MDM2 amplified sarcomas

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Introduction

Murine Double Minute Clone 2 is an oncogene, the function of which was first described in DNA associated with paired acentric chromatin bodies, termed double minutes, harbored in spontaneously transformed mouse 3T3 fibroblasts (1). MDM2 (located at 12q15) is an E3 ubiquitin ligase that targets the p53 protein for proteasomal degradation. Thus, the most important function of MDM2 is to control p53 activity. For normal cells it is of utmost importance that p53 is maintained at low levels since p53 has potent growth suppressive activities. In fact, p53 is lethal in the absence of MDM2. Mouse MDM2-/- embryos are inviable and deletion of p53 rescues these embryos. There are different mechanisms by which MDM2 can block p53 activity. On the one hand, MDM2 stimulates the degradation of p53 by escorting p53 from the nucleus to the cytoplasm and by catalyzing the ubiquitination of p53 and hence proteosomal degradation. On the other hand, MDM2 blocks the activity of intact p53 by inhibiting the p53 transactivation domain. Indeed it is well known that p53 trans-activates a number of genes that mediate cell cycle arrest or apoptosis (1).

Mutations of the tumor suppressor gene p53 represent the most frequent genetic change in human cancers. By overexpressing MDM2, cancer cells have another means to block p53. It is no surprise that tumors that show MDM2 amplification do not require p53 mutations. In view of this, MDM2 has become a hot topic in cancer treatment, because anti-MDM2 therapy has become a reality: we actually know of molecules that block the MDM2-p53 interaction, and thus reestablish wild type p53 activity (2-5).

The overall MDM2 gene amplification frequency in human cancer is about 7%. Some gliomas, carcinomas and hematological malignancies have been described to amplify MDM2, but this feature is most frequently seen in sarcomas, the topic of the review (6).

Well differentiated liposarcoma/atypical lipomatous tumor (WDL/ATL)

This tumor represents the most common malignant adipocytic neoplasm and is mainly seen in middle-aged adults. The deep soft tissues of the extremities are most frequently involved (75%), followed by the retroperitoneum (20%). The groin, paratesticularum and mediastinum are also known locations. The overall mortality is zero for lesions of the extremities and more than 80% for exactly the same tumors in the retroperitoneum. The basic morphological hallmark is the presence of variation in adipocyte diameter, hyperchromatic/atypical nuclei and lipoblasts. Three morphological subtypes are classically described; lipoma-like, sclerosing and inflammatory (7). These phenotypes can be admixed in the same tumor. Whatever it looks like, WDL/ATL is characterized by giant marker and/or supernumerary ring chromosomes, both of which contain multiple copies of MDM2. This amplification results in nuclear MDM2 protein overexpression. There is frequently co-amplification of other genes of the 12q14-15 region, like CDK4, GLI1 and HMGA2, but MDM2 amplification is the
main driver. Immunohistochemistry and/or FISH for MDM2 is frequently used to support the diagnosis of WDL/ATL, FISH being much more sensitive and specific than protein detection (8-10). An important pitfall is the presence of nuclear MDM2 immunoreactivity in histiocytes/lipophages which are very often seen in traumatized fatty tumors. The pathologist is often faced with lesions in which the histological changes are not convincing enough for WL/ATL and thus the differential diagnosis with an ordinary lipoma cannot be made on morphological grounds alone. This does not mean that every lipoma should be FISHed for MDM2, the following features justify the use of this test: (1) recurrent lesion, (2) deep extremity lesion larger than 10 cm in a patient over 50 years of age, (3) lesion with equivocal atypia, (4) lesion in the retroperitoneum/pelvis/abdomen, and (5) lesions not fitting the above criteria but having worrisome clinical or radiological features (11).

It is of interest that the well differentiated spindle cell liposarcoma subtype has a different genetic background, and more closely relates to spindle cell lipoma, with deletion of the Rb-1 gene (12).

