Lipomatous tumors - how we have reached our present views, which controversies remain and why we still face diagnostic problems

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Lipomatous tumors are one of the most complex areas of soft tissue pathology. The different subtypes vary greatly with regard to incidence, clinical presentation, morphologic appearance, and behavior. Hence, this tumor group includes some of the most common human neoplasms as well as exotic rarities, minute superficial lesions indistinguishable from normal fat to deep-seated masses - among the largest ever seen, without any resemblance to normal or embryonal fat.

To a large extent, Dr. Franz Enzinger’s work in this area of soft tissue pathology over the last four decades has shaped our present classification and concepts of fatty tumors (as in so many other areas of soft tissue pathology). In addition to clearly defining the different main subtypes of liposarcoma and their morphologic spectrum, he has identified several previously unknown entities that in the past caused frequent overdiagnosis of malignancy.

This brief overview does not attempt to summarize all current views on lipomatous tumors, but rather highlight some of Dr. Enzinger’s important contributions, what we have learned, and what problems and controversies still remain.

The WHO classification of adipocytic tumors
The current WHO classification (2002) includes 12 benign subtypes, one intermediate and 5 main types of malignant lipomatous tumors.

Benign adipocytic tumors
These include the very common lipomas (with a very wide spectrum in terms of site, size, growth characteristics, and clinical significance)(Kindblom et al. 1974), the relatively common angiolipomas, spindle cell lipomas and pleomorphic lipomas, as well as the rare lipomatosis, myolipomas, chondroid lipomas, extra-renal angiomyolipomas, extra-adrenal myelolipomas and hibernomas.

Of particular diagnostic importance has been the recognition of spindle cell and pleomorphic lipoma and chondroid lipoma, since they have frequently in the past been misdiagnosed as liposarcoma or other sarcoma types. In addition, Dr. Enzinger and coworkers have also described abdominal myolipoma, lipofibromatosis occurring in the pediatric age group and the largest and best defined series of childhood liposarcomas (Shmookler and Enzinger, 1983),
lipoblastomatosis (Chung and Enzinger, 1973) and fibrolipomatous hamartoma of nerve (lipomatosis of nerve) (Silverman and Enzinger, 1985).

**Spindle cell lipoma and pleomorphic lipoma**

These were first defined by Enzinger and Harvey in 1975 and by Shmookler and Enzinger in 1981, respectively and are today recognized as some of the most common pseudosarcomas. Because of their overlapping morphologic features, the occurrence of hybrid forms and the very similar clinical presentation in terms of age, gender and site distribution (typically middle-aged and elderly men, in the subcutis of neck, shoulders and back), they are currently viewed as representing different ends of a continuous spectrum. Even for experienced soft tissue tumor pathologists, these tumors sometimes continue to cause problems, particularly the entirely myxoid variants and the very cellular, fascicular variants of spindle cell lipoma that may virtually lack any lipomatous component (Angervall, Kindblom, Dahl, 1976; Fletcher, 1987). Difficulties also arise with pleomorphic lipomas that in addition to the characteristic floret-like giant cells may contain multivacuolated lipoblasts. Another problem is those the tumors that don’t follow the book and occur at unusual, even deep-seated, sites. Both sporadic and familial cases of multicentric spindle cell lipomas have been reported (Fanburg-Smith, Devaney, Miettinen et al, 1998).

In 1993, Meis and Enzinger described and defined *chondroid lipoma* as a unique, benign lipomatous tumor simulating myxoid/round cell liposarcoma or extraskeletal myxoid chondrosarcoma. These rare tumors can occur both superficially and deep and tend to involve extremities and limb girdles. They may reach considerable size, adding to the risk of misdiagnosing them as sarcomas. There is a predilection for adult women but pediatric cases also occur. Subsequent ultrastructural and immunohistochemical studies have shown that chondroid lipomas are truly biphenotypic with both lipoblastic differentiation and features of primitive cartilage (Kindblom, Meis-Kindblom, 1995).

