Recent advances in Bone and Soft tissue tumors: lipomatous tumors

Dr. David Creytens

Department of Pathology, Ghent University Hospital, Ghent, Belgium

The classification of liposarcoma has evolved significantly over past several decades, in large part owing to the advances in our understanding of its molecular genetics. It is now clear that liposarcomas cluster into 3 main subtypes consisting of: **atypical lipomatous tumor-well differentiated liposarcoma (WDLPS) (lipoma-like, sclerosing and inflammatory)/dedifferentiated liposarcoma (DDLPS), myxoid/round cell liposarcoma (MLPS) and pleiomorphic liposarcoma (PLPS).**

WDLPS/DDLPS

A characteristic feature of WDLPS/DDLPS is the presence of supernumary ring and/or giant rod chromosomes containing amplified segments from the 12q13-15 region that can be identified by fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH). Intensive research has identified several oncogenes residing in this region, including MDM2, CDK4, HMGA2, TSPAN31 (SAS), YEATS4, CPM, OS1, OS9, CHOP and GLI1. The most evidence to date demonstrates an oncogenic role in WDLPS/DDLPS for MDM2, CDK4, HMGA2 and TSPAN31 (SAS). Recently *Wang et al.* (Genes, Chromosomes & Cancer, 2011) described consistent amplification of the Fibroblast Growth Factor Receptor Substrate 2 Gene (FRS2) in WDLPS and DDLPS. MDM2 is the most frequent amplification (close to 100%) however CDK4 is shown to be amplified in over 90% of cases. Co-amplification of MDM2 and CDK4 is a common feature and may result in proliferation through combined effects upon p53 (by inactivating TP53) and the cell cycle (by RB1 phosphorylation). The corresponding proteins are potential therapeutic targets (*Singer et al.;* Cancer Res, 2007). Interestingly, the rearrangements of chromosome 12 on the giant rod chromosome are discontinuously and MDM2 and CDK4 may belong to different amplicons. It has been suggested that CDK4 provides a selection advantage in WDLPS/DDLPS and may contribute to transformation as CDK4 negative WDLPS exhibit more favourable prognostic features (*Italiano A et al.;* Clin Cancer Res, 2009). *Louis Brennetat et al.* (Genes, Chromosomes & Cancer, 2011) demonstrate that an alteration of the CDKN2A/CDKN2B/CDK4/CCND1 pathway in almost all cases without CDK4 amplification compensate for the lack of CDK4 expression, theraby confirming the pivotal role of this pathway in liposarcoma oncogenesis. A recent study by *Thway et al.* (Am J Surg Pathol 2012) have suggested that the immunohistochemical trio of CDK4, MDM2 and the cell cycle regulator p16 is a useful ancillary diagnostic tool distinguishing atypical lipomatous tumor-WDLPS from benign neoplasms and DDLPS from pleiomorphic and myxoid liposarcomas.

Well differentiated spindle cell liposarcomas represent a rare atypical/low-grade malignant lipogenic neoplasm that has been regarded as a variant of atypical lipomatous tumor. *Mentzel et al.* (Modern Pathology, 2010) have speculated on the basis of clinicopathologic and molecular findings (FISH analysis showed RB 1 deletion and no MDM2 amplification) that well-differentiated spindle cell liposarcoma may constitute an independent entity rather than a morphologic variant of atypical lipomatous tumor, and may represent the atypical/low-grade counterpart of spindle cell lipoma.

