoglycan particles {1116,1559}.
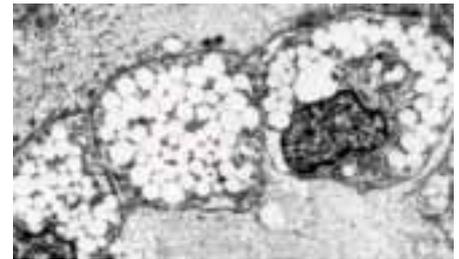

Fig. 1.18 EM of lipoblasts arranged in cords and a prominent chondroid matrix.

Cytogenetics
Two chondroid lipomas reported have displayed a seemingly balanced translocation, t(11;16)(q13;p12-13), in one case as the sole anomaly {1477}. Recurrent involvement of 11q13 has been found also in ordinary lipoma and hibernoma. However, in these tumour entities, 11q13 has never been found to recombine with 16p12-13 {1477}.

Prognostic factors
Chondroid lipoma does not recur locally or metastasize. Surgical excision is curative.
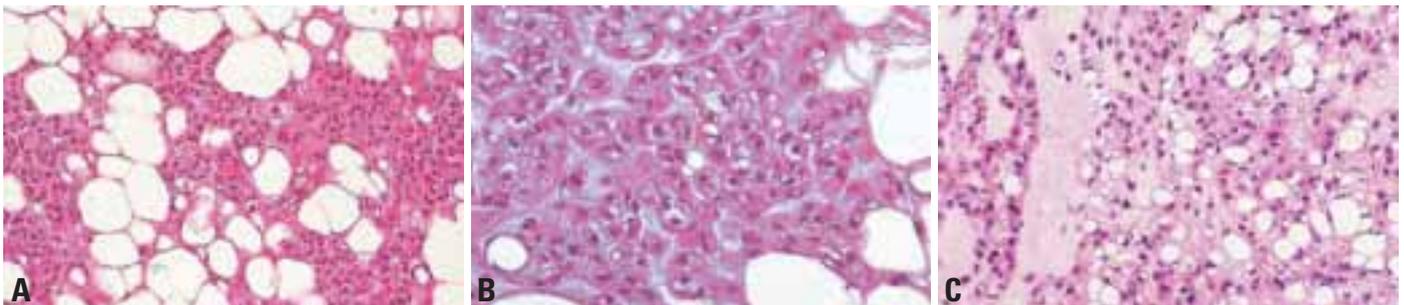

Fig. 1.17 Chondroid lipoma. **A** Mature fat and nests of small lipoblasts. **B** High magnification shows cellular details. **C** Mature fat and nests of small lipoblasts in chondroid lipoma showing a more prominent myxoid matrix.

Spindle cell lipoma / Pleomorphic lipoma

M.M. Miettinen
N. Mandahl

Definition

Spindle cell and pleomorphic lipoma, ends of a common histological spectrum, are circumscribed subcutaneous lesions occurring typically on the neck and back usually of males and composed of a variable admixture of bland spindled cells, hyperchromatic rounded cells, and multinucleate giant cells associated with ropey collagen.

ICD-O codes

Spindle cell lipoma	8857/0
Pleomorphic lipoma	8854/0

Sites of involvement

Spindle cell / pleomorphic lipomas occur predominantly in the posterior neck and shoulder area. Face, forehead, scalp, buccal-perioral area and upper arm are less common sites, and occurrence in the lower extremity is distinctly rare.

Clinical features

Spindle cell / pleomorphic lipomas typically present in older men with a median age of over 55 years, and only 10% of patients are women {60,102,595,684, 1944}. The tumour forms an asymptomatic, mobile dermal or subcutaneous mass, and there is often a long history. Rare patients have multiple lesions, and familial occurrence has been reported, mostly in men {633}. Spindle cell / pleomorphic lipomas have benign behaviour and conservative local excision is considered sufficient.

Macroscopy

Grossly spindle cell lipoma / pleomorphic lipoma forms an oval or discoid yellowish to greyish-white mass depending on the relative extent of the fatty and spindle cell components. The tumour often has a firmer texture than ordinary lipoma, but some examples have a gelatinous texture.

Histopathology

Histologically, at one end at the histological spectrum, spindle cell lipoma is composed of bland mitotically inactive
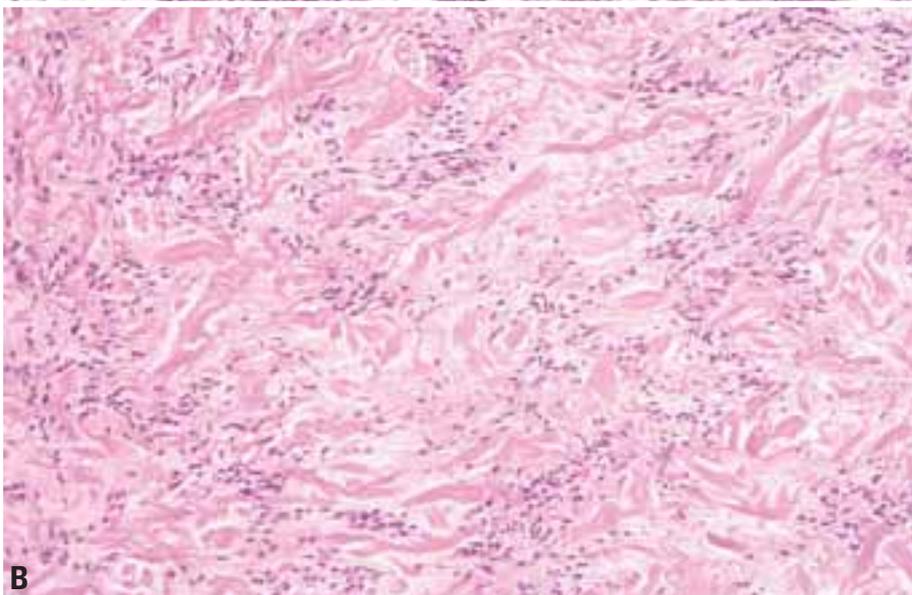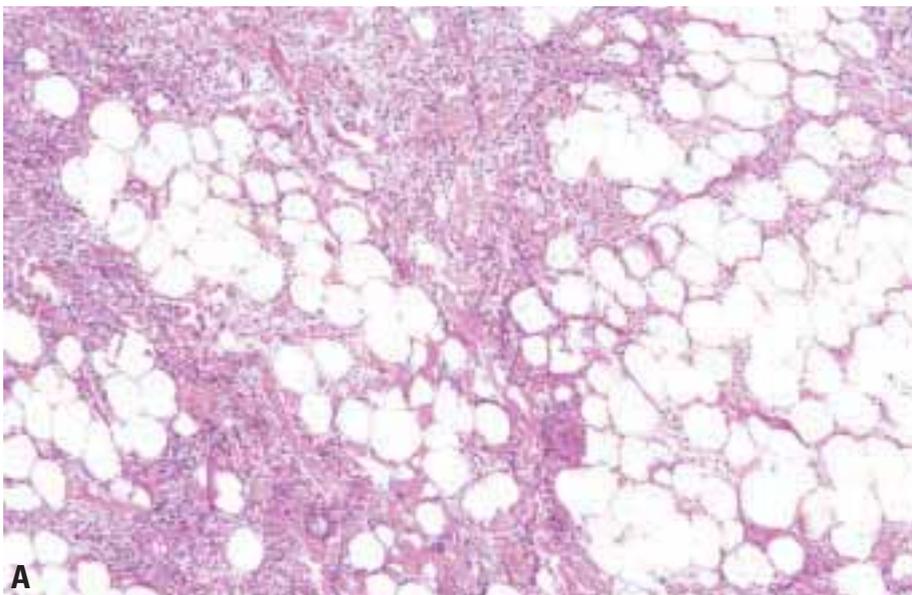
Fig. 1.19 Spindle cell lipoma. **A** The relative proportions of the adipocytic and spindle cell components are variable. **B** Some lesions are almost devoid of adipocytes and show vague nuclear palisading. Note the typically ropey collagen bundles.
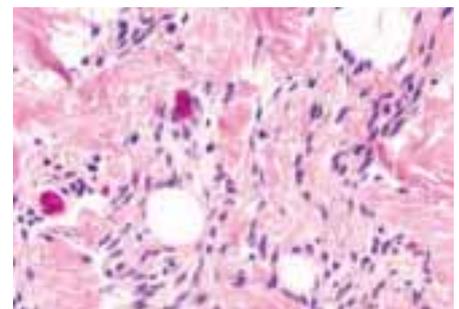
Fig. 1.20 Spindle cell lipoma. Typical case with bland spindle cells in a background with thick collagen fibres and a small number of adipocytes.
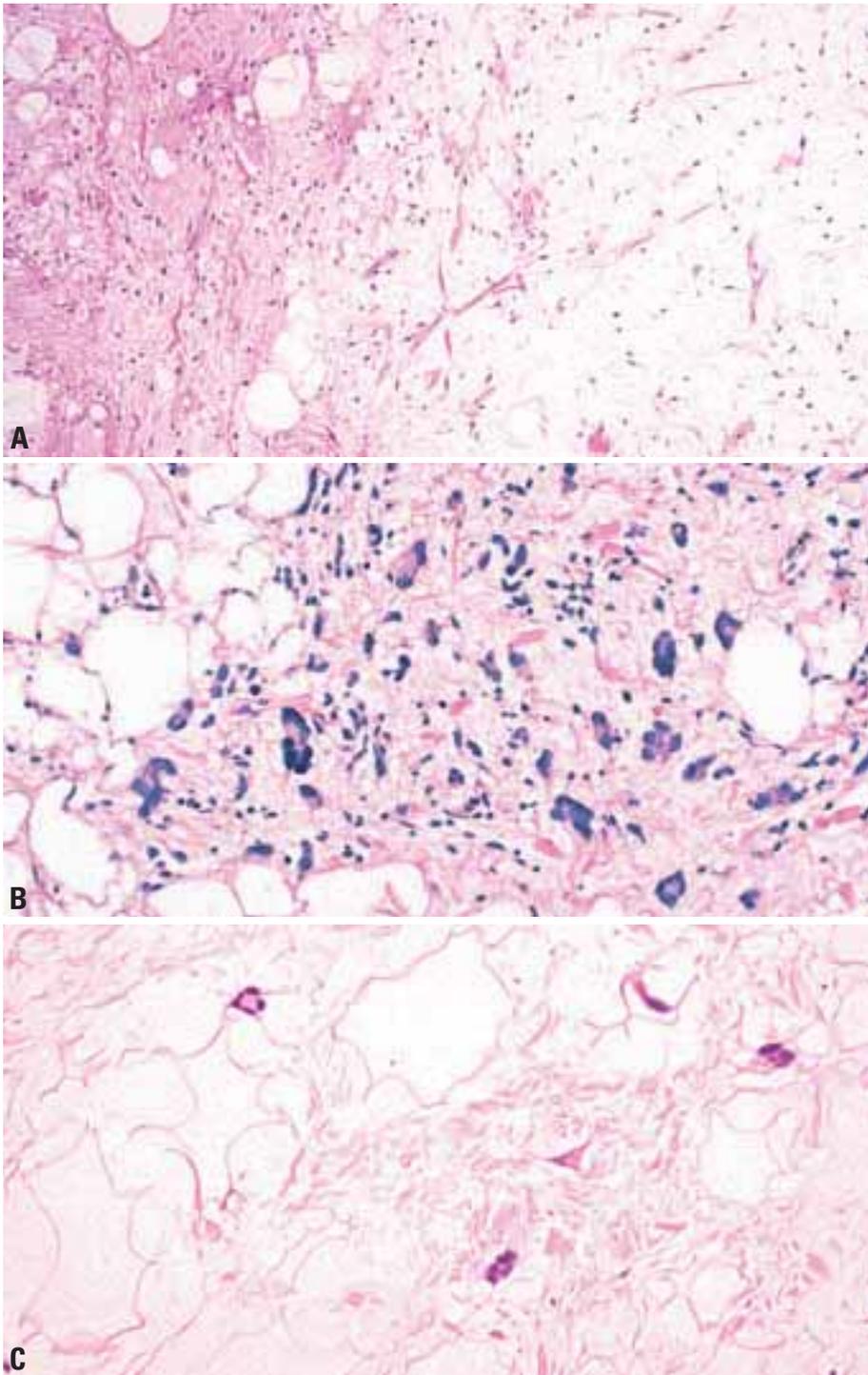
Fig. 1.21 Pleomorphic lipoma. **A** Prominent myxoid change of the stroma is not an uncommon feature. **B** Classical example showing numerous floret-like multinucleate cells. **C** Some pleomorphic lipomas consist almost entirely of mature adipocytes with admixed multinucleated stroma cells, often having floret-like nuclei.