*Myolipoma*, first described by Meis and Enzinger in 1991, is a rare lesion predominantly seen in women and mostly in deep soft tissues, particularly within the abdomen and retroperitoneum, but occasionally also occurring more superficially in the abdominal wall and groins. This entirely benign lesion, composed of a usually dominating bland smooth muscle component intermingled with mature looking fat, should not be mistaken for angiomylipoma, dedifferentiated liposarcoma with a smooth muscle component or the so called lipoleiomyosarcoma (Folpe and Weiss, 2002).

*Lipofibromatosis* has been suggested as a unifying term for a group of lesions predominantly occurring in the hands and feet of pediatric patients (Fetsch, Miettinen, Laskin, Michal and Enzinger, 2000). These lesions, composed of adipose tissue and spindled fibroblastic elements, involving fibrous septae in fat and skeletal muscle, had previously been classified as various types of infantile or juvenile fibromatosis, fibrous hamartoma of infancy or fibrosing variants of lipoblastoma. Recurrent or persistent tumor was seen in almost three-fourths of patients.

**Intermediate and malignant adipocytic tumors**

Traditionally, *liposarcoma* is defined as a malignant mesenchymal neoplasm exhibiting features of adipocytic differentiation usually in the form of tumor cells resembling embryonal
fat cells, so called lipoblasts (complications of this diagnostic approach are outlined below). However, the diversity and complexity of this group of sarcomas, being one of the most common among soft tissue sarcomas, is such that the term liposarcoma becomes meaningless unless qualified by subtype and indication of their malignant potential. In the early literature (starting with Virchow in 1857), the terminology for various subtypes is quite confusing (for a review see Kindblom et al., 1975). In the classical work of Enzinger and Winslow (1962), they state that “among mesenchymal tumors, liposarcomas are probably unsurpassed by their wide range in structure and behavior” and that they should rather be regarded as a group of related neoplasms than a well defined entity. Their proposed classification of liposarcomas into the subtypes of well-differentiated liposarcoma, myxoid and round cell liposarcoma and pleomorphic liposarcoma was shown to be of great prognostic significance and is largely unchanged in the current WHO classification. So-called dedifferentiated liposarcoma, now added to the classification, is a variant of well-differentiated liposarcoma with progression to a usually high grade, non-lipogenic sarcoma.

**Atypical lipoma, atypical lipomatous tumor and well-differentiated liposarcoma** are all terms that have been used for the most well-differentiated liposarcomas without progression (“dedifferentiation”) that never metastasize. In the current WHO classification, these tumors have been grouped under the “intermediate malignancy” label. The terms atypical lipoma and atypical lipomatous tumor were originally introduced to emphasize their almost invariably non-aggressive behavior, as long as they occurred outside the abdomen/retroperitoneum (Evans, Soule, Winkelman, 1979; Kindblom, Angervall, Fassina, 1982; Evans, 1988 ). The striking tendency for tumors in the abdomen/retroperitoneum and groin areas to recur and not infrequently progress to higher grade sarcomas that eventually lead to the patient’s death has motivated most soft tissue pathologists to retain the term well-differentiated liposarcoma (Weiss, Rao,1992; Lucas, Nascimento, Sanjay, Rock,1994). Also the deep-seated extremity tumors may, less frequently, show repeated recurrences and occasionally dedifferentiation. It has therefore been suggested to use the term atypical lipomatous tumor only for the superficial, subcutaneous lesions. Regardless of terminology, pathologists need to convey to the clinicians the current knowledge of the lesion’s behavior. Whether the dramatic difference in prognosis between the superficial atypical lipomatous tumors and the retroperitoneal tumors with an identical morphology is only a time-dependent phenomenon or indicate some true biologic differences remains unclear.

