
Review article

Challenges in the diagnosis of lipomatous tumours

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Lipomatous tumours (LT) are neoplasms that show a varying degree of differentiation towards fat forming cells, either white fat or brown fat and are certainly among the most frequently diagnosed mesenchymal neoplasms, both benign and malignant. This includes tumours with a wide spectrum in regard to the incidence, clinical presentation, morphology and behaviour. The diagnostic criteria for most of these tumors are well established and therefore the pathologists are quite familiar and comfortable with most of these lesions.

If so, why do we still need to talk about LT? The reasons are manifold. Many of these fatty tumours have a significant degree of morphological heterogeneity, partly because there are other connective tissue elements such as blood vessels, fibrous tissue or smooth muscle accompanying the fatty component. The amount of this secondary component varies from one lesion to another depending on the nature and

the age of the individual lesion that we examine, making the diagnosis a challenge.

As in many fields of diagnostic pathology, there are new entities being added, revisions being made to the existing terminology and new classification systems proposed, that makes the diagnostic pathologist exhausted and the clinicians confused. Therefore, it is important to be thorough with the current concepts, understand their clinical value and apply this knowledge in diagnosing individual cases in order to convey the proper message to the clinician in a clear and simple way.

The lipomatous category both benign and malignant, constitute the soft tissue tumours that are most frequently diagnosed (1). These are minute subcutaneous lipomas that are difficult to differentiate from normal fat to large deep seated liposarcomas that do not resemble fatty tissue at all. However, there are very rare entities included in the group of LT, that could be a 'once

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in life-time event' for a diagnostic pathologist. It is important to be aware of these rare entities to prevent diagnostic pitfalls and the possible over treatment or under treatment.

In comparison with the non-lipomatous soft tissue tumours, histochemistry and immunohistochemistry play a relatively lesser role in the diagnostic work up of LT. Traditional evaluation of haematoxylin and eosin stained sections combined with careful clinical and radiological evaluation remains the basis of

diagnosis in most of the cases. In the last two decades the technical evolution has brought powerful investigational and diagnostic tools to the field of surgical pathology.

Cytogenetic and molecular genetic studies have identified characteristic profiles of fatty tumours giving an insight into the biological behaviour of these tumours (Table 1) (2). This has given a new insight into the biological relationship between different morphologic variants and helped to support the accuracy of morphological classification.

Table1. Chromosomal aberrations and associated molecular events in adipocytic tumors (2)

Tumor type	Chromosomal aberration	Molecular event
Lipoma	t(3;12)(q27-28;q13-15) t(9;12)(p22;q13-15) t(2;12)(q37;q13-15) t(5;12)(q32-33;q13-15) t(12;13)(q13-15;q12) 6p21-23 rearrangement 13q deletion	HMGA2-LPP HMGA2-NFIB HMGA2-CXCR7 HMGA2-EBF1 HMGA2-LHFP HMGA1 rearrangement Not known
Chondroid lipoma	t(11;16)(q13;p13)	C11of95-MKL2
Spindle cell/pleomorphic lipoma	13q and/or 16q deletions	Not known
Hibernoma	11q13 rearrangement	MEN1,PPP1A deletion
Lipoblastoma	8q11-13 rearrangement	PLAG1 rearrangement
Atypical lipomatous tumor/ well differentiated liposarcoma	Ring/giant marker chromosome (12q13-15 amplification)	HMGA2 amplification MDM2, CDK4, CPM,

Dedifferentiated liposarcoma	Ring/giant marker chromosome* (12q13–15 amplification)	HMGA2 amplification MDM2, CDK4, CPM,
Myxoid/round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	FUS-DDIT3 EWSR1-DDIT3
Pleomorphic liposarcoma	Complex karyotype	Not known

*Dedifferentiated liposarcoma may contain complex aberrations in addition to ring or giant marker chromosomes

Hopefully in the future, clinical decisions will increasingly be based on a combination of histological criteria and specific molecular/cytogenetic aberrations. Furthermore, in certain tumours, identification of new molecular targets has opened the avenues for new therapeutic tools (3).

This brief overview certainly does not attempt to summarize all the current views of LT, but rather, highlights some of the important diagnostic problems both in benign and malignant LT and discusses the classification and terminology in liposarcomas.

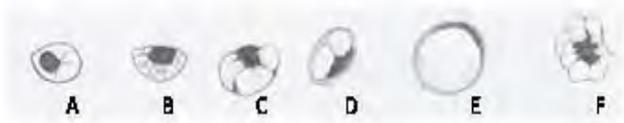
It is useful to begin this review with a brief discussion of the lipoblast (LB) as this is a key histological feature sought in the diagnosis of LT.

