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Review Article

Contributions of Cytogenetics and Molecular Cytogenetics to the Diagnosis of Adipocytic Tumors

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Over the last 20 years, a number of tumor-specific chromosomal translocations and associated fusion genes have been identified for mesenchymal neoplasms including adipocytic tumors. The addition of molecular cytogenetic techniques, especially fluorescence in situ hybridization (FISH), has further enhanced the sensitivity and accuracy of detecting nonrandom chromosomal translocations and/or other rearrangements in adipocytic tumors. Indeed, most resent molecular cytogenetic analysis has demonstrated a translocation t(11;16)(q13;p13) that produces a *C11orf95-MKL2* fusion gene in chondroid lipoma. Additionally, it is well recognized that supernumerary ring and/or giant rod chromosomes are characteristic for atypical lipomatous tumor/well-differentiated liposarcoma and dedifferentiated liposarcoma, and amplification of 12q13–15 involving the *MDM2*, *CDK4*, and *CPM* genes is shown by FISH in these tumors. Moreover, myxoid/round cell liposarcoma is characterized by a translocation t(12;16)(q13;p11) that fuses the *DDIT3* and *FUS* genes. This paper provides an overview of the role of conventional cytogenetics and molecular cytogenetics in the diagnosis of adipocytic tumors.

1. Introduction

Adipocytic tumors represent the largest group of soft tissue tumors that have been studied by cytogenetic analysis. In 1986, the first consistent karyotypic abnormality was discovered in adipocytic tumors [1–3]. The current World Health Organization (WHO) classification of adipocytic tumors includes eleven benign, one intermediate, and five malignant subtypes [4].

The diagnosis of adipocytic tumors is primarily based on clinical features and histologic patterns. However, atypical lipomatous tumor/well-differentiated liposarcoma dedifferentiated liposarcoma are often difficult to distinguish morphologically from benign adipocytic tumors and other high-grade sarcomas, respectively. Immunohistochemistry plays little role in the differential diagnosis of adipocytic tumors [4]. Moreover, the use of minimally invasive biopsies to diagnose adipocytic tumors has become increasingly common, and this shift has created additional challenges. In such instances, molecular genetic testing can serve as a useful diagnostic adjunct for adipocytic tumors.

Most types of adipocytic tumor have distinctive cytogenetic aberrations which can be of considerable help in diagnosis. This paper reviews the cytogenetic and molecular cytogenetic characteristics of adipocytic tumors as well as their clinicopathologic features. The consistent chromosomal alterations are summarized in Table 1.

2. Methods of Cytogenetic and Molecular Cytogenetic Analyses

A soft tissue sample submitted for conventional cytogenetic analysis must be fresh and should be representative of the neoplastic process. Also, necrotic tissue should be dissected from the sample. Generally, a 1-2 cm^3 fresh sample is provided for cytogenetics [5]. The basic process of cell culturing is the same for all adipocytic lesions. Briefly, sterile tumor tissue is minced with scissors and then disaggregated with collagenase. The isolated cells are washed, diluted in culture medium, and seeded in culture flaks or chamber slides. The cultures are incubated in a 5% CO_2 atmosphere

Table 1: Chromosomal aberrations and associated molecular events in adipocytic tumors.

Tumor type	Chromosomal aberration	Molecular event
Benign		
Lipoma	t(3;12)(q27-28;q13–15)	*HMGA2-LPP*
	t(9;12)(p22;q13–15)	*HMGA2-NFIB*
	t(2;12)(q37;q13–15)	*HMGA2-CXCR7*
	t(5;12)(q32-33;q13–15)	*HMGA2-EBF1*
	t(12;13)(q13–15;q12)	*HMGA2-LHFP*
	6p21–23 rearrangement	*HMGA1* rearrangement
	13q deletion	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
Intermediate (locally aggressive)		
Atypical lipomatous tumor/ well differentiated liposarcoma	Ring/giant marker chromosome (12q13–15 amplification)	*MDM2, CDK4, CPM, HMGA2* amplification
Malignant		
Dedifferentiated liposarcoma	Ring/giant marker chromosome* (12q13–15 amplification)	*MDM2, CDK4, CPM, HMGA2* amplification
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3*
	t(12;22)(q13;q12)	*EWSR1-DDIT3*
Pleomorphic liposarcoma	Complex karyotype	Not known