Four main subtypes of atypical lipomatous tumor/well-differentiated liposarcoma are recognized in the current WHO classification: the common *lipoma-like* and *sclerosing* subtypes that frequently are mixed and the much rarer *inflammatory* (Argani, Facchetti, Inghirami, Rosai, 1997; Kraus, Guillou, Fletcher, 1997) and *spindle cell* variants (Dei Tos, Mentzel, Newman, Fletcher,1994). Interestingly, the textbook of Enzinger and Weiss illustrates spindle cell liposarcoma (seemingly indistinguishable from those illustrated by Dei Tos et al.). as part of the spectrum of myxoid liposarcoma. Whether spindle cell liposarcoma truly represents a distinct subgroup or only a pattern occurring in different types of liposarcoma remains somewhat unclear. We have also seen such low grade spindle cell liposarcoma areas as part of pleomorphic liposarcoma as well as low grade areas of dedifferentiated liposarcoma with sometimes gradual transition to high grade fibrosarcomatous areas. Well-differentiated liposarcoma within the retroperitoneum and deep soft tissues of the extremity may contain areas indistinguishable from spindle cell and pleomorphic lipoma (Kindblom et al. 1975).
Dedifferentiated liposarcoma (DDLS) was originally defined as a well-differentiated liposarcoma juxtaposed to a high grade non-lipogenic sarcoma component (Evans, 1979). Such tumors had earlier been described in descriptive terms as well-differentiated liposarcomas mixed with various types of high grade sarcoma patterns (Enzinger & Winslow, 1962; Kindblom et al. 1975). DDLS are by far most commonly seen in the retroperitoneum, followed by deep soft tissues of the extremities, trunk, and head and neck areas; they are virtually never seen in the subcutis (Weiss & Rao, 1992, Henricks et al. 1997). In most cases, the high-grade areas are recognized from the onset; in some cases, however, they are seen in recurrences. Many times the high-grade areas dominate and the well-differentiated lipoma-like areas can only be found after careful search (generous sampling is therefore important!). When diagnosing abdominal/retroperitoneal tumors in needle biopsies, close review of imaging studies are essential in order to detect the composite nature of DDLS (Kransdorf, Meis, Jelinek, 1993). The high-grade components can display a wide range of appearances; MFH, myxofibrosarcoma and fibrosarcoma-like features are the most common; both leiomyosarcomatous and rhabdomyosarcomatous differentiation can be seen as well as hemangiopericytoma-like areas and cartilage and osteoid/bone matrix producing tumor components. A peculiar morphologic variant is the neural-like or meningothelial-like whirling pattern that can be seen associated with metaplastic bone formation (Fanburg-Smith et al. 1999; Nascimento et al. 1998). In rare instances the dedifferentiated component has had features of so called inflammatory MFH; such cases have presented with a leukemoid blood reaction (Hisaoka et al. 1997).

More recently the concept of DDLS has widened since it has been recognized that the dedifferentiated component may be of lower grade, resembling fibromatosis and low-grade fibrosarcoma (Elgar et al. 1997, Hendricks et al. 1997). It is not always obvious where to draw the line between low grade variants of DDLS and well-differentiated liposarcomas with focal progression to somewhat higher grade spindle type liposarcomas.

The outcome of DDLS depends largely on tumor site; the most common retroperitoneal tumors tend to recur repeatedly and patients often succumb to local complications. Extra-abdominal and retroperitoneal metastases are surprisingly rare for such high-grade sarcomas, suggesting a divergent biology (McCormick et al. 1994). It has been argued, however, that the low metastatic rate in dedifferentiated liposarcoma may be partially time related since many patients die relatively early in the course of disease of local complications (Henricks et al., 1997). Patients with DDLS in the extremity have a significantly better survival.

The myxoid/round cell liposarcoma (MRCLS) group is the most common subtype and represents close to half of all liposarcomas. As pointed our already in Enzinger’s and Winslow’s original work, the purely myxoid and solid round cell patterns represent different ends of a continuous spectrum. The similar clinical characteristics, the frequent occurrence of intermediate and hybrid forms and more lately the unique karyotypic and molecular genetic findings indicate that these tumors all belong to the same family (see below). The vast majority of these tumors have features of classical myxoid liposarcoma or mixed/intermediate myxoid-round cell liposarcoma, while the purely round cell type is extremely rare.

In very rare instances MRCLS may have cartilage, osseous and leiomyomatous and exceptionally even rhabdomyoblastic differentiation. A few MRCLS have also been reported
to contain dedifferentiated areas similar to that seen in well-differentiated liposarcoma (Mentzel et al. 1997).

A puzzling phenomenon, described and discussed in detail already in Enzinger’s and Winslow’s original work, is the so called multicentric MRCLS. In this condition, numerous tumors occur in various soft tissue sites and at other locations rarely affected by metastases. We have seen such patients develop up to 31 tumors over a 10 year period. Molecular genetic confirmation of monoclonality of such tumors in a single patient has confirmed that this indeed is an unusual presentation of metastatic disease (Antonescu et al., 2000).