Fig. 1.22 Immunopositivity for CD34 is a consistent feature of the spindle cell component.

spindled cells arranged in parallel registers between the fat cells and associated with thick rope-like collagen bundles. {60,595,684,1944}. Large numbers of mast cells are often seen in between the spindle cells, and lymphocytes and plasma cells may occur, especially in pleomorphic lipoma. Some spindle cell lipomas show myxoid stromal change or display slit-like cleavage spaces resembling vascular slits ("pseudoangiomatoid variant") {911}.
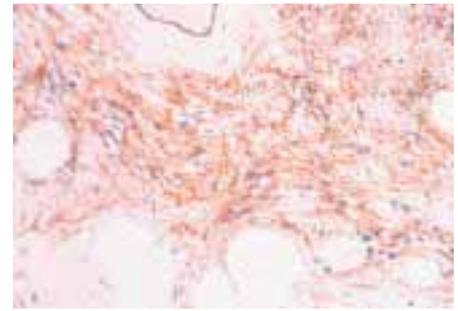
At the opposite end of the spectrum, pleomorphic lipoma is characterized by small spindled and rounded hyperchromatic cells and multinucleated giant cells with radially arranged nuclei in a"floret-like" pattern, like petals of flowers. Cases with features intermediate between classic spindle cell lipoma and pleomorphic lipoma quite often occur.

Immunophenotype

The spindle cells in both spindle cell and pleomorphic lipomas are strongly positive for CD34 and may rarely be positive for S100 protein {626,2059,2102}.

Cytogenetics

Spindle cell lipomas and pleomorphic lipomas show similar cytogenetic aberrations. The karyotypes are, on average, more complex than those found in ordinary lipomas and are frequently hypodiploid, often with multiple partial losses, no gain of sequences, and few balanced rearrangements. Monosomy or partial loss of chromosomes 13 and/or 16 have been found in seven to eight out of ten cases. Half of the tumours with involvement of chromosome 16 have had a breakpoint in 16q13, and all of them have had loss of 16q13-qter. The most frequently lost segments of chromosome 13 include 13q12 and 13q14-q22. Other chromosome segments lost in two to three of the ten cases are 6pter-p23, 6q15-q21, 10pter-p15, 10q23-qter, and 17pter-p13 {442}.

Prognostic factors

These are benign lesions which only rarely recur locally.

Hibernoma

M.M. Miettinen
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N. Mandahl

Definition
Hibernoma is a rare benign adipose tumour composed at least in part of brown fat cells with granular, multivacuolated cytoplasm. This brown fat component is admixed in variable proportion with white adipose tissue. Residual brown fat, mostly seen around cervical and axillary lymph nodes, should not be classified as hibernoma.

ICD-O codes   8880/0

Epidemiology
Recognized since around the turn of the century {1424}, hibernoma comprises 1.6% of benign lipomatous tumours and approximately 1.1% of all adipocytic tumours in AFIP files. Based on AFIP data on 170 cases {747}, hibernoma occurs predominantly in young adults, with a mean age of 38 years. 60% occur in the third and fourth decades, only 5% occur in children 2-18 years, and 7% in patients over 60 years. There is a slight male predominance {747}.

Sites of involvement
Hibernoma occurs in a wide variety of locations. The most common site is the thigh, followed by the trunk, upper extremity, and head and neck. The myxoid and spindle cell variants tend to be located in the posterior neck and shoulders, similar to spindle cell lipoma {747}. Less than 10% occur in the intra-abdominal or thoracic cavities {19}.

Clinical features
Hibernoma is a relatively slow growing tumour of the subcutis. At least 10% of cases are intramuscular. Hibernomas are usually painless. MRI reveals non-fat septations in hibernoma, not found in lipoma. By CT scan, hibernoma has a tissue attenuation intermediate between fat and skeletal muscle and enhances with contrast {1172}.

Aetiology
The aetiology of hibernoma is unknown, although many lesions arise at the sites where brown fat is normally found in hibernating animals and human fetuses/newborns {754}.

Macroscopy
The median size for hibernoma is 9.3 centimeters, range 1-24 centimeters {747}. Hibernomas are lobular, well-demarcated, and vary in colour from yellow to brown. They have a greasy, soft, and spongy cut surface {747,1113}.

Histopathology
Histologically, hibernomas vary in the content and appearance of the polygonal brown fat cells, the associated small capillary proliferation, and the stromal background, resulting in six variants. Most tumours contain large numbers of multivacuolated brown fat cells with abundant, granular cytoplasm and a
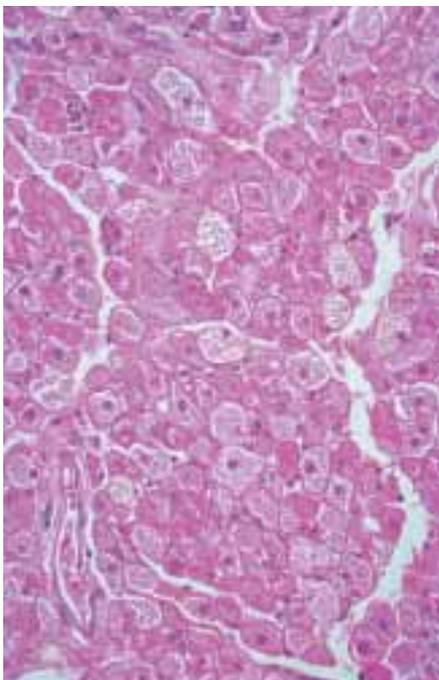

Fig. 1.23 Hibernoma. The eosinophilic variant is composed mostly of granular-appearing, multivacuolated brown fat cells with prominent nucleoli.
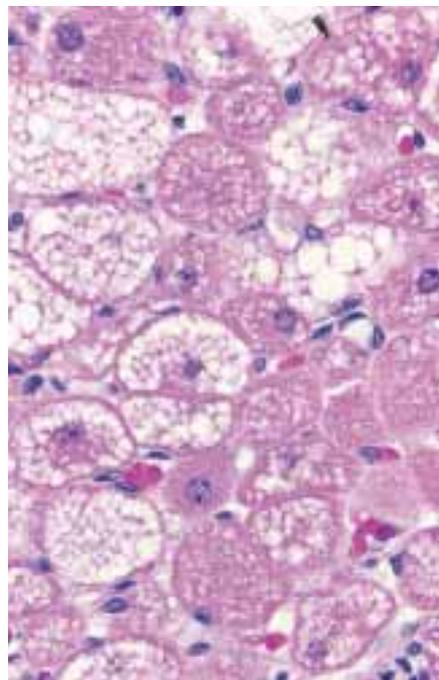

Fig. 1.24 Hibernoma. Detail of the eosinophilic variant with granular, multivacuolated brown fat cells and prominent nucleoli.
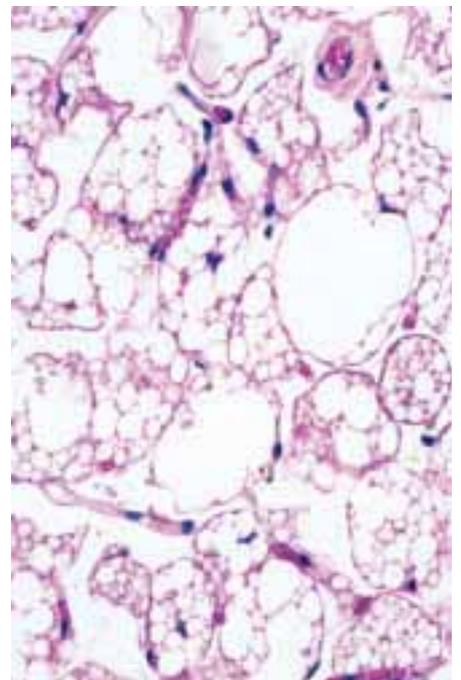

Fig. 1.25 Hibernoma. The pale cell variant has a pale tinctorial quality of the multivacuolated brown fat cells.
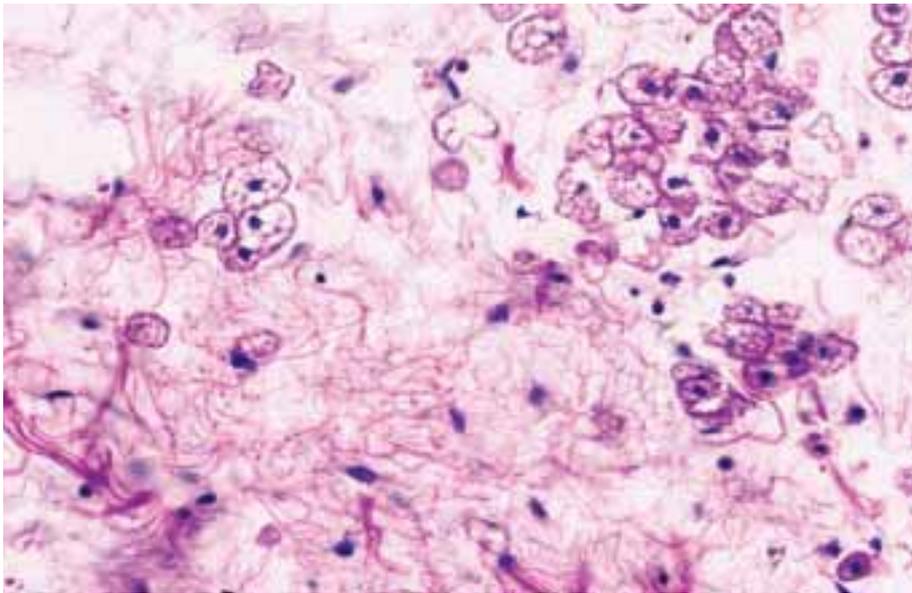
Fig. 1.26 Hibernoma. The myxoid variant has a myxoid background with floating brown fat cells.
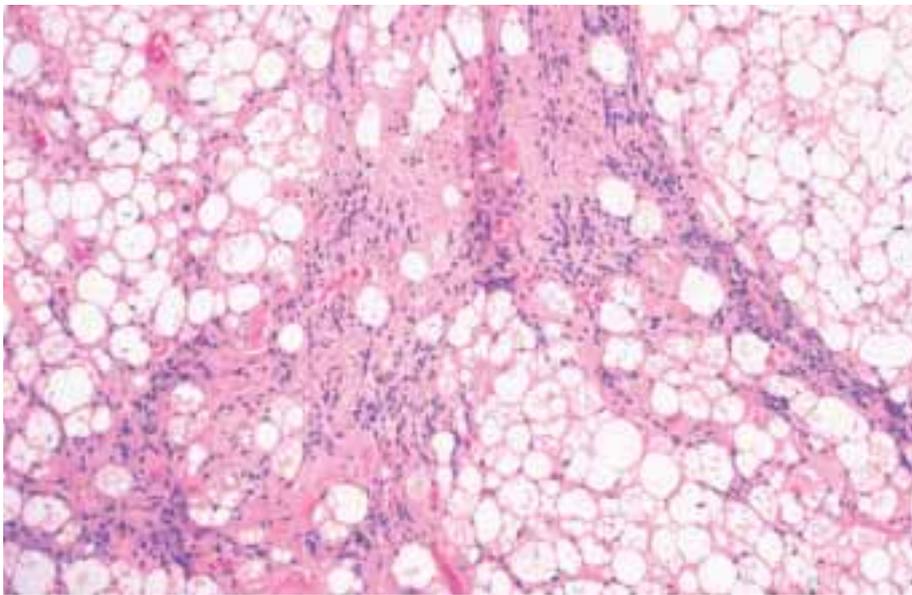

Fig. 1.27 Hibernoma. The spindle cell variant, a hybrid tumour between hibernoma and spindle cell lipoma, shows brown fat cells, mature white fat cells, scattered mast cells, bland spindled cells.