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

at 37°C. A short-term culturing usually results in a sufficient number of mitoses within 5–10 days. Then, dividing cells are arrested in metaphase by the addition of a mitotic-spindle inhibitor such as colcemid. The cells are fixed with methanol/glacial acetic acid (3 : 1) and stained using a trypsin-Giemsa method to produce characteristic banding patterns. Ideally, 20 metaphase cells are analyzed for each specimen.

During the last two decades, the ability to identify chromosomal abnormalities has been markedly improved by the development of molecular cytogenetic technologies such as fluorescence in situ hybridization (FISH) and comparative genomic hybridization (CGH). FISH is a technique that involves detection of specific DNA sequences by hybridization with complimentary DNA probes. A major advantage of FISH is that nondividing (interphase) nuclei from fresh, frozen, or formalin-fixed samples can be evaluated. It has been realized that FISH is an effective adjunct in the diagnosis of soft tissue tumors including adipocytic tumors [6]. On the other hand, FISH cannot detect smaller genetic alterations such as point mutations. Recently, multicolor FISH (M-FISH) can be used to detect cryptic rearrangements or decipher the origin of marker chromosomes in complex karyotypes [7]. The combination of chromosome banding analysis with M-FISH has the potential to identify and describe most karyotypic changes of sarcoma cells. CGH is a technique for the analysis of DNA sequence copy number changes across the genome in a single hybridization experiment [8]. Briefly, tumor (test) and reference (control) DNAs are differentially labeled with green or red fluorescence dyes, mixed in a 1 : 1 ratio in the presence of human Cot-1 DNA (to block repetitive sequences), and cohybridized to normal metaphase chromosome spreads. Metaphase spreads are captured using a high resolution or cooled charge-coupled device camera, and the images are analyzed with the CGH software. The sensitivity of CGH is restricted by purity of the cell population and depends on the level and size of the copy number changes. In addition, CGH cannot detect rearrangements such as inversions or balanced translocations. Recently, a higher resolution version of CGH, so-called array CGH, has been made available [9]. In this novel technique, test and reference DNAs are differentially labeled and competitively hybridized to glass slides (chips) containing multiple DNA fragments. A distinct advantage of array CGH is the ability to directly map the copy number changes to the genome sequence. Moreover, low copy number gains and losses can be detected by array CGH at a resolution about 100 kb.

3. Benign Adipocytic Tumors

3.1. Lipoma. Ordinary lipoma is the most common soft tissue tumor and may appear at any site. It occurs mainly in the fifth to seventh decades of life, frequently in obese individuals. Lipomas are rare in children. Approximately 5% of patients have multiple lipomas [4]. Ordinary lipomas

present as painless, slowly growing soft tissue masses and can arise within subcutaneous tissue or deep soft tissue. Deep-seated lipomas (e.g., intramuscular or intermuscular lipomas) are larger and grossly less well-defined than their subcutaneous counterparts and can mimic atypical lipomatous tumor/well differentiated liposarcoma. Histologically, the tumor is composed of lobules of mature fat cells which vary slightly in size and shape.

