

MDM2 and CDK 4 immunostains in the diagnosis of atypical lipomatous tumor / well-differentiated liposarcoma and dedifferentiated liposarcoma

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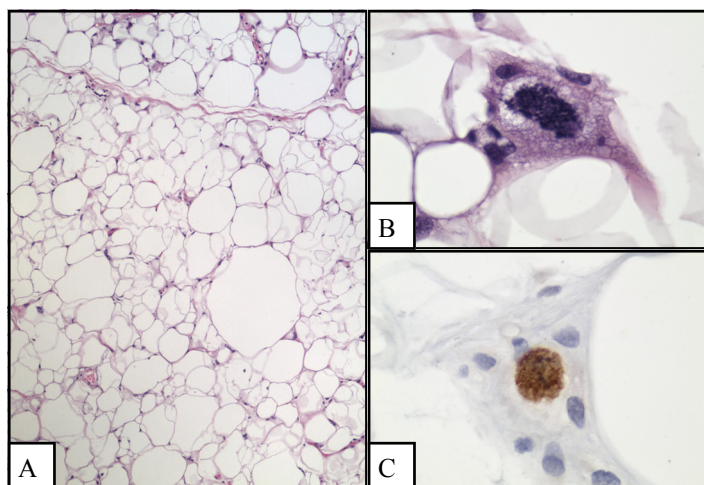
by Rodney T. Miller, M.D., Director of Immunohistochemistry

Diagnosis of well-differentiated liposarcoma and dedifferentiated liposarcoma can be a challenging task. This month, we call attention to a study published in the October 2005 issue of *The American Journal of Surgical Pathology* that discusses the utility of two immunohistochemical markers, MDM2 and CDK4, that can be of use in recognizing these tumors.

Atypical lipomatous tumor / well-differentiated liposarcoma (ALT-WDLPS) may show locally recurrent behavior, but does not metastasize unless it undergoes dedifferentiation. When it does dedifferentiate, only about 15% of cases demonstrate metastatic behavior. Since dedifferentiated liposarcoma can morphologically mimic other sarcomas that have substantially higher metastatic rates, accurate identification of dedifferentiated liposarcoma is clinically important. One of the tumors that dedifferentiated liposarcoma can closely mimic is so-called malignant fibrous histiocytoma (MFH). In fact, there is evidence that a subpopulation (about 20%) of poorly differentiated sarcomas of the retroperitoneum previously classified as MFH likely represent dedifferentiated liposarcoma.

ALT-WDLPS has been found to contain supernumerary ring chromosomes or giant chromosomes, and genetic studies have shown that these abnormal chromosomes are composed of 12q13-15 amplicons that contain amplified MDM2 and frequently CDK4 genes. Amplification of these genes results in overexpression of the corresponding gene products, and these overexpressed proteins can be detected using immunohistochemistry.

In their study, Binh et al analyzed 559 soft tissue



ALT-WDLPS, lipoma-like subtype, showing wide variation in size of fat cells (A) and scattered highly atypical cells (B). The atypical cells were positive for MDM2 (C).

tumors from 522 patients. Cases studied included the following: 44 ALT-WDLPS, 61 dedifferentiated liposarcomas, 49 benign fatty tumors (including 16 spindle cell / pleomorphic lipomas, 15 superficial lipomas, 12 deep-seated lipomas, 4 angiomyolipomas, and 2 hibernomas.), 72 leiomyosarcomas, 64 MFH, 40 embryonal rhabdomyosarcomas, 39 synovial sarcomas, 34 malignant peripheral nerve sheath tumors (MPNST), 24 myxoid-round cell liposarcomas, 24 myxofibrosarcomas, 20 alveolar rhabdomyosarcomas, 15 gastrointestinal stromal tumors (GIST), 12 dermatofibrosarcoma protuberans (DFSP), 11 angiosarcomas, 9 primitive neuroectodermal tumors (PNET), 7 clear cell sarcomas, 6 extraskeletal osteosarcomas, 5 pleomorphic liposarcomas, 5 pleomorphic rhabdomyosarcomas, 4 extraskeletal myxoid chondrosarcomas, 4 Kaposi's sarcomas, 4 alveolar soft part sarcomas, 3 desmoplastic round cell tumors, 2 epithelioid sarcomas, and 1 malignant solitary fibrous tumor. All of these cases were immunostained