Fig. 1.28 Hibernoma. Partial G-banded karyotype showing a translocation t(11;17)(q13;p13).

small, central nucleus, the granular or eosinophilic variant. The brown fat cells vary from pale staining to variably eosinophilic, and some cases have a mixture of pale and eosinophilic cells, the mixed variant, while other cases have pure pale brown fat cells, the pale variant. Some hibernomas contain small clusters of brown fat amidst ordinary white fat, the "lipoma-like" variant. Multivacuolated lipoblast-like cells are often seen. Rare variants with myxoid stroma (myxoid variant), or a spindle cell

component, with thick bundles of collagen fibres, scattered mast cells, and mature adipose tissue (spindle cell variant), a hybrid between hibernoma and spindle cell lipoma, have been described. Mitoses are exceptional and cytological atypia is unusual. Such features should not be equated with malignancy as the biologic behaviour of hibernoma is invariably benign. However, scattered normal brown fat cells may be found in an otherwise classic myxoid or well differentiated liposarcoma.
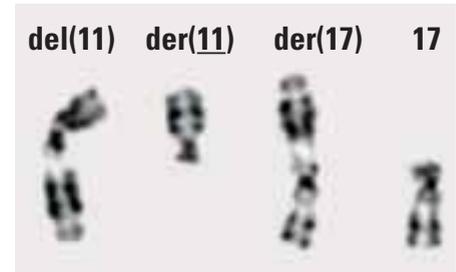
Immunophenotype

Hibernoma cells are variably, sometimes strongly, positive for S100 protein. The spindle cell variant has a CD34 positive spindle cell component, similar to spindle cell lipoma, whereas the other hibernoma variants are negative for CD34 {747}.

Genetics

Although hibernomas frequently show somewhat more complex chromosome changes than ordinary lipomas and lipoblastomas, the karyotypes are near- or pseudodiploid. The only recurrent aberration is the involvement of 11q13-21, most often 11q13, in structural rearrangements, which in the majority of cases affect three or more chromosomes. No chromosome band has been involved more than once as a translocation partner.

Metaphase FISH analyses have demonstrated that the chromosomal rearrangements are more complex than can be detected by chromosome banding analysis {793}. The aberrations not only affect the obviously rearranged chromosome 11, but also the seemingly normal homologue. Both heterozygous and homozygous deletions have been detected, with deletions comprising segments up to 4 Mb. Homozygous deletion of the multiple endocrine neoplasia type I tumour suppressor gene *MEN1* has been found in four of five tumours, whereas all five hibernomas investigated showed heterozygous loss of *PPP1A* {793}. Yet, no conclusive evidence of the pathogenetically important event is available.

Prognostic factors

Hibernoma is a benign tumour that does not recur with complete local excision {747}. All morphologic variants have the same good prognosis.

Atypical lipomatous tumour / Well differentiated liposarcoma

A.P. Dei Tos
F. Pedeutour

Definition

Atypical lipomatous tumour (ALT) / well-differentiated (WD) liposarcoma is an intermediate (locally aggressive) malignant mesenchymal neoplasm composed either entirely or in part of a mature adipocytic proliferation showing significant variation in cell size and at least focal nuclear atypia in both adipocytes and stromal cells. The presence of scattered hyperchromatic, often multinucleate stromal cells and a varying number of monovacuolated or multivacuolated lipoblasts (defined by the presence of single or multiple sharply marginated cytoplasmic vacuoles scalloping an enlarged hyperchromatic nucleus) may contribute to the morphologic diagnosis. Use of the term 'atypical lipomatous tumour' is determined principally by tumour location and resectability.

ICD-O code   8851/3

Fig. 1.29 Atypical lipomatous tumour / Well differentiated liposarcoma. Surgical specimen showing a well circumscribed, lobulated mass.

Terminology in clinical practice

The fact that WD liposarcoma shows no potential for metastasis unless it undergoes dedifferentiation led, in the late 1970s, to the introduction of terms such as atypical lipoma or atypical lipomatous tumour {626}, particularly for lesions arising at surgically amenable locations in the limbs and on the trunk since, at these sites, wide excision should usually be curative and hence the designation 'sarcoma' is not warranted. However, the variable, sometimes controversial application of this new terminology has represented a source of potential diagnostic confusion {620, 1112, 2246}. Atypical lipomatous tumour and WD liposarcoma are synonyms describing lesions which are identical both morphologically and karyotypically (see below) and in terms of biologic potential. The choice of terminology is therefore best determined by the degree of reciprocal comprehension between the surgeon and the pathologist to prevent either inadequate or excessive treatment {486}. However, in sites such as the retroperitoneum and mediastinum it is commonly impossible to obtain a wide surgical excision margin and, in such cases, local recurrence (often repeated and ultimately uncontrolled) is almost inevitable and often leads to death, even in the absence of dedifferentiation and metastasis – hence, at these sites, retention of the term WD liposarcoma can readily be justified. Spindle cell/pleomorphic lipoma must be kept separated from the atypical lipoma category as it is morphologically as well as cytogenetically distinct, rarely recurs and has no potential to dedifferentiate (see page 31).

Synonyms

Atypical lipoma, adipocytic liposarcoma, lipoma-like liposarcoma, sclerosing liposarcoma, spindle cell liposarcoma, inflammatory liposarcoma.

Epidemiology

ALT/WD liposarcoma accounts for about 40-45% of all liposarcomas and therefore represents the largest subgroup of aggressive adipocytic neoplasms. These lesions mostly occur in middle aged adults with a peak incidence in the 6th decade. Convincing examples in childhood are extremely rare. Males and females are equally affected with the obvious exception of those lesions affecting the spermatic cord {588,678, 2242}.

Sites of involvement

ALT/WD liposarcoma occurs most frequently in deep soft tissue of the limbs, especially the thigh, followed by the retroperitoneum, the paratesticular area and the mediastinum {588, 678, 2242}. These lesions may also arise in subcutaneous tissue and, very rarely, in skin.

Clinical features

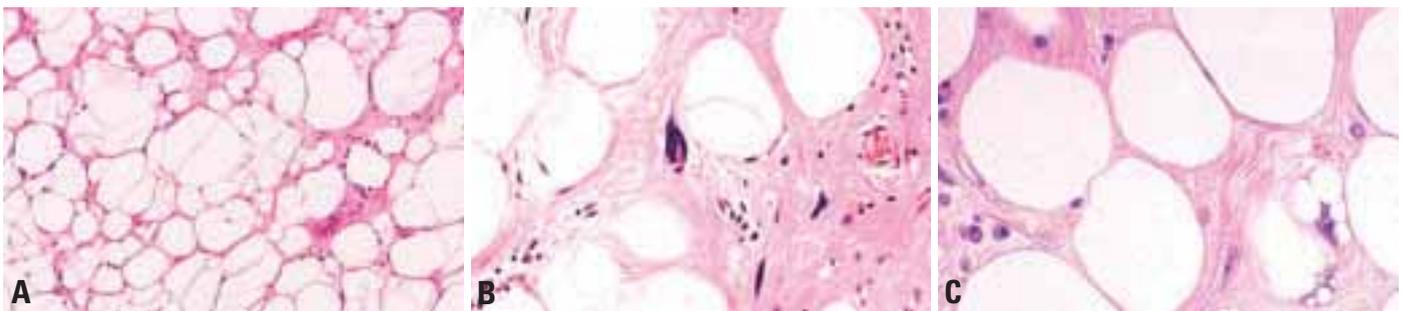ALT/WD liposarcoma usually presents as a deep-seated, painless enlarging mass

Fig. 1.30 Atypical lipomatous tumour / Well differentiated liposarcoma. **A** Marked variation in adipocytic size is one of the most important diagnostic clues for the diagnosis. **B** The presence of atypical, hyperchromatic stromal cells represents a common finding. **C** A varying number of lipoblasts can be seen in well-differentiated liposarcoma but their presence does not make (nor is required for) a diagnosis of liposarcoma.
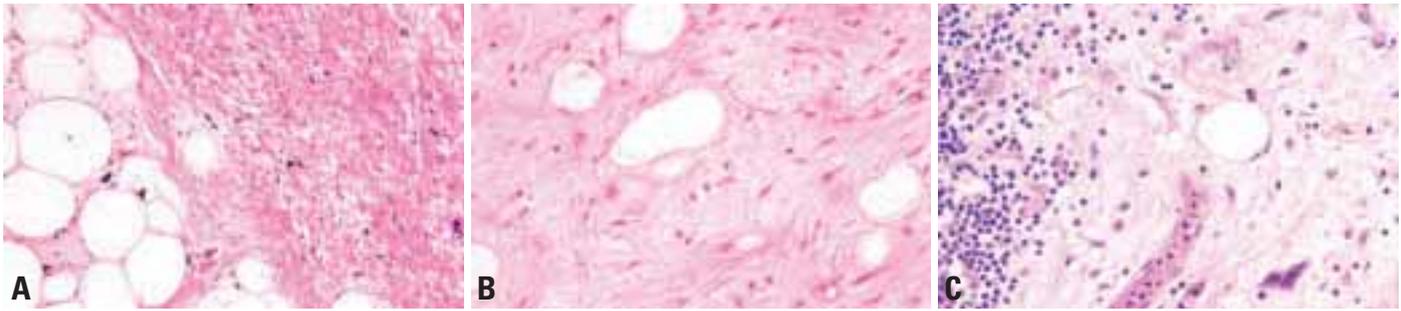
Fig. 1.31 Atypical lipomatous tumour / Well differentiated liposarcoma. **A** The presence of scattered bizarre stromal cells, exhibiting marked nuclear hyperchromasia set in a fibrillary collagenous background represent the most important diagnostic feature of sclerosing variant. **B** Neural-like spindle cell proliferation in a fibrous and / or myxoid background, associated with an atypical lipomatous component that usually includes lipoblasts, characterize the spindle cell variant. **C** Bizarre, often multinucleate cells in the stroma are an important diagnostic clue in the inflammatory variant. Note the accompanying inflammatory component.

that can slowly attain a very large size, particularly when arising in the retroperitoneum. Retroperitoneal lesions are often asymptomatic until the tumour has exceeded 20 cm in diameter and may be found by chance.