Clonal cytogenetic aberrations have been identified in nearly 60% of ordinary lipomas [4, 10–12]. The 12q13–15 region is the most commonly involved in such aberrations, followed by 6p21–23 and 13q [10, 13, 14]. This chromosomal region recombines with a large variety of other chromosome bands through translocations. The most frequent translocation is t(3;12)(q27-28;q13–15) that fuses the *HMGA2* and *LPP* genes [15]. *HMGA2* has also been reported to form fusion genes with *CXCR7* (at 2q37), *EBF1* (at 5q33), *NFIB* (at 9p22), and *LHFP* (at 13q12) [16–20]. Rearrangements of *HMGA2* can be identified by FISH analysis [14, 17, 21, 22], but these probes are not widely available. About 15%–20% of ordinary lipomas show rearrangements or deletions of the long arm of chromosome 13, in particular 13q12–22 [14, 23]. Moreover, FISH analysis has revealed that chromosome 13 is involved in a variety of rearrangements and deletions that cover a limited segment (~2.5 Mb) of chromosome band 13q14, distal to the *RB1* gene [23]. Rearrangements of 6p21–23 involving the *HMGA1* gene has been described in ordinary lipomas without 12q13–15 aberrations [10, 14]. Recently, Wang et al. [24] detected the presence of an *HMGA1-LPP/TPRG1* gene fusion in an ordinary lipoma with t(3;6)(q27;p21). A CGH study has indicated that no copy number changes are found in ordinary lipomas, and this technique may help in the differential diagnosis of intermediate adipocytic tumors [25].

3.2. Chondroid Lipoma. Chondroid lipoma is a distinctive tumor composed of strands and nests of lipoblasts and mature fat cells in a variably myxoid or myxochondroid matrix. This tumor occurs predominantly in the proximal extremities and limb girdles of middle-aged adults. Chondroid lipoma may be mistaken for several other benign and malignant soft tissue tumors such as myxoid liposarcoma or extraskeletal myxoid chondrosarcoma [12].

A reciprocal translocation t(11;16)(q13;p13) has been found in six chondroid lipoma cases [26–29]. Most recently, Huang et al. [29] reported that this chromosomal translocation results in a fusion of *C11orf95* and *MKL2*. The presence of the t(11;16) or the *C11orf95-MKL2* fusion transcript is highly specific for chondroid lipoma, and is absent in any other related tumors. Therefore, an analysis of *C11orf95* or *MKL2* rearrangement using FISH is useful for the differential diagnosis of chondroid lipoma and its histologic mimickers.

3.3. Spindle Cell Lipoma/Pleomorphic Lipoma. Spindle cell and pleomorphic lipomas are histologic ends of a spectrum of a single clinicopathologic entity and supported by cytogenetic evidence [4]. These tumors present as circumscribed subcutaneous lesions occurring typically on the neck and upper back, particularly older males. Histologically, spindle cell lipoma is composed of a mixture of mature fat cells and small spindle cells associated with a myxoid matrix and collagen bundles. In the other end of the spectrum, pleomorphic lipoma is characterized by the presence of multinucleated floret-like giant cells. Immunohistochemically, the spindle cells in both spindle cell and pleomorphic lipomas are strongly positive for CD34 [4].

Spindle cell and pleomorphic lipomas show similar cytogenetic aberrations which are usually more complex than ordinary lipomas. The karyotypes of these tumors are frequently hypodiploid with multiple partial deletions and few balanced rearrangements. The recurrent cytogenetic aberrations appear to be deletion of 16q13-qter, monosomy for chromosome 13, or partial deletion of 13q [30–32]. However, it should be kept in mind that deletions and structural rearrangements of 13q have been described in other adipocytic tumors [23].

3.4. Hibernoma. Hibernoma is rare, benign adipocytic tumor composed of brown fat cells with granular, multivacuolated cytoplasm. The tumor occurs primarily in the thigh and scapular and interscapular regions of young adults. In cases with numerous univacuolated cells, histologic distinction from ordinary lipoma may be difficult. Also, hibernoma may be misdiagnosed as well differentiated or myxoid liposarcoma because of the paucity of diagnostic brown fat cells in the lipoma-like or myxoid variant [12].