**Dedifferentiated liposarcoma**

Dedifferentiated liposarcoma (DDL) is defined as the transition of WDL/ATL towards nonlipogenic sarcoma, either in the primary tumor or in a recurrence. The well differentiated component can be absent. 90% of DDL present de novo, +/- 10% of WDL/ATL dedifferentiate into DDL. Patients are most often older than 45 years. The retroperitoneum is the most frequent site (80%), and DDL is the most frequent retroperitoneal sarcoma. The transition to the nonlipogenic sarcoma is usually abrupt and the latter most often looks like undifferentiated pleomorphic or spindle cell sarcoma, but myxoid sarcoma-like pictures, or low grade desmoid-like areas can be seen as well. Heterologous differentiation is present in up to 10%. In fact, DDL can mimic any type of sarcoma. Once dedifferentiation is present, the tumor gains metastatic potential but is less aggressive than other pleomorphic sarcomas. Recurrence is seen in at least 40% of cases, metastatic rates vary between 15 and 30% and tumor related death is +/- 28% (13). The amount of dedifferentiation or the aspect of the dedifferentiated areas does not influence the prognosis except for retroperitoneal DDL, where myogenic (particularly rhabdomyoblastic) differentiation and grading are major prognostic determinants (14). As in WDL/ATL, complete surgical resection is the mainstay of treatment. DDL also harbors high level amplifications of 12q14-15, including the MDM2 and CDK4 genes. As opposed to WDL/ATL, DDL shows other genetic changes, as 6q23 and 1p32 co-amplifications. In this respect, JUN (1p32.2) is of interest since its amplification is probably involved in the progression from WDL/ATL to DDL. Another feature that favors dedifferentiation might be the loss of HMGA2 overexpression, which is frequent in in DDL (8).

**Intimal sarcoma**

Intimal sarcomas are very rare tumors that develop in the wall of large blood vessels, the proximal pulmonary arteries being the most frequent location (15). The aorta is the main involved vessel of the peripheral circulation, and intimal sarcoma has recently been described to be the most frequent primary cardiac sarcoma (16). The prognosis is very poor, which relates to the embolic dissemination. On histology, these tumors look like undifferentiated sarcomas and often have a very heterogeneous outlook. There is no specific immunohistochemical marker, but EGFR and nuclear MDM2 expression are classically seen. Amplification of the 12q12-15 region is a hallmark and is accompanied by amplification and activation of platelet derived growth factor alpha (at 4q12) and epidermal growth factor receptor (at 7p11)(15).
Low grade osteosarcoma
Low grade osteosarcomas are rare and are subdivided in parosteal and low grade central osteosarcoma. Parosteal osteosarcoma represents 4-5% of all osteosarcomas and typically develops on the posterior surface of the distal femur of young adults (third decade). Low grade central osteosarcoma only accounts for 1-2% of osteosarcomas and is mainly seen in the distal femur or proximal tibia of patients in the same age group. The prognosis of both is excellent, with 5 year survival rates of 90%. On histology, both lesions are characterized by a moderately cellular fascicular proliferation with minimal/no atypia and mature bone trabeculae, making the diagnosis often impossible in the absence and of imaging features (17). In this respect, MDM2 and/or CDK4 immunohistochemistry is also of diagnostic use. Indeed, both tumors harbor long marker or ring chromosomes with amplified 12q13-15 regions, including the MDM2 and CDK4 genes (17,18). Interestingly, when low grade central or parosteal osteosarcoma dedifferentiates into a high grade sarcoma (seen in 15-20% of cases), they retain their MDM2/CDK4 amplification and overexpression. In addition, the finding of MDM2 and CDK4 overexpression in a high grade osteosarcoma indicates progression/dedifferentiation from a low grade osteosarcoma and practically excludes a primary conventional high grade osteosarcoma (18).

References
relied upon to diagnose well-differentiated liposarcoma? Modern Pathology 2010;23:1301-1306


12. Mentzel T, Palmedo G, Kuhnen C. Well-differentiated spindle cell liposarcoma (‘atypical spindle cell lipomatous tumor’) does not belong to the spectrum of atypical lipomatous tumor but has a close relationship to spindle cell lipoma: clinicopathologic, immunohistochemical and molecular analysis of six cases. Modern Pathology 2010;23:729-736