Macroscopy

ALT/WD liposarcoma consists usually of a large, usually well-circumscribed, lobulated mass. In the retroperitoneum there may be muliple discontiguous masses. Rarely an infiltrative growth pattern may be encountered. Colour varies from yellow to white (and firm) depending on the proportion of adipocytic, fibrous and/or myxoid areas. Areas of fat necrosis are common in larger lesions.

Histopathology

ALT/WD liposarcoma can be subdivided morphologically into four main subtypes: adipocytic (lipoma-like), sclerosing, inflammatory {2234} and spindle cell {490}. The presence of more than one morphological pattern in the same lesion is common, particularly in retroperitoneal tumors.

Microscopically, ALT/WD liposarcoma is composed of a relatively mature adipocytic proliferation in which, in contrast to benign lipoma, significant variation in cell size is easily appreciable. Focal adipocytic nuclear atypia as well as hyperchromasia also contributes to the usual morphologic picture and scattered hyperchromatic as well as multinucleate stromal cells are often identified. Hyperchromatic stromal cells tend to be more numerous within fibrous septa. A varying number (from many to none) of monovacuolated or multivacuolated lipoblasts may be found. It is commonly believed that lipoblasts represent the hallmark of any liposarcoma subtype; however, it is important to emphasise that the mere presence of lipoblasts does not make (nor is required for) a diagnosis of liposarcoma.

Sclerosing liposarcoma ranks second in frequency among the group of ALT/WD liposarcoma. This pattern is most often seen in retroperitoneal or paratesticular lesions. Microscopically, the main histological finding is the presence of scattered bizarre stromal cells, exhibiting marked nuclear hyperchromasia and associated with rare multivacuolated lipoblasts set in an extensive fibrillary collagenous stroma. As occasionally the fibrous component may represent the majority of the neoplasm, lipogenic areas (which are often limited in extent) can be easily overlooked or even missed in a small tissue sample. Extensive sampling of the surgical specimen is therefore mandatory, and blocks should be taken from any area showing variation in gross appearance.

Inflammatory liposarcoma represents a rare variant of ALT/WD liposarcoma, occurring most often in the retroperitoneum, in which a chronic inflammatory infiltrate predominates to the extent that the adipocytic nature of the neoplasm can be obscured. In such instances, the differential diagnosis is mainly with non adipocytic lesions such as inflammatory myofibroblastic tumour, Castleman disease and Hodgkin as well as non-Hodgkin lymphomas {78, 1174}. The inflammatory infiltrate is usually composed of polyphenotypic lymphoplasmacytic aggregates in which a B-cell phenotype tends to predominate. Cases exist in which a polyclonal T-cell population represents the main inflammatory component. When dealing with cases in which the adipocytic component is scarce the presence of bizarre multinucleate stromal cells represents a useful diagnostic clue and should raise the suspicion of inflammatory liposarcoma.

The spindle cell variant of ALT/WD liposarcoma {490} is composed morphologically of a fairly bland neural-like spindle cell proliferation set in a fibrous and/or myxoid background and is associated with an atypical lipomatous component which usually includes lipoblasts. An interesting albeit rare finding in ALT/WD liposarcoma, is the presence of heterologous differentiation. In addition to metaplastic bone formation, a well differentiated smooth or striated muscle component can rarely be seen and should be distinguished from heterologous differentiation arising in the context of dedifferentiated liposarcoma (see page 38) {2063}.

Immunophenotype

Immunohistochemistry plays a very minor role in the differential diagnosis of ALT / WD liposarcoma. Adipocytic cells usually exhibit S-100 protein immunoreactivity that may be helpful in highlighting the presence of lipoblasts {493}. HMB-45 immunonegativity has proved useful in the differential diagnosis with angiomyolipoma that occasionally may mimic liposarcoma.

Genetics

The defining genetic features of ALT/WD liposarcoma cells are supernumerary circular ("ring") and giant rod chromosomes. These rings and giant markers contain amplification of the 12q14-15 region, including the *MDM2* gene, associated with co-amplification of various other chromosomal regions; they most

often lack alpha-satellite centromeric sequences.

Cytogenetics

The supernumerary ring and giant marker chromosomes have been observed as the sole change or concomitant with a few other numerical or structural abnormalities {1477}. Metaphase cells are usually near-diploid but often near-tetraploid. Random and non-random telomeric associations are frequently observed and may give a false impression of complexity to ALT/WD liposarcoma karyotypes {1322}. Cells containing either rings or giant markers or both can be observed in the same tumour sample. Varying stages of complexity are observed, from the simple, classical picture of a supernumerary ring or giant marker in addition to 46 apparently normal chromosomes up to more complex patterns showing several copies of rings and giant markers, telomeric associations, and other structural alterations.

Molecular cytogenetics and genetics

The combination of fluorescence in-situ hybridisation (FISH) using whole chromosome painting probes and comparative genomic hybridisation indicates that both supernumerary rings and giant markers are composed of interspersed amplified sequences consistently originating from the 12q14-15 region. A variety of other chromosomal regions, the most frequent of which are 12q21-22 and 1q21-25, have been shown to be co-amplified with 12q14-15 {434, 1678, 1680, 2053, 2072}. Investigations using FISH with unique probes and Southern blotting showed that *MDM2*, located in 12q14-15, was consistently amplified, usually accompanied by amplification of neighbouring genes, such as *SAS*, *CDK4*, and *HMGIC*. This 12q14-15 amplification is not observed in lipomas and its detection may therefore serve to distinguish ALT/WD liposarcoma from benign adipose tumours. More centromeric genes, located in 12q13, such as *GLI* or *DDIT3* (*CHOP*), have not been shown to be amplified. Nuclear blebs, anaphase bridges, and strings or micronuclei containing the amplified regions are frequently observed. The *TP53* gene is usually not subject to mutations in ALT/WD liposarcoma {1706,

1889}. Another striking feature of ALT/WDLPS supernumerary chromosomes is that they have a functional centromere, as indicated by positive labeling with anti-CENPC antibodies that bind to the kinetochore, but they do not contain alpha-satellite sequences, and C-banding is often negative {1962}.

Prognostic factors

The most important prognostic factor for ALT/WD liposarcoma is anatomic location. Lesions located in surgically amenable soft tissue do not recur following complete (preferably wide) excision with a clear margin. Tumours occurring in deep anatomic sites such as retroperitoneum, spermatic cord or mediastinum tend to recur repeatedly to the extent that they may cause the patient's death as a result of uncontrolled local effects or they may dedifferentiate and metastasise. The ultimate risk of dedifferentiation varies according to site and lesional duration and is probably >20% in the retroperitoneum but < 2% in the limbs. Overall mortality ranges from essentially 0% for ALT of the extremities to more than 80% for WD liposarcomas occurring in the retroperitoneum if the patients are followed up for 10-20 years. Median time to death ranges between 6 and 11 years {1290, 2246}.
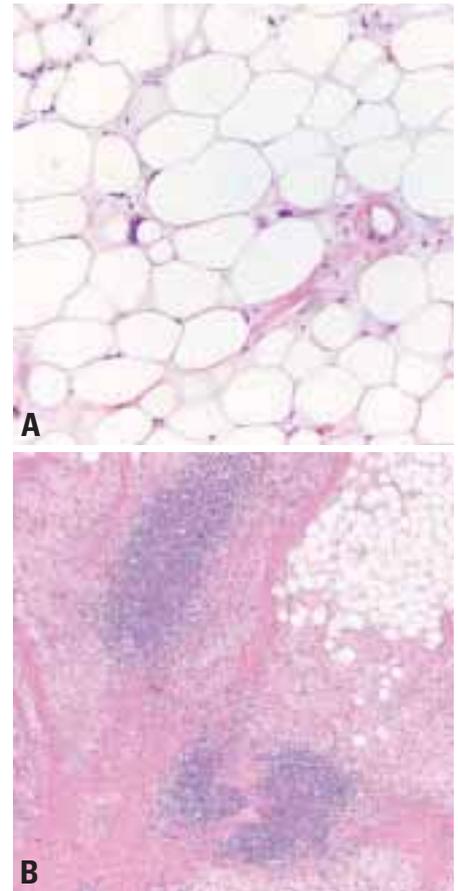
Fig. 1.32 Atypical lipomatous tumour / Well differentiated liposarcoma. **A** Lipoma-like subtype. **B** In the inflammatory subtype, the inflammatory infiltrate often predominates and may obscure the adipocytic nature of the neoplasm.

Fig. 1.33 Metaphase spread from an atypical lipomatous tumour, showing characteristic ring chromosome.

Dedifferentiated liposarcoma

A.P. Dei Tos
F. Pedeutour

Definition
Malignant adipocytic neoplasm showing transition, either in the primary or in a recurrence, from atypical lipomatous tumour/well differentiated liposarcoma to non-lipogenic sarcoma of variable histological grade, usually at least several milimeters in diameter.

ICD-O code   8858/3

Epidemiology
Dedifferentiation occurs in up to 10% of well differentiated (WD) liposarcomas of any subtype, although the risk of dedifferentiation appears to be higher when dealing with deep seated (particularly retroperitoneal) lesions and is significantly less in the limbs.

This most probably represents a time-dependent more than a site-dependent phenomenon. Dedifferentiated liposarcoma affects basically the same patient population as WD liposarcoma (see page 35).

No sex predilection is observed. About 90% of dedifferentiated liposarcomas arise "de novo" while 10% occur in recurrences {678, 2242}.

Sites of involvement
The retroperitoneum represents the most common anatomic location, outnumbering the soft tissue of the extremities by at least 3:1. Other locations include the spermatic cord and, more rarely, the head and neck and trunk. Occurrence in subcutaneous tissue is extremely rare {678, 2242}.

Clinical features
Dedifferentiated liposarcoma usually presents as a large painless mass, which may be found by chance (particularly in the retroperitoneum).

In the limbs, the history of a long-standing mass exhibiting recent increase in size often indicates dedifferentiation. Radiological imaging shows coexistence of both fatty and non-fatty solid components which, in the retroperitoneum, may be discontiguous.

Macroscopy
Dedifferentiated liposarcoma usually consists of large multinodular yellow masses containing discrete, solid, often tan-grey non-lipomatous (dedifferentiated) areas. Dedifferentiated areas often show necrosis. The transition between the lipomatous and the dedifferentiated areas sometimes may be gradual.

Histopathology
The histological hallmark of dedifferentiated liposarcoma is represented by the transition from ALT/WD liposarcoma of any type to non-lipogenic sarcoma which, in most cases, is high grade. The extent of dedifferentiation is variable but most often this component is evident to the naked eye. The prognostic significance of microscopic foci of dedifferentation is uncertain. The transition usually occurs abruptly. However in some cases this can be more gradual and, exceptionally, low grade and high grade areas appear to be intermingled. Dedifferentiated areas exhibit a variable histological picture but most frequently they resemble unclassified 'MFH'-like pleomorphic sarcoma or intermediate to high grade myxofibrosarcoma {1374, 2246}.

Although, originally, dedifferentiation was characterized definitionally by high grade morphology {617}, the concept of low grade dedifferentiation has increasingly been recognized {578,937}. Low grade dedifferentiation is characterized most often by the presence of uniform fibroblastic spindle cells with mild nuclear atypia, often organized in a fascicular pattern and exhibiting cellularity intermediate between WD sclerosing liposarcoma and usual high grade areas. Low grade dedifferentiation should not be confused with WD spindle cell liposarcoma which is invariably a lipogenic lesion (i.e. it contains atypical adipocytes or lipoblasts), whereas dedifferentiated areas, both low and high grade are generally non lipogenic.