Hibernomas have near or pseudodiploid karyotypes which are frequently somewhat more complex than ordinary lipomas. They are characterized by structural rearrangements involving the long arm of chromosome 11, in particular 11q13. No chromosomal band has been involved more than once as a translocation partner [4]. Metaphase FISH analyses have demonstrated that homozygous deletion of the *MEN1* tumor suppressor gene (at 11q13.1) and heterozygous deletion of *PPP1CA* (distal to *MEN1* at 11q13) are found in hibernomas [33]. Recently, Maire et al. [34] reported that the altered region at 11q13 is larger than previously reported and rearrangements of *GARP* (at 11q13.5) or a neighboring gene may be important in the pathogenesis of hibernomas.

3.5. Lipoblastoma. Lipoblastoma occurs predominantly in children younger than 3 years of age. It presents as a localized (lipoblastoma) or diffuse (lipoblastomatosis) tumor, resembling fetal white adipose tissue. The extremities are the most common site, but many other locations can be involved [4]. Histologically, lipoblastoma shows a lobular appearance and is composed of an admixture of mature adipocytes and lipoblasts in different stages of development. The matrix can be myxoid with plexiform vascular pattern. Lipoblastoma can be confused with intermediate and malignant adipocytic tumors, including atypical lipomatous tumor/well differentiated liposarcoma and myxoid liposarcoma [12].

Lipoblastomas usually have simple, pseudodiploid karyotypes with structural chromosomal alterations. They are characterized by rearrangements of 8q11–13 involving the *PLAG1* gene [35–38]. Excess copies of chromosome 8 may

be found in cases with or without 8q11–13 rearrangements [10, 39]. Among the several chromosomal aberrations targeting *PLAG1*, two partner genes have been indentified: *HAS2* at 8q24 and *COL1A2* at 7q22 [40]. Interestingly, *PLAG1* rearrangement can be demonstrated by FISH analysis [36, 37, 41–43]. These findings provide a useful distinguishing feature from the cytogenetic and molecular cytogenetic aberrations found in myxoid liposarcoma and other adipocytic tumors.

3.6. Miscellaneous Types of Lipoma. Angiolipoma occurs chiefly as a subcutaneous painful nodule in young adults. The forearm is the most common site, followed by the trunk and upper arm. Multiple angiolipomas are much more common than solitary ones. Histologically, angiolipoma is composed of mature fat cells separated by a branching network of small vessels. There has been only a single case report of an angiolipoma with a t(X;12)(p22;p12) [44].

Angiomyolipoma is an uncommon mesenchymal tumor composed of a variable mixture of mature fat cells, spindle and epithelioid smooth muscle cells, and abnormal thick-walled blood vessels. Although most commonly presenting in the kidney, angiomyolipomas may also occur in the extrarenal sites. Approximately one-third of patients with angiomyolipoma present with manifestations of the tuberous sclerosis [12]. Immunohistochemically, angiomyolipomas are characterized by a coexpression of the melanocytic marker HMB-45 and smooth muscle markers such as smooth muscle action and muscle-specific action. Cytogenetic studies in renal angiomyolipomas have shown chromosomal aberrations involving trisomy for chromosomes 7 and/or 8 and rearrangements of the long arm of chromosome 12 [45–49]. A CGH study has indicated that chromosomal imbalances are common and the 5q33-34 region may contain a tumor suppressor gene significant in the pathogenesis of some renal angiomyolipomas [50].

Myelolipoma, most common in the adrenal grand, is a rare, benign tumor or tumor-like lesion composed of mature fat cells and haematopoietic elements comprising myeloid and erythroid cells as well as megakaryocytes. It can also occur in extra-adrenal soft tissue. There has been only a single case report of an adrenal myelolipoma with a t(3;21)(q25;p11) [51].