Lipoblast (LB)

The LB is a neoplastic cell that to some

extent recapitulates the differentiation cascade of normal fat (4). The primitive LB arises as a spindled cell that closely resembles a fibroblast. These spindled cells that have ample endoplasmic reticulum slowly acquire fat droplets, first at the poles of the cell and later throughout the cytoplasm. As fat accumulates in the cytoplasm, the cell loses its endoplasmic reticulum and assumes a round shape. Gradually, the nucleus becomes indented and pushed to one side of the cell. Further accumulation of fat gives rise to the mature adipocyte. In addition, pleomorphic cells with the features of LB can be identified in LS, but these cells have no equivalent in the differentiation sequence of normal fat (Fig.1). The task for the pathologist is to decide at what point in the differentiation scheme the cell becomes sufficiently diagnostic to warrant the designation “LB.”

Fig. 1. Different stages of a developing lipoblast



A. Early spindled cell

B, C & D Intermediate stages with vacuoles of fat in cytoplasm and indented nucleus

E. Univacuolated cytoplasm

F. Pleomorphic lipoblast

Criteria useful for diagnosing LB

1. A hyperchromatic, indented or sharply scalloped nucleus
2. Lipid-rich (neutral fat) droplets in the cytoplasm
3. An “appropriate” histological background

The diagnostic value of the third criteria cannot be overemphasized as failure to appreciate the overall features can lead to an erroneous diagnosis of a liposarcoma (LS) as there are lipoblast-like cells /pseudolipoblasts in some conditions (Table 2).

Table 2. Mimics of lipoblast

<ul style="list-style-type: none"> • Scattered macrophages in fat necrosis • Severely atrophic fat cells • Mucin filled pleomorphic cells in non-lipomatous malignancies <ul style="list-style-type: none"> - Hyaluronic acid filled cells in myxofibrosarcoma • Artifacts <ul style="list-style-type: none"> - Post treatment artifacts in malignancies - Fixation and retraction artifacts

It is essential to know that the mere presence of LB will not enable the diagnosis of a LS as we all know that there are number of benign LT that harbour true LB (Table 3). Furthermore, contrary to the popular belief, LB may be totally absent in some of the liposarcomas (Table 4).

Table 3. Benign lesions that have true lipoblasts

<ul style="list-style-type: none"> • Spindle cell /Pleomorphic lipoma • Chondroid lipoma • Lipoblastoma
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Table 4. Liposarcomas that could be diagnosed without demonstrating lipoblasts

<ul style="list-style-type: none"> • Well-differentiated liposarcoma • Myxoid liposarcomas (Some) • Round cell liposarcomas (rare)

Benign LT

Subcutaneous lipoma represents by far the most common mesenchymal neoplasm diagnosed in routine consultation and usually poses no diagnostic problems. The reported incidence is definitely lower than the true incidence as many lipomas remain unrecorded or are brought to the attention of a clinician only if they reach a large size, cause cosmetic problems or cause complications because of their anatomic site. They arise frequently in the subcutaneous tissue and uncommonly in the deep tissue such as subfascial tissue of extremities, juxta-articular tissue, chest wall, pleura and mediastinum (4).

Lipomas vary in size from few millimetres to 5cm (average 3cm) or more (4). Lipomas larger than 10 cm are rare. It is a good practice to consider a lipoma more than 5cm as 'cautious' and sample adequately to rule out the possibility of a LT with an intermediate behaviour. Lipomas differ very little from the surrounding normal fat. They are lobulated and thinly encapsulated but the capsule often gets stripped off during slicing. They consist of lobules of mature fat cells with a slight variation in cellular size and shape (Fig. 2). Though they are richly vascularized, the vascularity is not prominent under normal conditions but becomes obvious when the lipoma gets atrophied.