Dedifferentiated liposarcoma may exhibit heterologous differentiation in about 5-10% of cases which apparently does not affect the clinical outcome. Most often the line of heterologous differentiation is myogenic or osteo/chondrosarcomatous but angiosarcomatous elements have also been reported. A peculiar "neural-like" or "meningothelial-like" whorling pattern of dedifferentiation has recently been described {636, 1538}. This pattern is often associated with ossification.

Dedifferentiated liposarcoma appears to exhibit less aggressive clinical behaviour when compared with other high grade pleomorphic sarcomas. Careful and extensive sampling is therefore mandatory, particularly in large retroperitoneal lesions, as the well differentiated component may be overlooked. Additionally, it should be noted that local recurrences of dedifferentiated liposarcoma may be entirely well differentiated {1374, 2246}.

Immunophenotype
Immunohistochemistry plays its main role in permitting the recognition of divergent differentiation and in excluding other tumour types.

Genetics
Cytogenetics
Similar to ALT/WD liposarcoma, dedifferentiated liposarcoma most often has ring or giant marker chromosomes {680,794, 1389,1425,1706,1962}. However, the number of karyotyped cases is presently too small to establish whether significant

Fig. 1.34 Dedifferentiated liposarcoma. Note the solid, fleshy areas with haemorrhage, indicating the presence of a high grade component in this otherwise well differentiated retroperitoneal liposarcoma.
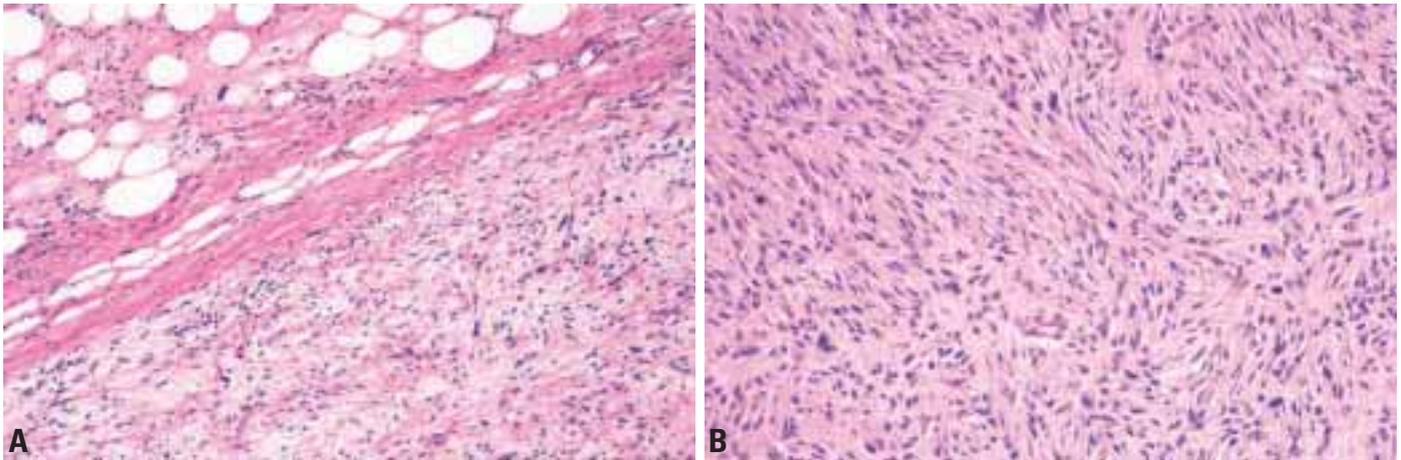
Fig. 1.35 Dedifferentiated liposarcoma. **A** Abrupt transition between well differentiated liposarcoma and high grade non lipogenic area is seen. **B** The morphology of the dedifferentiated component usually overlaps with so called storiform and pleomorphic MFH.

differences between the well differentiated and dedifferentiated types exist. A peculiarity of dedifferentiated liposarcoma might be the presence of multiple abnormal clones, with one or more containing supernumerary rings or large markers {1389,1425}.

Molecular cytogenetics and genetics
Comparative genomic hybridization and fluorescence in situ hybridisation analyses revealed amplification of the 12q13-21 region associated with the co-amplification of other regions, as also observed in WD liposarcomas {794, 1389, 1706, 1962, 2072}. Southern blot studies showed *MDM2* amplification in 5/5 retroperitoneal, but not in 4/4 non-retroperitoneal dedifferentiated liposarcoma cases {1706,1889}. These 4 non-retroperitoneal cases negative for *MDM2*

amplification were found to have *TP53* mutations, whereas in another series of 14 dedifferentiated liposarcoma, a majority of which expressed *MDM2*, *TP53* mutation was detected only in the dedifferentiated component of a single case {487}.

Prognostic factors
Dedifferentiated liposarcoma is characterized by a tendency to recur locally in at least 40% of cases. However, almost all retroperitoneal examples seem to recur locally if the patients are followed for 10-20 years. Distant metastases are observed in 15-20% of cases with an overall mortality ranging between 28 and 30% at 5 years follow-up {937, 1374, 2246}, although this figure is undoubtedly much higher at 10-20 years. The most important prognostic factor is represent-

ed by anatomic location, with retroperitoneal lesions exhibiting the worst clinical behaviour. The extent of dedifferentiated areas does not seem to predict the outcome. Interestingly, dedifferentiated liposarcoma, despite its high grade morphology, exhibits a less aggressive clinical course than other types of high grade pleomorphic sarcoma, although the basis for this difference is unknown {937, 1374, 2246}. Relative absence of complex karyotypic aberrations as well as integrity of the *TP53* gene in most cases (at variance with what is observed in high grade pleomorphic sarcomas) may at least in part explain the discrepancy between morphology and clinical outcome {399,487}.
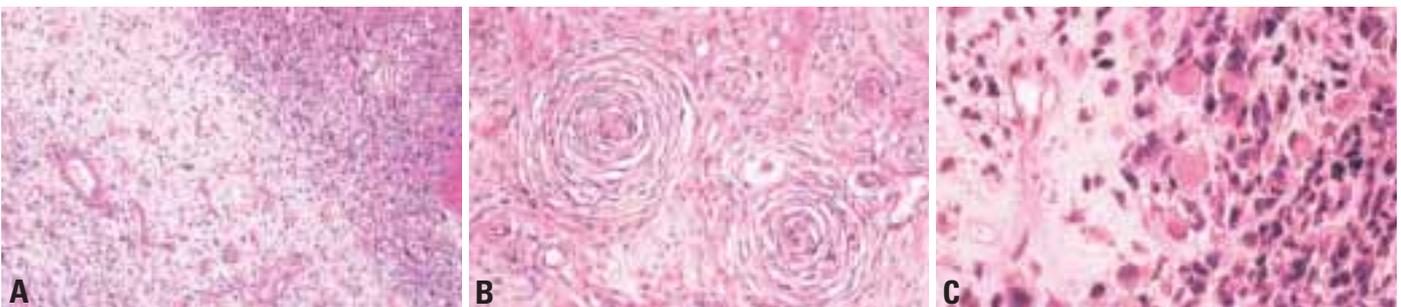

Fig. 1.36 Dedifferentiated liposarcoma. **A** Often the dedifferentiated component exhibits morphologic features indistinguishable from myxofibrosarcoma. **B** Rarely, dedifferentiated liposarcoma features a peculiar whorling growth pattern reminiscent of neural or meningothelial structures. **C** Approximately 5% of cases exhibit heterologous differentiation, most often myogenic. This example shows rhabdomyosarcomatous differentiation.

Myxoid liposarcoma

C. Antonescu
M. Ladanyi

Definition
A malignant tumour composed of uniform round to oval shaped primitive non-lipogenic mesenchymal cells and a variable number of small signet-ring lipoblasts in a prominent myxoid stroma with a characteristic branching vascular pattern. Included in this category are lesions formerly known as round cell liposarcoma.

ICD-O codes
Myxoid liposarcoma   8852/3
Round cell liposarcoma   8853/3

Synonyms
Myxoid / round cell (RC) liposarcoma, round cell liposarcoma.

Epidemiology
Myxoid liposarcoma (MLS) is the second most common subtype of liposarcoma, accounting for more than one third of liposarcomas and representing about 10% of all adult soft tissue sarcomas.

Sites of involvement
MLS occurs with predilection in the deep soft tissues of the extremities, and in more than two-thirds of cases arises within the musculature of the thigh. MLS rarely arises primarily in the retroperitoneum or in subcutaneous tissue.

Clinical features
MLS typically occurs as a large painless mass within the deep soft tissues of the limbs. MLS is a disease of young adults, with the age at presentation on average a decade younger than with other histological subtypes of liposarcoma. It has a peak incidence in the 4th and 5th decades of life and, although very rare, it is the commonest form of liposarcoma in patients younger than 20 years old. There is no gender predilection. MLS is prone to recur locally and one-third of patients develop distant metastases, but this is dependent on the histological grade. In contrast to other types of liposarcoma or other myxoid sarcomas of the extremities, MLS tends to metasta-

sise to unusual soft tissue (such as retroperitoneum, opposite extremity, axilla, etc) or bone (with predilection to spine) locations, even before spread to lung. In a significant number of cases, MLS patients present clinically with synchronous or metachronous multifocal disease {73}. This unusual clinical phenomenon most likely represents a pattern of haematogenous metastases to other sites by tumour cells seemingly incompetent to seed the lungs.

Macroscopy
Grossly, MLS are well-circumscribed, multinodular intramuscular tumours, showing a tan, gelatinous cut surface in predominantly low-grade tumours. In contrast, areas of RC component, representing high-grade sarcoma, have a white fleshy appearance. Gross evidence of tumour necrosis is uncommon.

