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EDITORIAL

The Marriage Between Pathology and Genetics: Are We Ready for Clinical Use?

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The integration of cytogenetics and molecular genetics into the histopathologic evaluation of soft tissue tumors has certainly represented one of the major advances of the last decade.[1] It has not only served as both a validation and a refinement of available classification schemes but has also offered new diagnostic tools that have led to significant improvement of diagnostic accuracy. Among mesenchymal neoplasms, adipocytic tumor certainly represents an ideal model of such integration. In fact, with the notable exception of angiolipoma, most benign and malignant adipocytic tumors harbor distinctive genetic aberration that parallels their histomorphology. This has also proved true for adipocytic malignancies. Liposarcoma is currently subclassified genetically into three broad categories: (1) well-differentiated (WD) liposarcoma/atypical lipomatous tumors (ALT) and dedifferentiated liposarcoma featuring aberrations of the 12q13–15 chromosome region; (2) myxoid/round cell liposarcoma harboring a t(12;16) or more rarely a t(12;22) reciprocal translocation, leading to fusion of *DDIT3* and *FUS* genes (95% of cases) or *DDIT3* and *EWS* genes (5% of cases), respectively; and (3) pleomorphic liposarcoma showing (similarly to other pleomorphic sarcomas) complex karyotypic aberrations.

With the advent (or the development) of more selective, histotype-related, systemic treatments, accurate diagnosis of mesenchymal tumors has become mandatory, as it not only provides fundamental prognostic information but also tends to determine treatment options.[2,3] In the current issue of *Annals of Surgical Oncology* both the diagnostic and clinical impact of genetic observation is addressed by de Vreeze et al.[4]

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The diagnostic application of 12q13–15 aberration in the differential diagnosis of well-differentiated/dedifferentiated liposarcoma dates back to the late 1990s, when pathologists first started considering the use of MDM2 and CDK4 increased protein expression (epiphenomenon of gene amplification) as a possible novel diagnostic marker.[5,6] Nuclear immunopositivity for MDM2 and CDK4 appears to be restricted to well-differentiated liposarcoma/ALT, allowing separation from challenging examples of benign lipomas. The same findings in the context of dedifferentiated liposarcoma permit its distinction from other unrelated pleomorphic sarcomas that may also occur in the retroperitoneum, and have also contributed to the decline of malignant fibrous histiocytoma (MFH) as a meaningful category.[6,7] Even if immunohistochemistry in expert hands appears to be acceptably reliable, fluorescence in situ hybridization (FISH) analysis as well as quantitative polymerase chain reaction (PCR)-based techniques can be used to evaluate *MDM2* gene status.[8]

Of course a few caveats need to be underscored in order to avoid major pitfalls. First of all, *MDM2* aberrations, as well as *DDIT3/FUS* abnormalities, whatever the technique used, should be evaluated in context with morphology. Actually this represents a general principle whenever dealing with rare form of cancers, for which diagnostic expertise is certainly crucial but also hard to achieve without access to a substantial number of cases. A second point that has been raised is related to the fact that MDM2 and CDK4 represent cell-cycle regulators, the activation of which may be not restricted to WD/dedifferentiated liposarcoma. While it is true that *MDM2* gene amplification has been reported in both malignant peripheral nerve sheath tumors and undifferentiated (MFH) pleomorphic sarcomas, in the context of adipocytic malignancies it appears to be quite restricted to the well-differentiated/dedifferentiated liposarcoma category. As a consequence MDM2 analysis, as shown in the study of de Vreeze and

colleagues, in addition to telling apart benign lipomas from WD liposarcomas, can also be useful in discriminating myxoid liposarcoma from well-differentiated liposarcoma with myxoid change, as well as dedifferentiated liposarcoma from pleomorphic liposarcoma.

However there certainly remain a number of cases in which, despite the presence of a convincing morphology, the expected genetic aberration is missing. We have also encountered examples of classic myxoid liposarcoma or WD liposarcoma lacking any genetic aberration. However, it should be underlined that the mere absence of a given genetic abnormality may simply reflect a technical failure. As a consequence, even in the presence of state-of-the-art molecular techniques, accurate morphologic assessment should still represent the diagnostic mainstay. This assumption is supported by two very simple reasons: (1) no distinctive genetic aberration is present in 100% of cases of a given tumor (i.e., PAX2 and PAX7 aberrations in alveolar rhabdomyosarcoma), and therefore a diagnosis can be reliably rendered even if the associated genetic feature is absent, and (2) the same genetic aberration may be present in unrelated entities (i.e., ALK1 aberrations in anaplastic large lymphoma and inflammatory myofibroblastic tumor or EWSR1/CREB3/ATF1 aberrations in angiomatoid fibrous histiocytoma and clear cell sarcoma), which would be misdiagnosed if only genetic findings were to be taken into account.

In conclusion, as underlined by the work of de Vreeze et al., the analysis of genetic abnormalities associated with adipocytic neoplasm is certainly a powerful tool that significantly increases diagnostic accuracy. The current role of genetic analysis is to complement and not to replace expert morphologic observation. The combination of pathology and genetics sets the rationale for appropriate clinical decision-making and possibly leads to improvement of outcome.

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