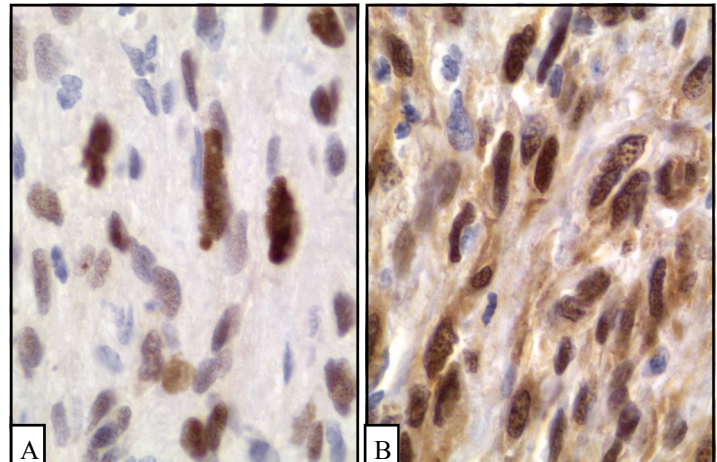
using antibodies directed against the MDM2 and CDK4 gene products.

A tumor was regarded as positive for MDM2 or CDK4 when one or more nuclei were stained per individual high-power field. MDM2 typically showed scattered stained nuclei, with increased numbers of positive cells in the most cellular areas. In most cases reactivity with CDK4 was stronger and more diffuse.

100% (44/44) of cases of ALT-WDLPS were positive for MDM2, and 91% (40/44) were positive for CDK4. 95% (58/61) of the dedifferentiated liposarcomas were positive for MDM2, with CDK4 reactivity noted in 92% (56/61). 12% (2/17) of spindle cell lipomas were positive for MDM2, with 6% (1/17) positive for CDK4. The remainder of the benign fatty tumors were negative for these markers.

Sarcomas that may morphologically simulate dedifferentiated liposarcoma that were positive for these markers included MPNST (64% positive for MDM2, 12% positive for CDK4), myxofibrosarcoma (42% positive for MDM2, 17% positive for CDK4), embryonal rhabdomyosarcoma (29% positive for MDM2, 23% positive for CDK4), MFH (11% positive for MDM2, 3% positive for CDK4), leiomyosarcoma (6% positive for MDM2, 1% positive for CDK4), and myxoid / round cell liposarcoma (4% positive for MDM2, 4% positive for CDK4).

A number of other sarcomas not likely to be confused with dedifferentiated liposarcoma also expressed these markers. 25% (3/12) of DFSP's were positive for MDM2, and 9% (1/11) positive for CDK4. Other tumors positive for MDM2 included angiosarcoma (36%, 4/11), clear cell sarcoma (43%, 3/7), Kaposi's sarcoma (2/3), epithelioid sarcoma (2/2), and desmoplastic small round cell tumor (1/3). These tumors were all negative for CDK4. As such,



MDM2 (A) and CDK4 (B) immunostains on a spindle cell sarcoma. In the appropriate context, these findings support the interpretation of dedifferentiated liposarcoma.

CDK4 has greater specificity for dedifferentiated liposarcoma than MDM2. At PROPATH, we have also seen MDM2 and CDK4 staining in leiomyosarcoma, spindle cell rhabdomyosarcoma, adrenal oncocytoma, and some cases of lung carcinoma. Several urothelial and colon carcinomas have also shown reactivity with MDM2.

Like most immunohistochemical markers, MDM2 and CDK4 are not perfect, and as always it is important to use them as part of a panel of immunostains when approaching a particular case. However, in the appropriate clinical and pathologic context, immunoreactivity with these markers can be useful in the accurate diagnosis of ALT-WDLPS and dedifferentiated liposarcoma. These markers are now available at PROPATH.

Reference:

Binh MBN, Sastre-Garau X, Guillou L et al: MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes. A comparative analysis of 559 soft tissue neoplasms with genetic data. *Am J Surg Pathol* 29 (10): 1340-1347, Oct 2005.



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After completing an AP/CP residency and Surgical Pathology Fellowship, Dr. Miller spent 10 years in hospital-based Pathology, and set up and directed several hospital IHC labs. He joined PROPATH in 1993, and developed a large, sophisticated, and thriving IHC lab and IHC consultation service. He is a nationally and internationally recognized expert in the field, and has lectured on the subject numerous times. He has authored multiple scientific articles on IHC, and is a member of the Editorial Board of The American Journal of Clinical Pathology.

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