Histopathology
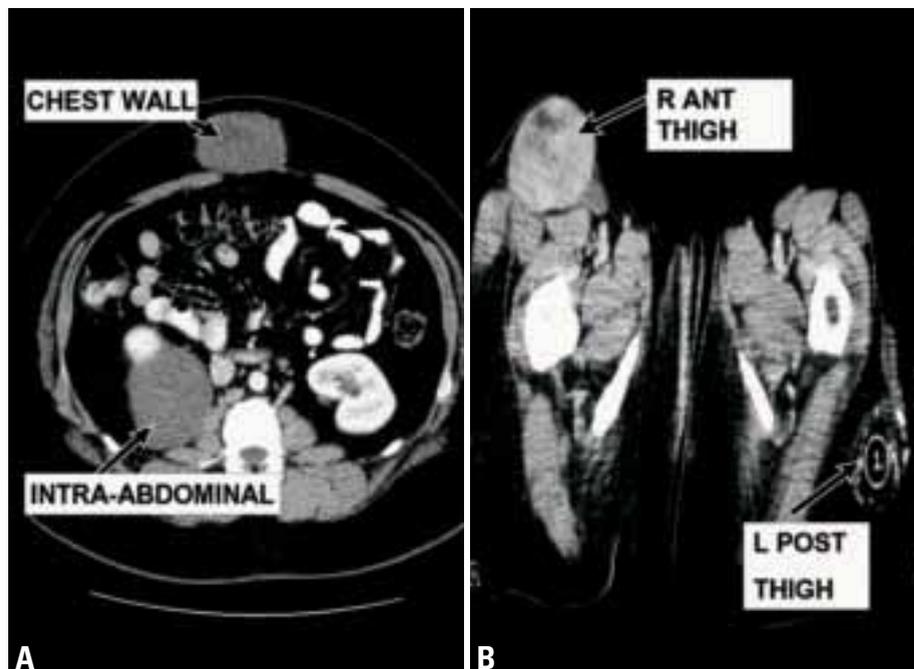At low-power MLS has a nodular growth pattern, with enhanced cellularity at the

Fig. 1.37 A,B Myxoid liposarcoma. CT images of multifocal myxoid liposarcoma, showing synchronous soft tissue masses, likely representing multiple soft tissue metastases.
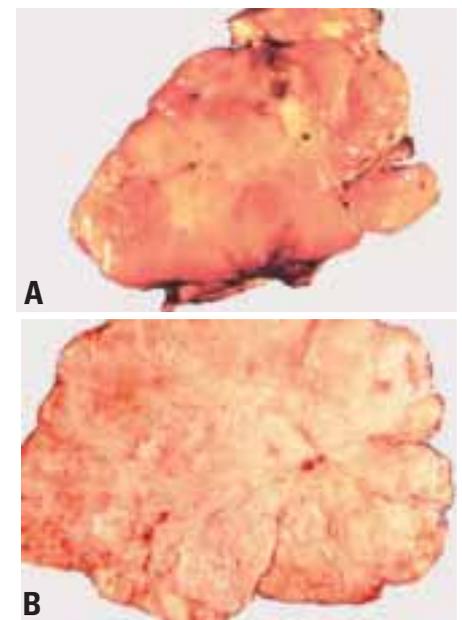
Fig. 1.38 Myxoid liposarcoma. Gross appearance of MLS with **(A)** a gelatinous cut surface in low grade myxoid areas and **(B)** a yellow-white appearance in the high grade round cell component.
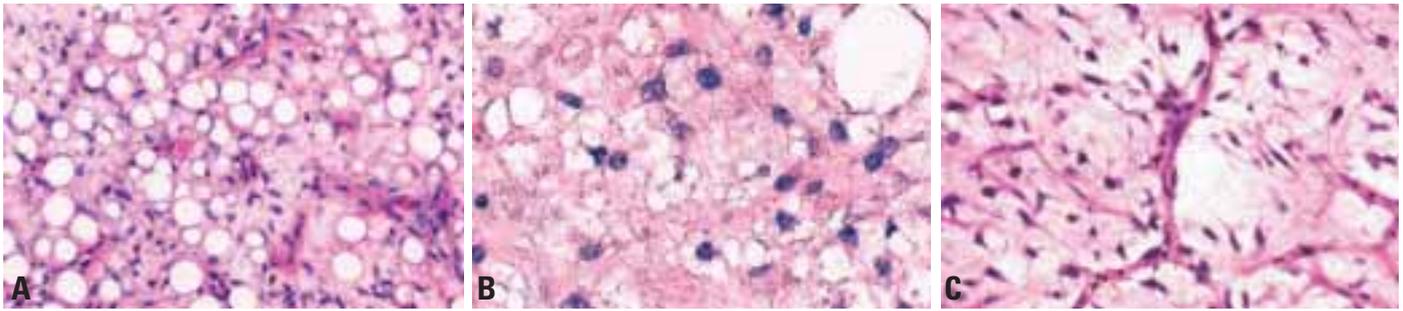
Fig. 1.39 Histological spectrum of myxoid liposarcoma (MLS). **A** Uniform round to oval shaped primitive nonlipogenic mesenchymal cells and a variable number of small lipoblasts in a prominent myxoid stroma. **B** Signet-ring lipoblasts with multivacuolated cytoplasm. **C** Delicate arborizing vasculature.

periphery of the lobules. There is a mixture of uniform round to oval shaped primitive nonlipogenic mesenchymal cells and small signet-ring lipoblasts in a prominent myxoid stroma, rich in a delicate, arborising, "chicken-wire" capillary vasculature. Frequently the extracellular mucin forms large confluent pools, creating a microcystic lymphangioma-like or so-called "pulmonary oedema" growth pattern. Interstitial haemorrhage is common. Typically, MLS lacks nuclear pleomorphism, giant tumour cells, prominent areas of spindling, or significant mitotic activity. A subset of MLS shows histological progression to hypercellular or RC morphology, which is associated with a significantly poorer prognosis. The RC areas are characterized by solid sheets of back-to-back primitive round cells with a high nuclear/cytoplasmic ratio and conspicuous nucleoli, with no intervening myxoid stroma {677}. The RC (hypercellular) areas may be composed of close-packed relatively small cells similar to those in the myxoid areas or may less often consist of larger rounded cells
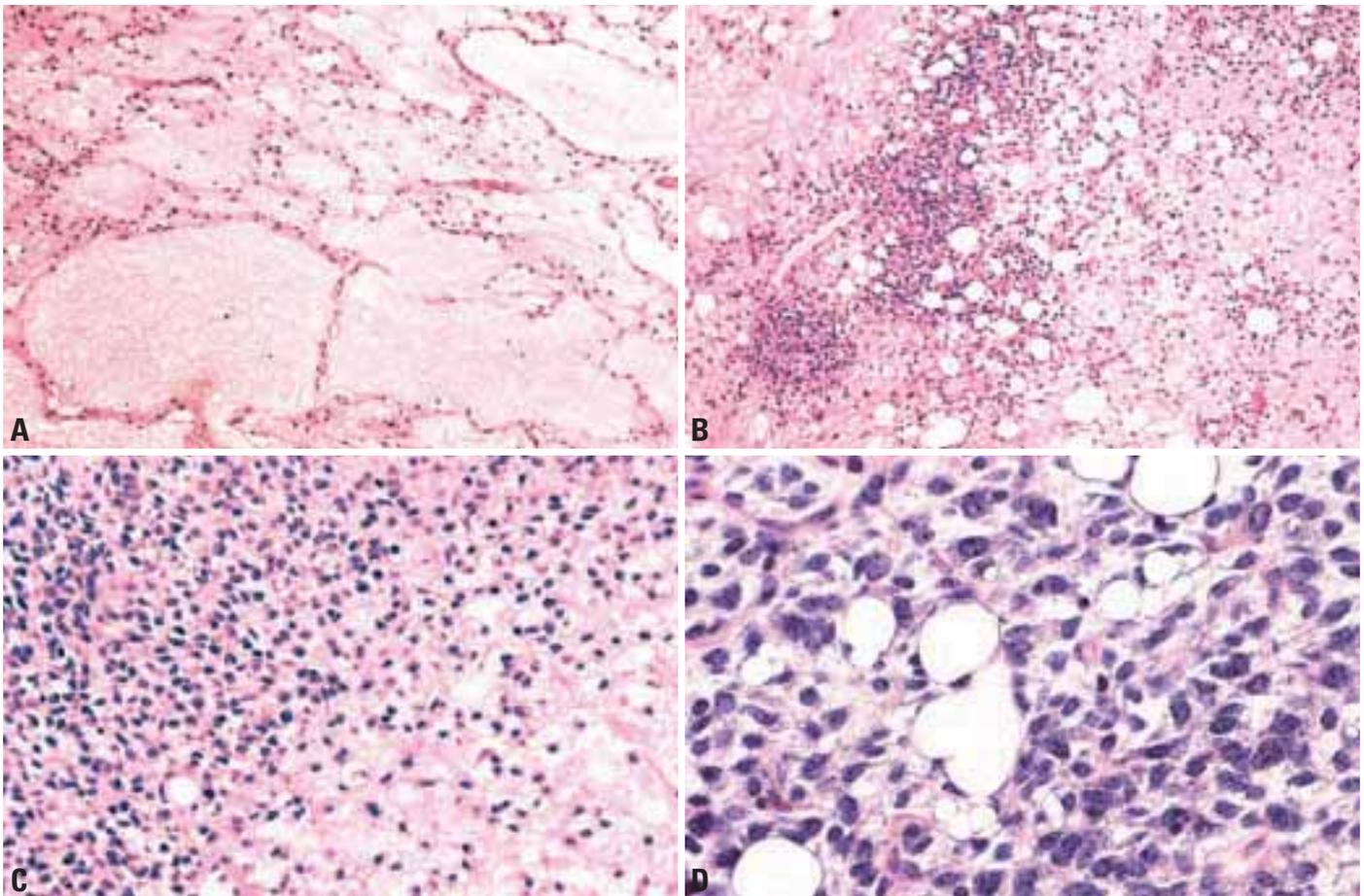

Fig. 1.40 Histological spectrum of myxoid liposarcoma (MLS). **A** Characteristic "pulmonary oedema" growth pattern due to pools of stromal mucin. **B** Low power view of a low grade MLS showing focal areas of increased cellularity. **C** High power view of a "transitional area", showing increased cellularity. Tumour cells are not closely packed, retaining a small amount of intercellular myxoid stroma. **D** Round cell MLS characterized by solid sheets of back-to-back primitive round cells with a high nuclear / cytoplasmic ratio and conspicuous nucleoli, with no intervening myxoid stroma.
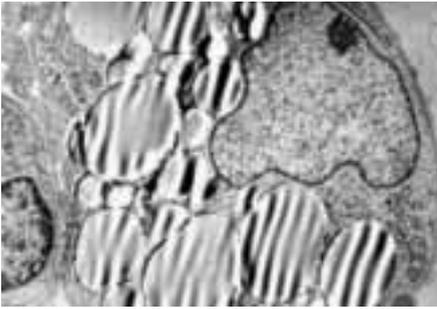
Fig. 1.41 Myxoid liposarcoma. Ultrastructural appearance of signet ring lipoblast, with microvesicular fat droplets.

with variable amounts of eosinophilic cytoplasm. These two morphologic patterns show no clear difference in prognosis but have been responsible for some of the confusion regarding definition of the round cell variant. The presence of gradual transition from myxoid to hypercellular/ RC areas, commonly observed in MLS, provides strong evidence that myxoid and RC liposarcoma represent a histological continuum of MLS. The so-called areas of transition are defined as areas of increased cellularity, not reaching the level of RC component and still retaining small amount of intercellular myxoid stroma. The existence of a morphologic spectrum, in which purely myxoid and RC liposarcoma represent the well and poorly differentiated components is supported by the same recurrent genetic alteration in both.

Immunophenotype

Although, for most MLS cases, immunohistochemical studies are not needed for establishing a correct diagnosis, it can be useful in cases showing predominantly round cell morphology. In the majority of cases this shows a diffuse staining for S100 protein.

Ultrastructure

Ultrastructurally the proportion of undifferentiated cells, devoid of lipid droplets and rich in clusters of vimentin-type intermediate filaments, and signet-ring lipoblasts vary from case to case. Lipoblasts in variable stages of adipocytic maturation can be identified, containing either relatively few small lipid droplets, or large confluent lipid droplets that displace the nucleus to the periphery. Flocculent mucoid stromal material coating the cells and extracellular spaces is common.