4. Intermediate and Malignant Adipocytic Tumors

4.1. Atypical Lipomatous Tumor/Well Differentiated Liposarcoma. In the current WHO classification, atypical lipomatous tumor and well differentiated liposarcoma have been grouped under the "intermediate (locally aggressive) malignancy" label [4]. It has been suggested to use the term "atypical lipomatous tumor" only for the superficial or subcutaneous locations. Atypical lipomatous tumor/well differentiated liposarcoma accounts for about 40%–45% of all liposarcomas and occurs most frequently in the thigh, retroperitoneum, and paratesticular/inguinal region of middle-aged and older individuals [4]. It usually presents as a painless, slowly growing mass that can attain a very large size. Histologically, the tumor is composed entirely or partially of a mature adipocytic proliferation showing significant variation in cell size and at least focal nuclear atypia in both adipocytes and stromal cells. Four main subtypes of atypical lipomatous tumor/well differentiated liposarcoma are recognized in the current WHO classification: adipocytic (lipoma-like), sclerosing, inflammatory, and spindle cell [4]. The presence of more than one histologic pattern in the same lesion is common. In some situations, atypical lipomatous tumor/well differentiated liposarcoma may be indistinguishable from benign adipocytic tumors at the histologic level, and inadequate samples can lead to misdiagnosis.

Cytogetically, atypical lipomatous tumor/well differentiated liposarcoma is characterized by the presence of supernumerary ring and/or giant marker chromosomes, lacking alpha-satellite centromeric sequences. These ring and giant marker chromosomes have been observed as the sole change or concomitant with a few other numerical or structural aberrations in mostly near-diploid karyotypes. Random and nonrandom telomeric associations can be found [52]. FISH and CGH studies have shown that ring and giant marker chromosomes are composed mainly of amplified sequences from the 12q13–15 region, including the *MDM2*, *CDK4*, *HMGA2*, and *SAS* genes [53–61]. Recently, Erickson-Johnson et al. [62] demonstrated that *CPM* (at 12q15) is coamplified with *MDM2* in atypical lipomatous tumors/well differentiated liposarcomas. Coamplification of 1q21–23 involving the *COAS* genes has also been reported [63]. This 12q13–15 amplification is not observed in benign adipocytic tumors, and its detection can therefore be used as an ancillary diagnostic technique for the diagnosis of atypical lipomatous tumor/well differentiated liposarcoma [64, 65]. More importantly, FISH for *MDM2* amplification can be performed on nondividing cells from limited tissue samples and is a more sensitive and specific adjunctive tool than MDM2 immunohistochemistry [66].

4.2. Dedifferentiated Liposarcoma. Dedifferentiated liposarcoma is a malignant adipocytic tumor showing transition from atypical lipomatous tumor/well differentiated liposarcoma to a nonlipogenic sarcoma of variable histologic grade. Dedifferentiation is thought to be a time-dependent phenomenon that occurs in up to 10% of atypical lipomatous tumor/well differentiated liposarcoma. About 90% of dedifferentiated liposarcomas arise "de novo," while 10% occur in recurrences [4]. The risk of dedifferentiation appears to be higher in deep-seated lesions. Dedifferentiated liposarcoma occurs typically in the retroperitoneum of elderly individuals and can also affect the extremities. It usually presents as a painless, large mass, which may be found by chance. In contrast to atypical lipomatous tumor/well differentiated liposarcoma, dedifferentiated liposarcoma has a 15%–20% metastatic rate [67]. Histologically, dedifferentiated liposarcoma is traditionally defined by the association of atypical lipomatous tumor/well differentiated liposarcoma areas and a nonlipogenic component, most often in an abrupt fashion.

In about 90% of cases, the dedifferentiated components have the appearance of a high-grade poorly differentiated sarcoma [12]. Recently, the concept of low-grade dedifferentiation has increasingly been recognized [68]. Due to the histologic complexity of dedifferentiated liposarcoma, many differential diagnoses may be raised on the morphologic aspect alone.