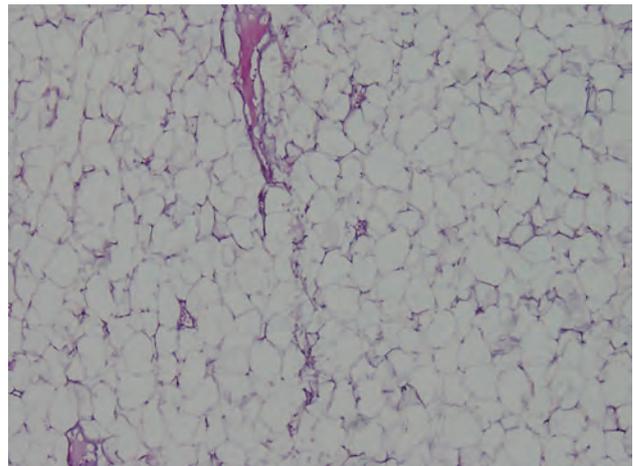


Fig.2. Minimal variation in fat cell size in a lipoma ; compare this with Fig.3 (H& E x 200)

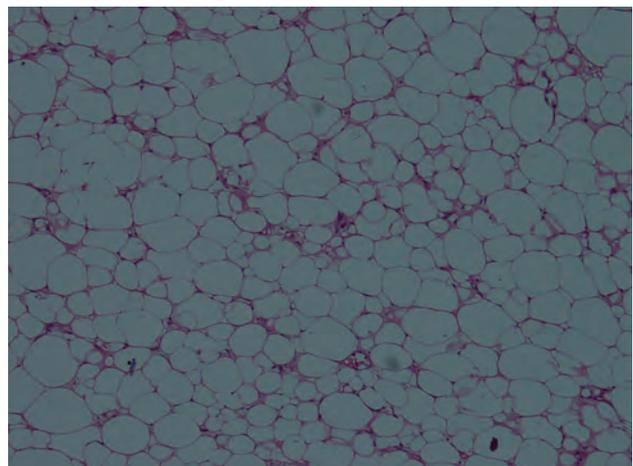


Fig 3. Easily appreciable cell size variation in well differentiated lipoma-like liposarcoma (H& E x 200)

The diagnostic problems in lipoma are mainly two fold. One is to differentiate it from the surrounding normal fat which could be assisted by the gross appearance, encapsulation and lobulation. However, this could be impossible in a biopsy sample. The other is to differentiate it from a well differentiated

lipoma-like liposarcoma in which the size, anatomical location, variation in the size and the atypia of adipocytes are helpful (Fig.3). Lipomas of the retroperitoneum are a poorly documented and contentious entity (5). Although theoretically they could occur, all LT of the retroperitoneum should probably be regarded with a high level of suspicion for malignancy.(5)

The conventional lipomas change its appearance due to the admixture of other mesenchymal elements, metaplastic change or secondary degenerative change. Depending on the proportion of the pure lipomatous component and the 'secondary' component, the differential diagnoses will differ (Table 5).

Table 5. Variants of lipoma

Secondary component/change	Name	Differential diagnosis
Fibrous tissue	Fibrolipoma Sclerotic fibroma	Sclerotic lipoma Collagenous fibroma Nuchal fibroma Dermatofibroma
Blood vessels	Angiolipoma	Intramuscular haemangioma Kaposi sarcoma
Smooth muscle	Myolipoma	Cellular spindle cell lipoma Leiomyoma with lipomatous degeneration Extra renal angiomyolipoma
Chondroid metaplasia	Chondrolipoma	
Osseous metaplasia	Osteolipoma	
Chondro myxoid stroma	Chondroid lipoma	Myxoid liposarcoma Extraskeletal-myxoid chondrosarcoma Myoepithelioma Chondroma
Myxoid change	Myxolipoma	Myxoid liposarcoma
Fat necrosis/cystic degeneration	Lipoma with fatty degeneration	Well differentiated lipoma-like LS

When the lipomatous component predominates the diagnosis is straightforward. The maximum error that can result is misdiagnosis or under diagnosis as a conventional lipoma, which is only an academic exercise. When an equal proportion of lipomatous and non-lipomatous mesenchymal components are present the classification is not straightforward. If the lipomatous component is masked by a secondary component the diagnostic accuracy of a lipomatous tumour could be low.

Lipomas are completely benign, but they may recur locally if the surgical removal is incomplete. Deep lipomas have a greater tendency to recur, presumably because of the difficulty of complete surgical removal. Lipomas are not the precursors of LS. Nonetheless, an atypical lipomatous tumour/well differentiated liposarcoma (ALT/WDLS) could be mistaken as a benign lipoma when the specific characteristics are absent or missed on the initial examination of the tumour.

Intramuscular lipoma (IML)

IML are relatively common lesions that usually arise in the large muscles of the extremities. They concern both clinicians and pathologists because of the deep location, large size, infiltrative growth pattern and tendency to recur. An important differential diagnosis is infiltration of the muscle by ALT/WDLS which

is probably a commoner lesion than the IML (6). In IML, the muscle fibres are seen in the centre of the lesion with a varying degree of atrophy and an infiltrative edge is evident in contrast to ALT/WDLS (Fig. 4). In addition, the adipocytes show minimum variation in size, no cellular atypia and absence of LB in IML. However, careful sampling of these tumours is mandatory and the general recommendation is to submit at least one section per centimetre of tumour for histological evaluation.