Genetics

The karyotypic hallmark of myxoid and round cell liposarcoma is the t(12;16)(q13;p11) present cytogenetically in more than 90% of cases {2018, 2145}. The translocation leads to the fusion of the *DDIT3* (a.k.a. *CHOP*) and *FUS* (a.k.a. *TLS*) genes at 12q13 and 16p11, respectively, and the generation of FUS/DDIT3 hybrid protein {104, 410, 1687, 1741}. In rare cases of MLS a variant chromosomal translocation
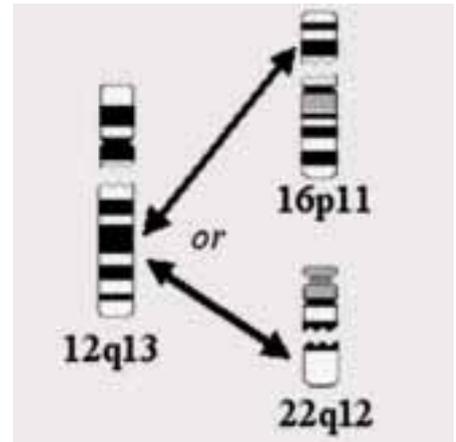

Fig. 1.42 Myxoid liposarcoma. Schematic illustration of the breakpoints involved in the specific translocations of myxoid/round cell liposarcoma, t(12;16)(q13;p11) and t(12;22)(q13;q12).

t(12;22)(q13;q12) has been described, in which *DDIT3* fuses instead with *EWS*, a gene highly related to *FUS* {1641}. *FUS/DDIT3* fusion transcripts occur as different recurrent structural variants based on the presence or absence of *FUS* exons 6 to 8 in the fusion product. Of the possible *FUS* genomic breakpoints, only breaks in *FUS* introns 5, 7, and 8 give rise to in-frame fusion transcripts joining *FUS* exons 5, 7, and 8, respectively, to exon 2 of *DDIT3* {1061, 1642}. Thus, three major recurrent fusion transcript types have been reported: type 7-2 (a.k.a. type I), seen in about 20% of cases, type 5-2 (a.k.a. type II), seen in approximately two-thirds of cases, and type 8-2 (a.k.a. type III), seen in about 10% {73, 1143, 1642}. Sequence analysis of the genomic t(12;16) breakpoints in *FUS* and *DDIT3* and associated functional studies suggest the involvement of translin and topoisomerase II in the process of translocation {971,1061}.

The monoclonal origin of the synchronous and/or metachronous multifocal MLS has been confirmed by comparing FUS/DDIT3 or EWS/DDIT3 genomic rearrangement structure in tumours from different sites {66}.

The presence of the *FUS/DDIT3* fusion is highly sensitive and specific for the MLS entity, and is absent in other morphologic mimics, such as the predominantly myxoid well differentiated liposarcomas of the retroperitoneum and myxofibrosarcomas {67}. No convincing genetic evidence has been provided to date to
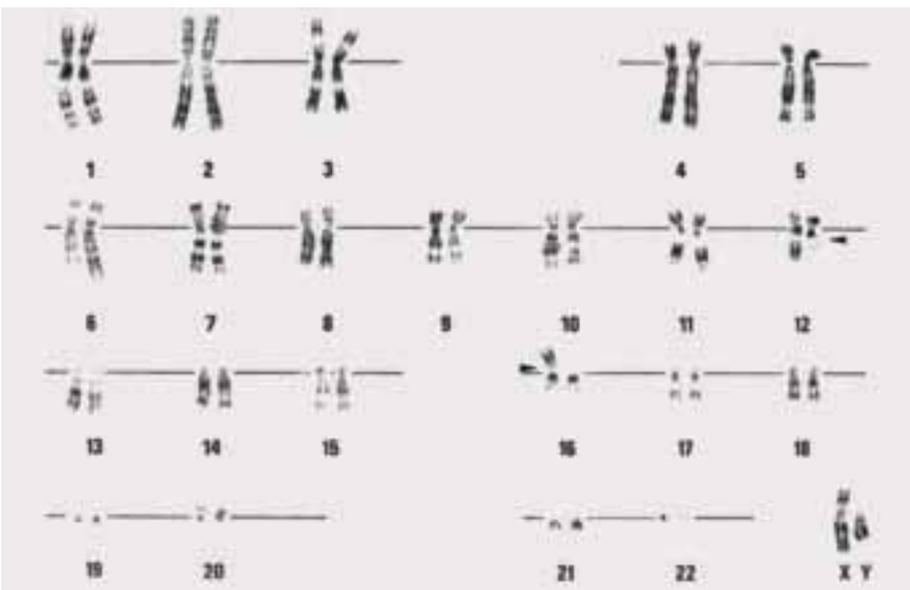

Fig. 1.43 Myxoid liposarcoma. Karyotype showing the characteristic translocation t(12;16)(q13;p11) in a myxoid liposarcoma. Arrowheads indicate breakpoints.

support the concept of mixed type liposarcoma composed of MLS and dedifferentiated liposarcoma.

Prognostic factors

High histological grade, often defined as ≥5%RC areas, presence of necrosis, and TP53 overexpression are predictors of unfavourable outcome in localized MLS {73, 1103, 1976}. The prognostic significance of more limited hypercellularity (transitional areas) is less certain. The clinical outcome of multifocal MLS is poor, regardless of its often bland or "low grade" histological appearance. In contrast with some other translocation-associated sarcomas, the molecular variability of fusion transcripts in MLS does not appear to have a significant impact on histological grade or clinical outcome {73}.
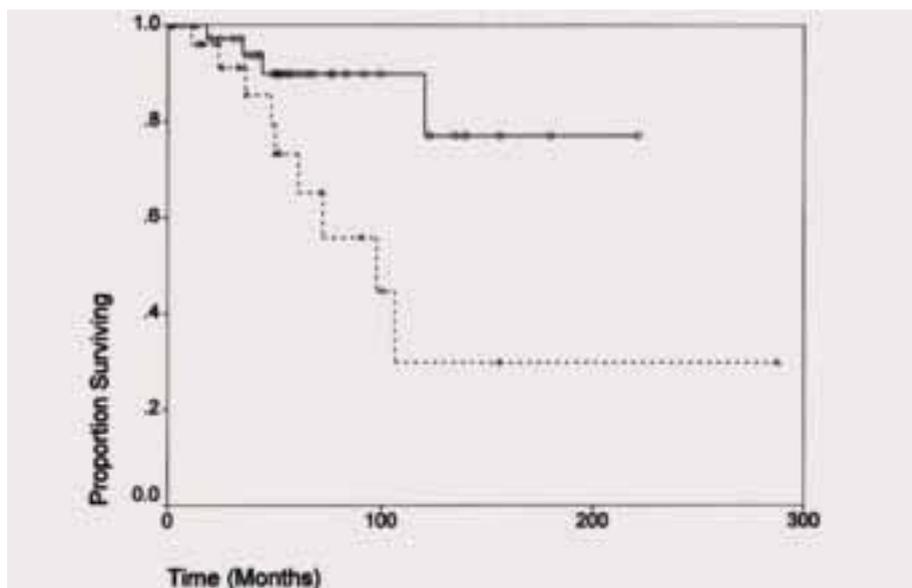

Fig. 1.44 Myxoid liposarcoma. Kaplan-Meier curve showing a correlation between high histological grade (≥5%RC) and disease specific survival in patients with localized MLS (From C.R. Antonescu et al. {73}).

Pleomorphic liposarcoma

T. Mentzel
F. Pedeutour

Definition
Pleomorphic liposarcoma is a pleomorphic, high grade sarcoma containing a variable number of pleomorphic lipoblasts. No areas of atypical lipomatous tumour (well differentiated liposarcoma) or another line of differentiation (malignant mesenchymoma) are evident.

ICD-O code   8854/3

Epidemiology
Pleomorphic liposarcoma represents the rarest subtype of liposarcoma, accounting for approximately 5% of all liposarcomas {101} and 20% of pleomorphic sarcomas {675}. The majority of neoplasms arise in elderly patients (>50 years) with an equal sex distribution.

Sites of involvement
Pleomorphic liposarcoma tends to occur on the extremities (lower>upper limbs), whereas the trunk and the retroperitoneum are less frequently affected; rare sites of involvement include the mediastinum, the paratesticular region, the scalp, the abdominal/pelvic cavities, and the orbit {290, 489, 548, 1139, 1445, 1609}. Although most cases arise in deep soft tissues, examples in subcutis or rare purely dermal pleomorphic liposarcomas have been reported {489, 548, 774}.

Clinical features
As in other deep seated sarcomas, most patients complain of a firm, enlarging mass; many cases have a notably short preoperative history. In general, pleomorphic liposarcoma is an aggressive mesenchymal neoplasm showing a 30% to 50% metastasis rate and an overall tumour associated mortality of 40% to 50% {548, 1445, 2332}. Many patients die within a short period of time {1445}, and the lung represents the preferred site of metastases {548}. In contrast, dedifferentiated liposarcomas and high-grade myxofibrosarcomas have a prolonged clinical course, whereas pleomorphic myogenic sarcomas of deep soft tissues show an even more aggressive clinical course emphasising the need for subclassification of pleomorphic sarcomas.

Macroscopy
Grossly, the neoplasms are typically described as firm, often multinodular lesions with white to yellow cut surfaces. In many cases myxoid areas and areas of necrosis are noted. The majority of neoplasms are large with a median greatest diameter of more than 10 cm.

Histopathology
Histologically, well circumscribed, non-encapsulated cases as well as ill defined and infiltrative neoplasms composed of a varying number of pleomorphic lipoblasts in a background of a high grade, pleomorphic sarcoma are seen. The majority of neoplasms consist of pleomorphic spindle shaped tumour cells and fascicles of spindled and smaller, round cells admixed with multinucleated giant cells (similar to so called malignant fibrous histiocytoma), as well as pleomorphic, multivacuolated lipoblasts, with bizarre, hyperchromatic and scalloped nuclei. In some cases only scattered pleomorphic lipoblasts are found, whereas sheets of pleomorphic lipoblasts are evident in other examples. Frequently, intra- and extra-cellular eosinophilic hyaline droplets or globules are noted, that most likely represent lysosomal structures. Rarely a prominent inflammatory infiltrate is evident. In a number of cases, areas with morphological features of pleomorphic sarcoma resembling intermediate to high
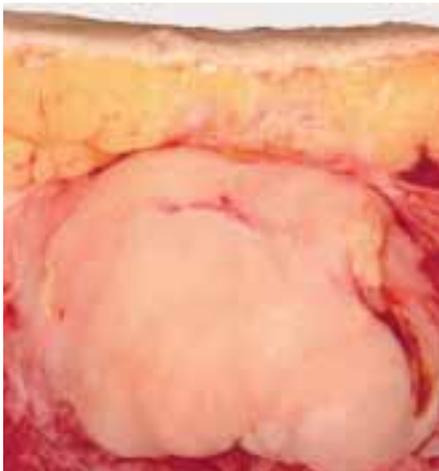

Fig. 1.45 Pleomorphic liposarcoma. Deep seated tumour with grey-white cut surface.
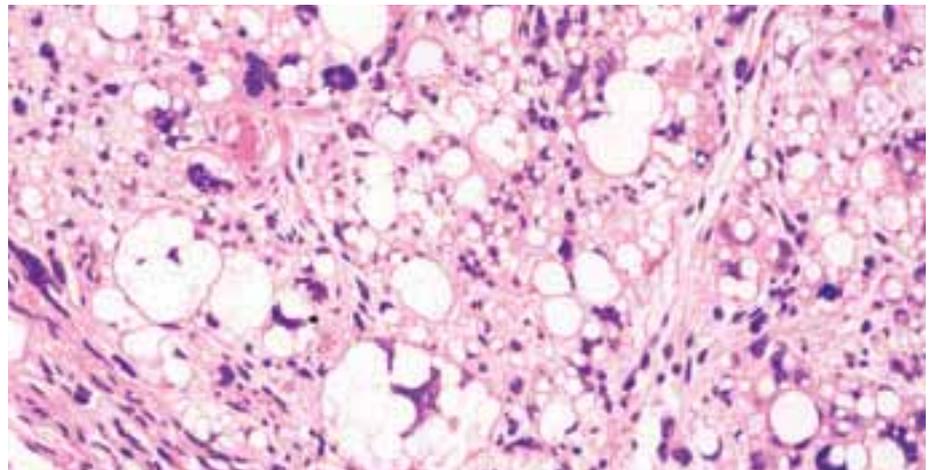

Fig. 1.46 Pleomorphic liposarcoma. Pleomorphic spindle and giant cells as well as pleomorphic lipoblasts which contain enlarged and hyperchromatic nuclei scalloped by cytoplasmic vacuoles.

grade myxofibrosarcoma associated with pleomorphic lipoblasts are noted. The recently described epithelioid variant of pleomorphic liposarcoma {1445} is composed predominantly of solid, cohesive sheets of epithelioid tumour cells with distinct cell borders, eosinophilic cytoplasm and round to oval nuclei with prominent nucleoli separated by narrow fibrous septa with thin-walled capillaries; at least focally, lipogenic differentiation with pleomorphic lipoblasts is noted also in these neoplasms. The mitotic rate is higher in the epithelioid variant, but areas of tumour necrosis are seen in the majority of cases irrespective of the morphological subtype. Most recently a small round cell variant containing pleomorphic lipoblasts and small round cells virtually indistinguishable from round cell liposarcoma has been proposed {1389}.