Similar to atypical lipomatous tumor/well differentiated liposarcoma, dedifferentiated liposarcoma is characterized by the presence of ring or giant marker chromosomes and double minutes. A peculiarity of dedifferentiated liposarcoma might be the presence of multiple abnormal clones [4]. FISH and CGH studies have demonstrated that ring and giant marker chromosomes are composed, exclusively or partly, of amplified 12q13–15 material, involving *MDM2*, *CDK4*, and *HMGA2* [56, 69]. In a previous analysis, we established the first human dedifferentiated liposarcoma cell line (FU-DDLS-1) and showed that giant marker chromosomes were composed partly of chromosome 12 material [70]. In addition to the 12q13–15 amplification, 1p32 and 6q23 amplifications have been detected by CGH in dedifferentiated liposarcomas [71–73]. Array CGH analyses have shown that the target genes are *JUN* in the 1p32 band [74] and *ASK1* in the 6q23 band [75]. Interestingly, co-amplifications of 1p32 and 6q23 are absent in atypical lipomatous tumor/well differentiated liposarcoma, suggesting that CGH is a helpful diagnostic adjunct in the discrimination between dedifferentiated liposarcoma and atypical lipomatous tumor/well differentiated liposarcoma.

4.3. Myxoid Liposarcoma/Round Cell Liposarcoma. The WHO Committee combined myxoid and round cell liposarcomas (previously two distinct subtypes) under the umbrella of myxoid liposarcoma [4]. Myxoid liposarcoma, the second most common subtype of liposarcoma, occurs predominantly in the extremities of young to middle-aged adults and has a tendency to recur locally or to metastasize to unusual sites such as the retroperitoneum, opposite extremity, and bone. Histologically, the tumor is composed of a mixture of uniform round- to oval- shaped primitive mesenchymal cells and a variable number of small lipoblasts in a prominent myxoid stroma. The presence of round cell component is associated with a poor prognosis. Pure myxoid liposarcoma must be differentiated from a number of benign and malignant soft tissue lesions characterized by a myxoid stroma, such as lipoblastoma, myxoma, myxofibrosarcoma, low-grade fibromyxoid sarcoma, and extraskeletal myxoid chondrosarcoma.

Myxoid/round cell liposarcoma is generally associated with a chromosome number in the diploid range, with only rare cases being hyperdiploid or near-triploid [76]. It is characterized by a translocation t(12;16)(q13;p11) in more than 90% of cases, resulting in an *FUS-DDIT3* fusion gene [77–80]. A variant translocation t(12;22)(q13;q12) has also been described, resulting in an *EWR1-DDIT3* fusion gene [81–83]. In addition, several nonrandom secondary aberrations have been identified, including del(6q), i(7)(q10), +8, and der(16)t(1;16) [84–86]. The presence of these translocations and molecular alterations is highly sensitive and specific for myxoid/round cell liposarcoma and is absent in other liposarcoma subtypes or in other myxoid soft tissue tumors. Therefore, cytogenetics is an excellent analytic method for the initial workup of a suspected myxoid/round cell liposarcoma. Moreover, dual color, break apart rearrangement probes spanning the genomic regions of *DDIT3* (12q13), *FUS* (16p11), and *EWSR1* (22q12) (Abbott Molecular/Vysis, Des Plaines, IL) are readily available, and FISH can be used to provide support for the diagnosis of myxoid/round cell liposarcoma [6, 87]. Conventional and array CGH studies have shown that genomic imbalances frequently include gains of 8p21–23, 8q, and 13q in myxoid/round cell liposarcomas [88–90].

