Somatic and germline molecular analysis and morphological aspects of unusual variants of malignant melanomas and uncommon melanocytic neoplasms

Abstract

Background: The histopathological diagnosis of melanocytic tumors represented one of the greatest challenges of pathology. In the last years, the concept of melanoma as a single entity have been questioned. In fact, several subgroups of melanocytic neoplasms have been recognized on the bases of their clinical and histological presentation. The microscopic assessment of these lesions is based upon the detection of a constellation of morphological features, some of which lack interobserver reproducibility. In recent years, thanks to the development of molecular biology, a significant step forward has been made in the diagnosis of melanocytic neoplasms. Considering clinicopathological and genetic data some authors have suggested a stepwise model of evolution of melanocytic neoplasm to melanoma from a conventional nevus. Moreover, in the era of precision medicine, several efforts are being made to identify molecular biomarkers to predict prognosis. These biomarkers can be detected also in germline status of the patients to identify predisposing factors to tumor development.

Aims: Primary aim of our projects is to perform of molecular analysis on morphologically selected melanocytic lesions and on normal tissue of the patients to analyze somatic molecular profile of unusual variants of malignant melanoma and uncommon melanocytic neoplasms and germline patient status to detect genetic factors that have relevance for prognosis, indication to treatment and cancer susceptibility.

Secondary aims are to perform a molecular histological correlation and to validate this approach in clinical practice.

Material and Methods: DNA and RNA analysis of histologically and immunohistochemical selected melanocytic neoplasm have been analyzed by Next Generation Sequencing (NGS) technology with Solid Tumor Panel and a Custom Panel for melanocytic tumors TruSight Tumor 170 panel (Illumina, San Diego, CA) and a Customized version of FusionPlex ArcherDX Solid Tumor panel (AST2). The analysis was performed on both tumoral tissues and blood lymphocytes of the patients.

FISH analysis for melanoma related genes with a four-probe assay investigating 6p25 (RRB1, 11q13 (CCND1), 6p23 (MYB) and CEP6, and a three-probe assay 9p21 investigating (CDKN2A), 8q24 (MYC), CEP9 was also performed.

Results: The results of our studies are summarized in four main research projects.

Conclusions: The use of a custom panel for DNA and RNA analysis of morphologically ambiguous melanocytic neoplasm provide genomic data that can be used to confirm the diagnosis, to avoid overtreatment, to stratify the biological risk of progression and to set up a specific treatment. Molecular analysis on tumor and normal samples allows to identify germline mutations predictive of tumor susceptibility syndrome and set up a specific screening in the first-degree family members. Morphological assessment should direct the molecular investigation for a cost-effective analysis.