Immunophenotype

The tumour cells stain positively for vimentin, but despite unequivocal lipogenic differentiation S-100 protein is seen in less than half of the cases. Some cases of the epithelioid variant of pleomorphic liposarcoma show focal expression of epithelial markers, an important finding in the differential diagnosis of these lesions {774, 1445}.

Ultrastructure

Neoplastic cells of pleomorphic liposarcoma contain abundant and coalescing lipid droplets, numerous cytoplasmic organelles and surrounding plasma membranes {2231}.

Genetics

Cytogenetics

All 11 pleomorphic liposarcomas from which karyotypic data exist have shown high chromosome counts and complex structural rearrangements {1425,2018}. This complexity, represented by numerous unidentifiable marker chromosomes, non-clonal alterations, polyploidy and intercellular heterogeneity has made the detection of specific rearrangements difficult. The presence of ring, large marker, or double minute chromosomes has
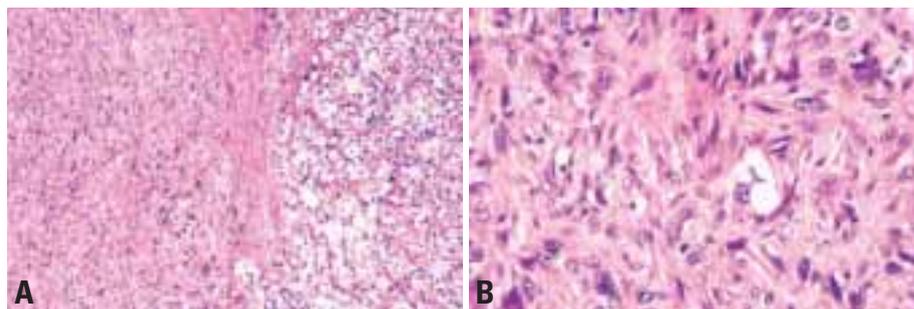

Fig. 1.47 Pleomorphic liposarcoma. In some neoplasms sheets of pleomorphic lipoblasts are seen (right part, **A**), whereas only scattered lipoblasts are present in other cases **(B)**.
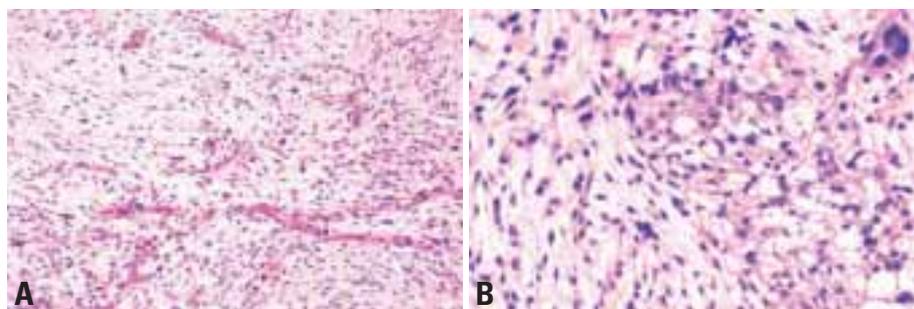

Fig. 1.48 This retroperitoneal neoplasm shows features of a myxoid sarcoma resembling myxofibrosarcoma **(A)**, however, focally, lipoblasts with hyperchromatic and scalloped nuclei were noted **(B)**

been reported in 6 of the 11 cases. The cytogenetic profile of pleomorphic liposarcoma appears therefore to be closer to other pleomorphic sarcomas than to well differentiated liposarcoma.

Molecular genetics

In contrast to well differentiated liposarcomas, amplification of the 12q14-15 region and the *MDM2* gene does not occur consistently in pleomorphic liposarcomas. A number of varied chromosomal gains and losses but no amplification of the 12q14-15 region were found in two cases studied by comparative genomic hybridisation {2072}. The amplification of *MDM2* was observed in approximately one third of the cases, and could be associated with the presence of ring chromosomes {1568, 1889}. *TP53* alterations, such as mutations in exons 7 or 8 or loss of heterozygosity, have been observed in 4/9 studied cases; all these 4 cases were negative for *MDM2* amplification {1889}.
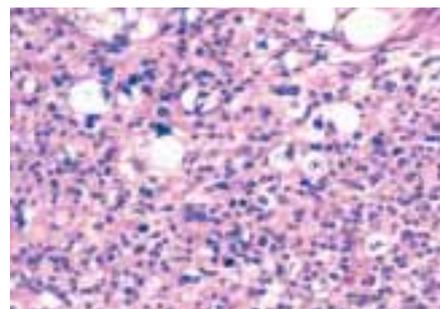

Fig. 1.49 Epithelioid variant of pleomorphic liposarcoma, characterized by sheets and clusters of atypical epithelioid tumour cells associated with pleomorphic lipoblasts (upper part).

Prognostic factors

Although no single morphological factor predicts the clinical prognosis reliably, tumour depth and size, more than 20 mitoses in 10 HPFs, and areas of tumour necrosis are associated with a worse clinical prognosis {548,1408,1445}.

Mixed-type liposarcoma

T. Mentzel
F. Pedeutour

Definition
Liposarcomas showing features of combined myxoid/round cell liposarcoma and atypical lipomatous tumour (well differentiated liposarcoma)/dedifferentiated liposarcoma or of myxoid/round cell liposarcoma and pleomorphic liposarcoma.

ICO-O codes
Mixed type liposarcoma   8855/3
Liposarcoma, NOS   8850/3

Epidemiology
True mixed-type liposarcomas are extremely rare and occur predominantly in elderly patients {1416}.

Sites of involvement
Most cases of mixed-type liposarcoma appear to arise in retroperitoneal or intraabdominal locations. More rarely, examples in the mediastinum and in deep soft tissue of the extremities have been reported {1114, 1139, 1389, 1416}.

Clinical features
The patients usually present with a large painless tumour mass, that is noted sometimes incidentally.

Macroscopy
Given the location, most cases of mixed-type liposarcoma are large, and often present as multinodular masses with cystic and solid areas and grey-yellow cut surfaces.

Histopathology
The occurrence of myxoid areas in the group of atypical lipomatous tumour (well differentiated liposarcoma)/dedifferentiated liposarcoma is well recognized and especially in retroperitoneal and intraabdominal location quite common. However, in most cases, this reflects either myxoid degeneration or dedifferentiation with myxofibrosarcoma-like features in atypical lipomatous tumour (well differentiated liposarcoma) instead of a true mixed-type liposarcoma {67, 955, 1389}. Rare mixed-type liposarcomas show a combination of morphological features of myxoid/round cell liposarcoma (small undifferentiated mesenchymal cells, often univacuolated lipoblasts, and round cells set in a myxoid matrix with mucin pooling and a prominent plexiform capillary pattern), pleomorphic liposarcoma (features of pleomorphic sarcoma with a variable number of pleomorphic lipoblasts), and/or atypical lipomatous tumour (well differentiated liposarcoma) (adipocytes with marked variation in size and shape, nuclear atypia). Cases of so called dedifferentiated myxoid liposarcoma may represent mixed-type liposarcomas showing a combination of myxoid/round cell liposarcoma and dedifferentiated liposarcoma.

Genetics
In the three karyotyped cases of mixed-type liposarcoma, the presence of ring or giant marker chromosomes was observed either as the sole abnormality {680} or in association with complex rearrangements {794, 1389}. Amplification of the 12q14-15 region and, more specifically, of the *MDM2* gene has been found, but not *TP53* mutations {794, 1389, 1889}.
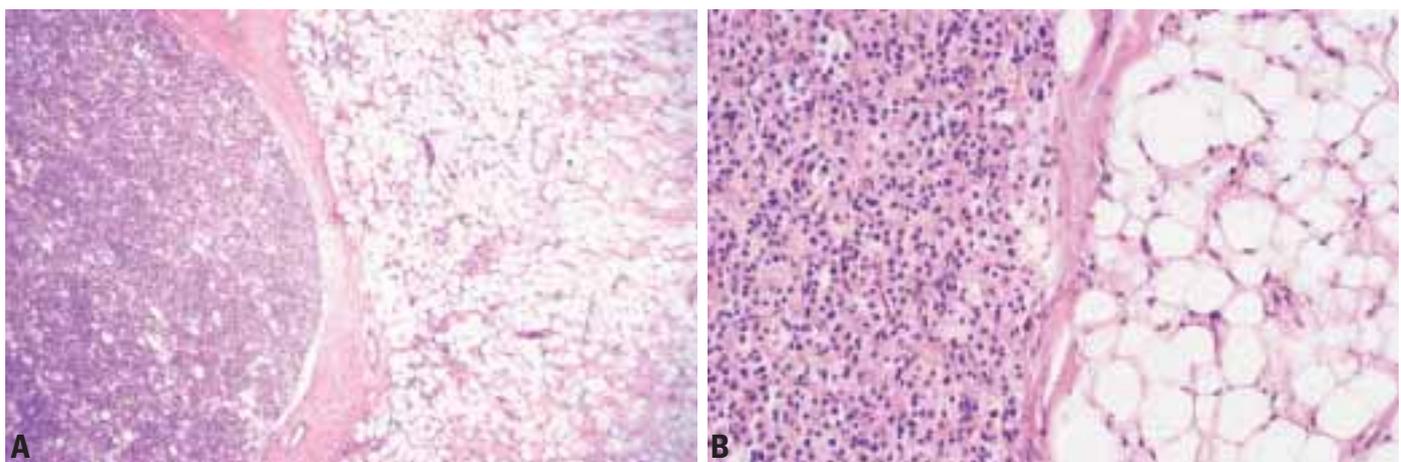
Fig. 1.50 This case of a mixed type liposarcoma shows morphological features of lipoma-like atypical lipomatous tumour (well differentiated liposarcoma) (right) and myxoid liposarcoma (left) **(A)**. High power view reveals small undifferentiated mesenchymal cells and lipoblasts set in a myxoid matrix with a plexiform vascular pattern in the myxoid liposarcoma areas **(B)**.