There is extensive literature testifying to the adverse prognostic impact of increasing cellularity and occurrence of a round cell component in these tumors. Enzinger and Winslow (1962) reported a 5-year survival of 77% for the purely myxoid subtype as opposed to 18% for the mixed myxoid-round cell and purely round cell types. We (Kindblom et al. 1975) found 5-year survivals for purely myxoid, mixed myxoid/round cell and purely round cell liposarcomas to be 80%, 40% and 15%, respectively. Many have subsequently attempted to refine the prognostication of these tumors by introducing different criteria for where to draw the line between cellular myxoid liposarcoma and round cell liposarcoma; in particular a number of different percentage cut off points for the round cell component have been suggested. A drastically worse prognosis has been seen in tumors with round cell components ranging from 5 to 25% (Kilpatrick et al.,1996; Smith et al. 1996; Antonescu et al., 2001). A disadvantage of simply applying a percentage approach is of course that this does not take into account the size factor that is probably of great importance, as in most high grade sarcomas.

Pleomorphic liposarcoma is the rarest subtype and constitutes probably less than 10% of all liposarcomas. These typically deep-seated sarcomas occur predominantly in the extremities, more rarely in the trunk and retroperitoneum, and involve mostly the elderly. Histologically, a number of patterns have been reported including the most common MFH-like, the lipoblastic type with numerous smaller and gigantic, multinucleated, bizarre lipoblasts, the epitheloid type, and the myxofibrosarcoma-like types (Enzinger & Winslow, 1962; Kindblom et al.1975; Downes at al. 2001; Miettinen & Enzinger, 1999; Hornick et al. 2004). We have also seen an unusual small cell variant that may resemble round cell liposarcoma, but that is clearly distinguished from it by the cytogenetic findings (Meis-Kindblom et al, 2001). Pleomorphic liposarcoma has an aggressive behavior with 5-year disease free survival figures ranging from 40 to virtually 0%.

What have we learned from adjunctive techniques?

Over the years and depending on the popularity and availability of different techniques, lipomatous tumors have been extensively studied with histochemistry (in particular to identify fat content and to characterize the nature of the myxoid matrix), electron-microscopy (for example, to show similarities with normal embryonal adipogenesis and documenting complex lines of differentiation) and immunohistochemistry (purportedly showing the usefulness of S-100 protein and CD34 as markers). Overall, however, such techniques play little role in the everyday diagnosis of lipomatous tumors; traditional evaluation of histology combined with careful clinical correlation remains the basis for most diagnoses. The details of such adjunctive studies are not in the scope of this short summary.
In contrast, the more recent cytogenetic and molecular genetic studies of lipomatous tumors have been remarkably successful in giving new insight into the biologic relationship between different morphologic variants, have helped to support the correctness of morphologic classifications and have, in some instances, revealed pathogenetic mechanisms. Cytogenetic techniques have become useful diagnostic tools. An example is the t(12;16)(q13;p11) causing the FUS/CHOP fusion that is highly sensitive and specific for MRCLS. Some of the more important and confirmed genetic findings in this tumor group are summarized in the following table:

**Summary of karyotypic and molecular genetic characteristics of lipomatous tumors**

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>KARYOTYPE</th>
<th>MOLECULAR GENETICS</th>
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<tbody>
<tr>
<td>Lipoma</td>
<td>Ab.12q13-15</td>
<td>HMGIC involvement</td>
</tr>
<tr>
<td></td>
<td>t(3;12)(q27-28;q13-15) Ab.6p21-23</td>
<td>HMGIC/LPP fusion transcript</td>
</tr>
<tr>
<td></td>
<td>13qdel</td>
<td>HMGIIY transcript activation</td>
</tr>
<tr>
<td>Lipoblastoma</td>
<td>Ab. 8q11-13</td>
<td>HAS2/PLAG1 and COL1A2/PLAG1 fusion transcript</td>
</tr>
<tr>
<td>Chondroid lipoma</td>
<td>t(11;16)(q13;p12-13)</td>
<td></td>
</tr>
<tr>
<td>Spindle cell/pleomorphic lipoma</td>
<td>Hypodiploid, loss or del. of chr.13 and/or 16</td>
<td></td>
</tr>
<tr>
<td>Hibernoma</td>
<td>Near-pseudodiploid, Ab.11q13-21</td>
<td>Homozygous del.MEN1 and PPP1A?</td>
</tr>
<tr>
<td>Atypical lipoma/</td>
<td>Ring and giant marker chromosomes (chr.)</td>
<td>12q14-15 ampl., incl. MDM2,SAS,CDK4,CMGIC</td>
</tr>
<tr>
<td>well-differentiated liposarcoma</td>
<td>Ring and giant marker chr.</td>
<td>12q13-21 ampl. MDM2 ampl. in retroperitoneal/TP53 mutations in non-retroperitoneal</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>liposarcoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid/round cell liposarcoma</td>
<td>t(12;16)(q13;q12) t(12;22)(q13;q12)</td>
<td>FUS/CHOP fusion transcript EWS/CHOP fusion transcript</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>Complex, polyploidy, ring and marker chr.</td>
<td>TP53 mutations or MDM2 ampl.</td>
</tr>
</tbody>
</table>

For extensive references regarding this table, please see “Pathology and Genetics: Tumours of Soft Tissue and Bone”, WHO Organization Classification of Tumours (eds. C.D.M. Fletcher, K.K. Unni and F. Mertens), 2002.
Why do we still face diagnostic problems?

The reasons for continuous diagnostic problems are many - the rarity and complexity of some of these lesions, the occurrence of lesions that do not fit well into our present ideas of tumor classification, the sometimes unpleasant feeling of being at the mercy of a surgeon that has taken a potentially non-representative biopsy, etc., etc. From our experience of consultation cases the main reasons seems to be:

1). The beliefs that a diagnosis of liposarcoma requires the demonstration of lipoblasts and that the presence of lipoblasts is synonymous with the diagnosis of liposarcoma. True lipoblasts (not lipoblast-like cells or pseudolipoblasts!) are seen in a number of benign lesions such as spindle cell/pleomorphic lipoma, chondroid lipoma and, of course, lipoblastoma. Conversely, lipoblasts may be totally absent in well-differentiated liposarcomas, some myxoid liposarcomas and occasionally very primitive round cell liposarcomas (the true nature of which may be revealed by cytogenetic analysis). At times the MFH-like pleomorphic liposarcomas contain only occasional bizarre lipoblasts found after painstaking sampling, this suggests that they are underdiagnosed.

2). Lipoblast-like cells can occur in a number of neoplasms and reactive conditions. Particularly common are juicy looking areas with vacuolated macrophages in fat necrosis that may be seen in lipomas, reactions around ruptured silicone implants and other injected compounds. Severely atrophic fat may have a worrisome appearance as may fat invaded by various neoplasms. Mucin-containing cells in carcinomas and tumor cells of myxofibrosarcoma and acral myxoinflammatory fibroblastic sarcoma may very closely simulate lipoblasts. Fixation artifacts may lead to a morphology resembling lipoblasts. A number of these examples have been illustrated in detail in the latest version of the Enzinger and Weiss’s Soft Tissue Tumor book.

3). Interpreting biopsies from lipomatous tumors, particularly needle biopsies, is treacherous if not done in close conjunction with all pertinent clinical information, including imaging studies. Always think twice before making a liposarcoma diagnosis in children as well as superficial lesions, but remember that pediatric liposarcomas (almost exclusively MRCLS) do occur as do superficial liposarcomas. Another good rule is to think twice before making a benign lipoma diagnosis in large fatty tumors of the retroperitoneum, groin and funicle and paratesticular areas.

4). Liposarcoma can be seen as part of the spectrum of heterologous components of carcinosarcoma and malignant mixed Mullerian tumors.

Conclusion

The lipomatous tumors constitute an unusually variegated and complex mosaic. A great deal of progress of vast clinical importance over the last four decades has been made recognizing patterns in this virtual maze of tumors. Dr. Franz Enzinger has, through his sharp eyes, analytical and scientific mind, and didactic skills played the key role in this development. The recent genetic discoveries in this field have confirmed morphologically-based theories and added new insight into pathogenetic mechanisms.
References


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