Dedifferentiated areas in DDLPS exhibit a wide morphological spectrum (*Coindre et al.;* Virchows Arch, 2010). Epithelial-like pattern composed of undifferentiated large round cells resembling a carcinoma or melanoma, areas with dense amianthoid-like fibers and areas composed of hibernoma-like cells have been described. **The concept of dedifferentiation has undergone an evolution in the last several years.** Where it was once assumed that all dedifferentiated tumors manifested themselves as high grade, undifferentiated sarcoma-like lesions, the concept of low grade dedifferentiation has increasingly been recognized, with areas resembling low grade myxofibrosarcoma, fibromatosis, well differentiated fibrosarcoma and even dermatofibrosarcoma protuberans. Low grade patterns of "neural-like", "meningothelial-like" and "paraganglioma-like" histologies have recently been described. The significance of this lower grade of progression is to date, not completely known. However, there is some suggestion that the lower grade progression carries a better prognosis than the high grade undifferentiated type of DDLPS. In about 5-10% of cases, the dedifferentiated component shows divergent differentiation featuring myogenic, angiosarcomatous or osteochondromatous components. The presence of a divergent differentiation does not affect the clinical outcome. The mechanisms responsible for progression from WDLPS to DDLPS are incompletely understood. Recent studies into the WDLPS de-differentiation process have suggested a role for c-Jun N-terminal kinase (JNK) pathway (*Snyder et al.;* J Pathol, 2009). Co-amplification of 1p32 and 6q23 that contain c-Jun and Apoptosis Signaling Kinase 1 (ASK1) are seen in DDLPS but not in WDLPS. *Crago et al.* (Clin Cancer Res; 2012) have described that copy number losses define subgroups of dedifferentiated liposarcoma with poor prognosis and genomic instability. In DDLPS loss of 11q23-24 is associated with genomic complexity and distinct morphology whereas loss of 19q13 predicts poor prognosis.

MLPS

MLPS is the second most common subtype and is characterized by the recurrent translocation t(12;16)(q13;p11), resulting in the FUS-CHOP gene fusion (95% of cases) and in rare cases a t(12;22)(q13;q12) resulting in the EWS-CHOP gene fusion. The exact function of this molecular deregulation and the mechanism by which it contributes to tumorogenesis are currently not fully elucidated. FUS-CHOP has been shown to induce adipogenic differentiation blockage and cell cycle evasion. Downstream targets of FUS-CHOP (DDIT3) include PPARγ2 and C/EBPα (*Pérez-Mancera et al.;* PLoS One, 2008). Recently evidence has indicated a role for the PI3K/Akt pathway in myxoid to round cell progression via activating mutation of PIK3CA, loss of PTEN, or IGF1R expression (*Demicco et al.*; Modern Pathology, 2012). The PI3K/Akt pathway may therefore a therapeutic target in round cell liposarcoma. The morphologic spectrum of myxoid liposarcoma is broad and often

underappreciated. *Fritchie et al.* (Am J Clin Pathol, 2012) described different patterns including the traditional myxoid, traditional round cell, pseudoacinar, lipoblast-rich, lipomatous, stroma hyalinization, cord-like, chondroid metaplasia, hemangiopericytoma-like, island and nested. Island and nested patterns had not previously been described.

PLPS

Molecular studies are limited by the scarcity of this disease. Tumors tend to show complex arrangements. *Taylor et al.* (PLoS One, 2008) described that 60% of PLPS have a deletion of 13q14.2-q14.3, a region that includes the tumor suppressor RB1. Mitotic Arrest Deficient 2 (MAD2), amplified in PLPS, may also play a critical role. Additional deletions described in PLPS include 17p13 and 17q11.2, where p53 and the sarcoma associated tumor suppressor gene, neurofibromatosis type 1 (NF1) are located. *Barretina et al.* (Nat Genet, 2010) showed 16,7% of PLPS cases had mutations identified in p53 which are rarely seen in MLPS and WDLPS/DDLPS.

"Mixed type" liposarcoma

Given the advances in the classification of liposarcoma and the extensive cytogenetic and molecular characterization of the subtypes of LS, the true mixed lesion represents an enigma. It has become increasingly apparent that the so-called mixed type liposarcoma does not exist as a distinct entity (*Boland et al;* Am J Surg Pathol, 2010) (*de Vreeze et al.;* Int J Cancer, 2011) and should not be regarded as collision tumors, but as an extreme variant of the morphologic spectrum within a single biologic entity. This is shown by different cases previously reported as mixed WDLPS and MLPS, which are now considered to represent extensively myxoid variants of WDLPS; by cases previously reported as mixed MLPS and PLPS in children which appear instead to represent a distinctive **pediatric "pleiomorphic myxoid liposarcoma"** (*Alaggio et al.;* Am J Surg Pathol, 2009) and by cases of PLPS arising in association with WDLPS representing tumors closely related to classic DDLPS (*Marino-Enriquez et al.;* Am J Surg Pathol, 2010) (*Boland et al.;* Am J Surg Pathol, 2010).