4.4. Pleomorphic Liposarcoma. Pleomorphic liposarcoma is a rare, high-grade sarcoma with at least focal adipocytic differentiation in the form of pleomorphic lipoblasts. It occurs predominantly in the extremities of elderly patients (>50 years) and is usually deep-seated but may be superficial. In general, pleomorphic liposarcoma has an aggressive behavior with a 30%–50% metastatic rate and an overall tumor-associated mortality of 40%–50% [4]. Histologically, the tumor is composed of pleomorphic multivacuolated lipoblasts admixed with pleomorphic spindle cells and multinucleated giant cells. In some cases of pleomorphic liposarcoma, a small round cell area indistinguishing from myxoid/round cell liposarcoma is observed with a varying number of pleomorphic lipoblasts [12].

Pleomorphic liposarcomas are generally associated with highly complex karyotypes lacking specific structural or numerical aberrations [76, 78, 91]. The presence of rings, large markers, or double minute chromosomes has been reported [4]. Recently, Sugita et al. [92] demonstrated that the number of *DDIT3* split signals in pleomorphic liposarcomas is extremely scarce compared with that of myxoid/round cell liposarcoma. Therefore, FISH for *DDIT3* rearrangement can play a role in distinguishing between these two liposarcoma subtypes. Conventional and array CGH analyses have shown gains of 1p21, 1q21-22, 5p13–15, 7q22, 9q22-qter, 13q, 17p11.2–12, 20q13, and 22q and losses of 2q, 3p, 4q, 10q, 11q, 12p13, 13q21, and 14q23-24 [72, 88, 89, 93, 94]. Interestingly, amplification of the 12q13–15 region and the *MDM2* gene does not occur consistently in pleomorphic liposarcomas, suggesting that CGH can be performed to distinguish pleomorphic liposarcoma from high grade dedifferentiated liposarcoma.

4.5. Mixed-Type Liposarcoma. Mixed-type liposarcoma represents the rarest subtype of liposarcoma and is still considered a controversial entity. It is defined as a liposarcoma showing a mixture of features of at least two main subtypes by histologic examination [4]. The tumor occurs predominantly in retroperitoneal or intra-abdominal locations of elderly patients. Most recently, de Vreeze et al. [95] proposed that mixed-type liposarcomas should not be regarded as collision tumors, but as an extreme variant of the morphologic spectrum within a single biologic entity.

Cytogenetic aberrations in mixed-type liposarcomas usually reflect at least one of the histologic components of the tumor. The presence of ring or giant marker chromosomes has been observed as the sole anomaly or in association with complex rearrangements [31, 69, 96]. Interestingly, Mentzel et al. [97] have reported that amplification of the *MDM2* and *CDK4* genes and rearrangements of the *DDIT3* and *FUS* genes were detected by FISH analysis in the atypical lipomatous tumor/well differentiated liposarcoma and myxoid/round cell liposarcoma components, respectively.

5. Molecular Diagnostic Algorithm for Adipocytic Tumors

Molecular genetic testing can be used to distinguish between (1) lipoma and atypical lipomatous tumor/well differentiated liposarcoma; (2) myxoid liposarcoma and a variety of myxoid soft tissue tumors including lipoblastoma; and (3) dedifferentiated liposarcoma and pleomorphic liposarcoma when histologic diagnosis is difficult. In addition, molecular genetic testing should be considered for recurrent lipomas, large adipocytic tumors (>15 cm) with minimal or no cytologic atypia [98], lesions arising in rare anatomic locations or unusual age groups, or small biopsy specimens.

6. Conclusions and Future Directions

Cytogenetics is the most comprehensive laboratory method for spotting the various translocations and other structural alterations that characterize adipocytic tumors. In addition, dramatic advances in molecular cytogenetic technologies have greatly improved diagnostic accuracy in adipocytic tumors. In our experience, FISH is very useful in the diagnosis of adipocytic tumors, which harbor consistent molecular alterations including nonrandom translocations and amplification of gene regions. Hopefully in the future, clinical decisions will increasingly be based on a combination of histologic criteria and specific molecular/cytogenetic aberrations. Better understanding of the molecular biology of adipocytic tumors will undoubtedly lead to the development of novel therapeutic strategies.

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