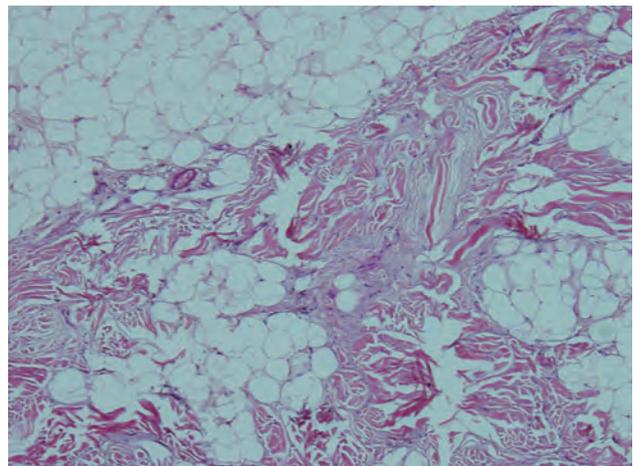


Fig. 4. Entrapped muscle fibres which show atrophy within benign fat in an intramuscular lipoma (H& E x 200)

Spindle cell/pleomorphic lipoma

Because of the clear-cut overlapping clinical, histological, immunohistochemical, and cytogenetic features, spindle cell lipoma and pleomorphic lipoma are now considered as one entity (4). These lesions represent a morphological continuum. Some cases may be

pure spindle cell or pleomorphic lipomas, but many show overlapping features of both these entities within the same tumour. Approximately 80% of these tumours arise in the subcutaneous tissue of upper back region, but 20% of tumours that have not read the text books arise in unusual locations, such as the oropharyngeal region (7,8,9) parotid gland (10), female genital tract (11) and spermatic cord (12) thereby making these cases more difficult to diagnose.

Some tumours are predominantly composed of mature adipose tissue with only scattered spindle cells or pleomorphic elements while others are predominantly solid and lack any significant lipomatous component (Fig.5). Very rarely, one encounters a spindle cell/pleomorphic lipoma nearly devoid of fat, and such cases are obviously quite challenging since the lipomatous nature of the neoplasm is hidden (13).

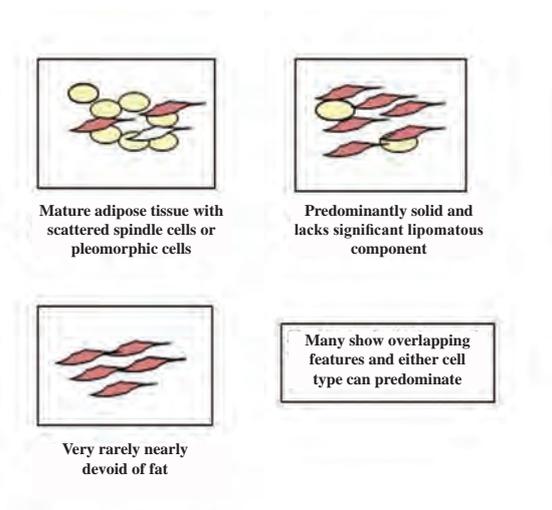


Fig. 5. Spindle cell/pleomorphic lipoma-variation in histology

The classic spindle cell lipoma consists of a relatively equal mixture of mature fat and spindle cells. The spindle cells are uniform, mitotically inactive, with a single elongated nucleus and narrow, bipolar cytoplasmic processes. The cells lie in a collagenous or myxoid matrix. Thick ‘rope-like’ collagen is seen in the background which is a feature that is quite useful in the differential diagnosis. In some of the variants there is striking nuclear palisading reminiscent of a neural tumour. Mast cells are commonly present. In pleomorphic lipomas there are small spindled and rounded cells with multinucleated giant cells which have radially arranged nuclei in a “floret-like” pattern. Although the adipocytes typically lack atypia, some of the spindle cell/pleomorphic lipoma contain atypical adipocytes and LB hence distinguishing these lesions from the sclerosing type of ALT/WDLs becomes difficult. Careful clinicopathologic correlation in terms of anatomic location, tissue plane and basic morphological features such as variation of adipocyte size, presence of ropey collagen in the background are essential in making the diagnosis. Detection of the characteristic cytogenetic aberrations present in each of these LT can be extremely helpful in difficult cases (Table1).

Immunohistochemically, the cells in spindle cell/pleomorphic lipoma stain strongly for CD34 but they are not immunoreactive for actin or desmin. Although S-100 protein stains

the nuclei of mature lipocytes, neither the spindled cells nor the atypical or floret-like giant cells stain for this antigen. Based on the finding of CD34 immunoreactivity in spindle cell lipomas, Suster and Fisher suggested that this lesion is a dendritic interstitial cell neoplasm located in fat rather than a true lipogenic neoplasm (14).

Liposarcoma (LS)

LS represents the most common type of soft tissue sarcoma, representing 24% of extremity sarcomas and 45% of retroperitoneal soft tissue sarcomas (3). Albeit rare it has been reported that LS can arise in subcutaneous tissue as well as in the skin (15). Even within this group, there is histological diversity and complexity. This is such that the term 'LS' becomes meaningless unless it is classified by subtyping to indicate their malignant potential. In no other group of sarcomas does the pathologist receive such a strong mandate to subclassify the tumour as it clearly reflects the histological grade and the biological behaviour.

The current World Health Organization classification of soft tissue and bone tumours recognizes four major LS subtypes: (i) ALT/WDLS (ii) de-differentiated liposarcoma (DDL) (iii) myxoid liposarcoma (MLS) and (iv) pleomorphic liposarcoma (PLS) (16). But from a pathogenetic and cytogenetic point of view it is useful to divide LS into 3 biologic groups

in which the groups (i) and (ii) of above are combined into a single group as it shares similar cytogenetic aberrations and molecular genetics hence describing the two ends of the same spectrum. With dedifferentiation, the tumour acquires metastatic potential, a phenomenon accompanied by additional cytogenetic abnormalities (3).

ALT/WDLS is a locally aggressive neoplasm, virtually incapable of systemic spread. However, the patient can die of repeated recurrences and uncontrolled local spread because of poor surgical amenability of the tumour. DDL despite high-grade morphology, metastasizes in only 15–20% of cases and recurs in 40% of cases. The most important prognostic factor of DDL is the anatomical location. The clinical behavior of MLS is determined mainly by the histological grade manifested by the degree of hypercellularity. The high grade MLS metastasizes to bone and soft tissues. PLS shares highly aggressive clinical behaviour with other pleomorphic sarcomas.

To achieve accuracy in the diagnosis of LT, we have to always take extra care in the case of fatty tumours that is more than 5cm in size, deeper to the deep fascia and in a recurrence. Careful gross inspection to identify variation in appearance and reasonably extensive sampling is mandatory as diagnosis and grading may depend upon features represented only focally.

Atypical lipomatous tumour / Well differentiated liposarcoma (ALT/WDLS)

ALT/WDLS is the most common form of LS encountered in late adult life and accounts for 40-45% of all LS (17). ALT/WDLS tends to occur equally in the retroperitoneum or the limbs followed by the paratesticular area and the mediastinum. Though rare, cutaneous ALT/WDLS are being reported (18). Despite the site of origin, all ALT/WDLS have a similar morphology and are composed of mature adipocytes exhibiting easily appreciable variation in cell size, with at least focal nuclear atypia and hyperchromasia in fat cells and/or stromal spindle cells. LB could be many to none.

ALT/WDLS is virtually a local disease that has no potential to metastasize unless it undergoes dedifferentiation. The probability of local recurrence largely depends on the surgical amenability. Overall mortality is close to 0% for lesions arising in somatic soft tissues compared to nearly 80% for tumours occurring in the retroperitoneum or other visceral sites because of repeated recurrences and multiple surgeries (19).

Because of this site dependent behaviour, these tumours were referred to, by different terms during different time periods. These terms varied from lipoma to liposarcoma making the

clinicians highly confused. “Atypical lipoma” was a term originally introduced in 1979 by Evans et al. for WDLS of the subcutis and deep muscles of the extremity (17). At that time, these authors suggested retaining the term ALT/WDLS for lesions in the retroperitoneum. Other authors suggested the use of the term “atypical lipoma” for the lesions with variation in adipocytic size and nuclear atypia but lacking LB (20).

In 1988 Evans extended the use of the term “atypical lipomatous tumour” to retroperitoneal tumours lacking LB and also suggested to abandon the term “WDLS” entirely (21). This approach was criticized by Weiss and Rao in 1992 who suggested the adoption of the term ALT for the tumours in the subcutaneous location and WDLS in other sites (22). This controversy and confusion was addressed by the WHO classification of soft tissue tumours which categorize this under intermediate malignancies and states that ALT and WDLS are synonymous and are of identical morphology, karyotype and biological potential (19). The choice of the term is best determined by the reciprocal understanding between the clinician and the pathologist. Therefore, it is best to convey the message clearly to the clinician in a footnote, after taking into account the site, size and completeness of resection in individual cases to prevent undesirable consequences (Fig. 6).

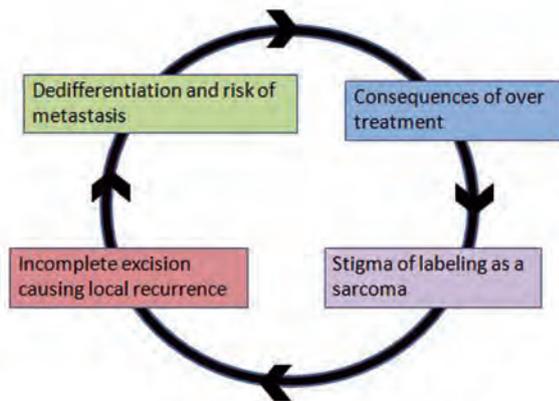


Fig. 6: Practical problems encountered with ALN/WDL

Four subtypes of ALT/WDLS were recognized by 2013 WHO classification of soft tissue tumours, namely adipocytic (or lipoma-like), sclerosing, inflammatory and spindle cell variants. The presence of more than one histologic pattern in the same lesion is common. Sometimes ALT/WDLS may be indistinguishable from benign adipocytic tumors on histology, and inadequate sampling can lead to misdiagnosis.

All subtypes except the spindle cell variant of ALT/WDLS share the same genetic aberration, represented by the presence of distinctive ring and/or giant marker chromosomes. Ring chromosomes contain amplified sequences derived from the 12q13–15 chromosome region, where several proto-oncogenes including MDM2, CDK4 and HMGA2 are located (3). Therefore, amplification of these proto-oncogenes HMGA2, MDM2 and CDK4 could be detected by molecular or immunohistochemical techniques in ALT/WDLS. This could be helpful in confirming the diagnosis in difficult cases.

Although spindle cell liposarcoma has been regarded as a variant of ALT/WDLS, it has been recently speculated that this may constitute an independent entity rather than a morphologic variant of ALT/WDLS (23). This was based on the observations that most of the spindle cell liposarcomas arise in subcutaneous tissue of the extremities, the head and neck region and the trunk, lacks amplification of MDM2 and CDK4 and express CD34 antigen in the spindle cells at least focally. Based on these findings it had been speculated that this group represents an atypical or low-grade counterpart of spindle cell lipoma rather than a variant of ALT/WDLS.

Dedifferentiated Liposarcoma (DDLs)

DDLs is a malignant LT showing transition from ALT/WDLS to a non-lipogenic sarcoma of variable histologic grade. Dedifferentiation is thought to be a time-dependent phenomenon that occurs in up to 10% of ALT/WDLS although the risk is higher for deep seated lesions. About 90% of DDLs arise “de novo,” while 10% occur in recurrences (24). DDLs are most commonly seen in the retroperitoneum, followed by deep soft tissue of the extremities, the trunk, mediastinum and the spermatic cord. DDLs are exceedingly rare in subcutis (25).

Mostly the dedifferentiated areas dominate and the well differentiated lipoma-like areas can only be found after careful and generous sampling. Inadequate resection by the surgeon

or inadequate sampling by the pathologist can result in misdiagnosis and this is one reason for the underestimation of the true incidence of DDLS.

Histologically the dedifferentiation is often seen as an abrupt transition from a juxtaposed ALT/WDLS. Less frequently, a gradual transition and rarely a mosaic pattern in which the dedifferentiated areas are intermingled with a well differentiated component are identified (Fig.7).

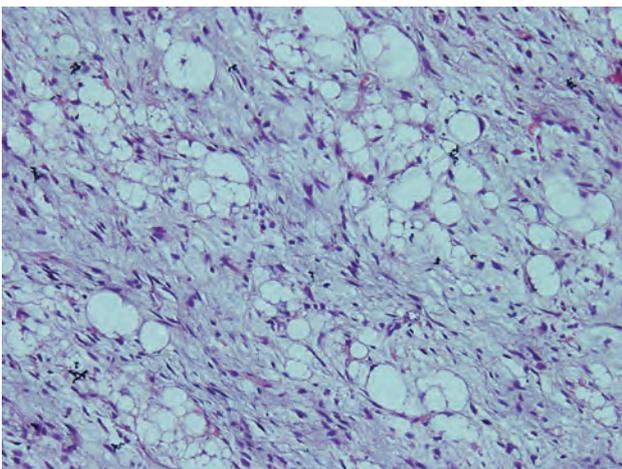


Fig 7: The dedifferentiated areas which show a low-grade spindle cell morphology are intermingled with well differentiated liposarcoma component; 'mosaic pattern' (H& E x 200)

The most frequent type of dedifferentiation is of a high-grade sarcoma resembling an undifferentiated pleomorphic sarcoma or a myxofibrosarcoma. Contrary to the popular belief that dedifferentiation is always towards a high-grade sarcoma, cases with low-grade

dedifferentiation have increasingly been reported (26). The low-grade dedifferentiation which usually shows proliferation of uniform spindle cells with minimum atypia needs to be distinguished from a well differentiated sclerosing LS and spindle cell LS (Fig. 8).

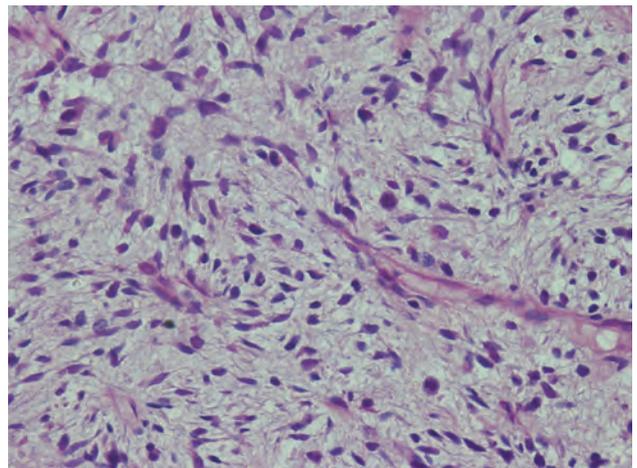


Fig.8: Low-grade dedifferentiation displaying proliferation of uniform spindle cells with minimum atypia. (H& E x 400)

Absence of atypical adipocytes and LB in either the high-grade or the low-grade dedifferentiated component is a feature that helps in differentiating these tumours from pleomorphic LS and WDLS respectively. However, it has recently been recognized that the dedifferentiated component may occasionally exhibit lipogenic features mimicking a PLS, a condition that has been referred to as 'homologous lipoblastic differentiation' (27). In this situation demonstration of diffuse nuclear staining of MDM2 and /or CDK4 in the homologous

lipoblastic component is extremely helpful in distinguishing DDLS from pleomorphic LS which has a considerably worse prognosis.

Pleomorphic or spindle cell sarcoma infiltrating the retroperitoneal fat is differentiated from DDLS by careful examination of the well differentiated lipogenic component for significant variation in fat cell size, nuclear atypia and LB. It is adopted that the dedifferentiation should be macroscopically visible (>1cm) to label these tumours as “DDLS”. Weiss and Goldblum have shown that even microscopic foci of dedifferentiation has been associated with poorer outcome hence use of the term ‘minimal dedifferentiation’(4).

Myxoid Liposarcoma (MLS)

MLS represent the second larger group of LS and accounts for 5% of all soft tissue sarcomas (28). When compared with the ALT/WDLS, MLS occurs at a relatively a younger age with a peak incidence in the fourth and fifth decade. It tends to occur in the limbs, especially in the thigh. Retroperitoneal lesions are exceptional and in most instances represent a metastatic deposit from an unknown primary (29). MLS has an intermediate prognosis between ALT/WDLS and pleomorphic LS.

However, some of the MLS, mainly those arising in the extremities, are multicentric in nature, tend to affect younger patients and follow a rather aggressive clinical course (30). In this

condition the tumours occur in various soft tissue sites that are not being usually affected by metastases. Monoclonality of such tumours has confirmed that this indeed is an unusual presentation of metastatic disease (31).

Pure MLS is remarkably hypocellular, featuring a bland spindle cell proliferation set in an abundant myxoid background. LBs are most often monovacuolated and tend to cluster around vessels or at the periphery of the lesion (Fig.9). It is worth noting that the most distinct histological clue of MLS is not represented by the adipocytic differentiation but by the presence of a thin walled capillary network organized in a plexiform pattern. Highlighting this capillary network by a vascular marker becomes a valuable diagnostic aid in some instances as it retains even in high-grade tumours.

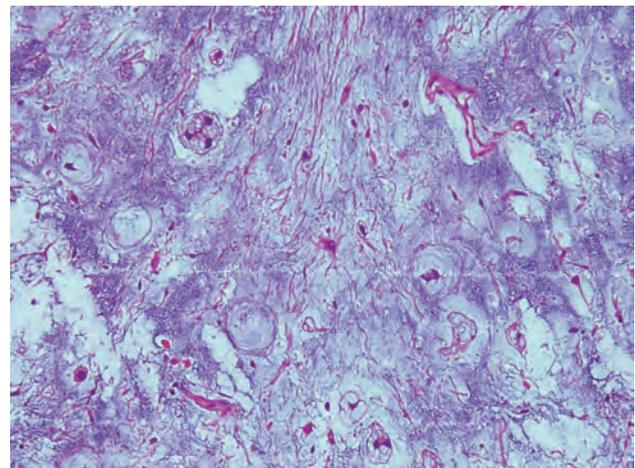


Fig.9: Myxoid liposarcomas are hypocellular lesions with an abundant myxoid background containing easily identified monovacuolated lipoblasts that tend to cluster around vessels. (H & E x200)

The concept that MLS and round cell LS are closely related, developed long years back based on the morphological observation of purely hypocellular myxoid areas blending with hypercellular areas (29). Recently this was validated conclusively by genetic analysis which showed that MLS and round cell LS share the same chromosome change represented most frequently by a reciprocal translocation $t(12;16)(q13;p11)$ that fuses the DDIT3 gene with the FUS gene or the EWSR1 gene (28).

In the current (2013) WHO classification round cell LS is included as a morphological continuum of MLS in which the round cells represents the high grade component. As the recognition and the quantification of hypercellular/round cell areas represent a crucial step in the evaluation of this LS subtype, a careful as well as extensive sampling is mandatory to permit detection of the smallest amount of hypercellularity. Different investigators have come out either with two-tiered or three-tiered systems of quantifying the round cell component using different cut-off values, ranging between 5% and 25%, both of which showed excellent correlation with survival and metastases (32,33). Currently, it is recommended that any amount of hypercellularity should be reported, and if this exceeds 5%, the tumour should be considered as high grade (28).

In a study by Tateishi et al in 2003, 50 cases

of MLS were graded by a MIB-1 score based grading system in which a summative grade was obtained by summing the tumour differentiation, tumour necrosis, and the MIB-1 scores (34). Multivariate analysis had shown that the tumour grade determined by the MIB-1 score is the most important adverse prognostic factor in patients with MLS.

Pleomorphic liposarcoma(PLS)

PLS is the rarest type of LS and accounts for about 10% of all LS (35). It involves the elderly and occurs predominantly in the extremities followed by the trunk and the retroperitoneum. PLS is a high-grade pleomorphic sarcoma showing variable amounts of lipoblastic differentiation which ranges from focal to extensive. Cytological atypia tends to be extreme. LBs are frequently very large and contain irregular, hyperchromatic, scalloped nuclei with prominent nucleoli and a multivacuolated cytoplasm. The lipogenic differentiation can be so limited in extent as to be overlooked resulting in misclassification as undifferentiated pleomorphic sarcoma. This feature again highlights the importance of extensive sampling of this lipogenic tumour. S100 immunopositivity may, at times, be helpful to highlight the presence of multivacuolated LB.

Similarly, as mentioned before, MDM2 immunostaining helps to differentiate homologous lipoblastic differentiation in a

DDLs from PLS. PLS tends to exhibit complex karyotypes. Therefore, molecular genetics does not help in differentiating PLS from other pleomorphic sarcomas.

Summary

This review attempts to highlight some of the important aspects in the diagnostic work-up and classification of LT. It is worth remembering the following facts whenever examining a LT.

- LS diagnosis can be made without the demonstration of LB.
- Presence of LB alone does not warrant a diagnosis of LS.
- Think twice before diagnosing LS in children or in a superficial location.
- Though rare, childhood LS and cutaneous LS do exist.
- LS do not arise from lipomas.
- Re-think before diagnosing a large fatty tumour as a lipoma in the retroperitoneum, abdomen, groin or paratesticular region.
- Take extra care in LT that are more than 5cm in size, deeper to the deep fascia and in a recurrence.
- Careful gross inspection to identify variation in appearance and reasonably

extensive sampling is mandatory in LT as diagnosis and grading may depend upon features represented only focally.

- LS becomes meaningless unless it is classified by sub typing to indicate the malignant potential.
- Dedifferentiation in DDLs can occur towards a low-grade sarcoma.
- Know the new entities, update on current terminology but pass your message to clinicians in a simple and clear language.

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