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Clinical Relevance of Biomarkers in Prostate Cancer: The Role of NKX3.1, AMACR, and Ki-67 in Risk Stratification – A Comprehensive Clinicopathological Analysis

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Abstract

Introduction: Accurate risk stratification, essential for the therapeutic approach (especially surgical) of prostate cancer, is based on standard histopathological criteria. The biological heterogeneity of this neoplasm requires the identification of complementary markers that reflect the molecular mechanisms of tumor progression. The aim of this study was to evaluate the correlation between immunohistochemical markers of metabolism (AMACR, NKX3.1) and proliferation (Ki-67) and histopathological aggressiveness in ADK (prostate adenocarcinoma).

Methods: This retrospective, single-center clinicopathological study included 385 patients with prostatic lesions from the Sf. Apostol Andrei Emergency Clinical Hospital in Constanţa (2023–2024). Of these, 198 cases of ADK were selected for the main immunohistochemical analysis. The cases were classified according to the Gleason system and Grade Groups. The expression of AMACR, NKX3.1 and Ki-67 markers was assessed by immunohistochemistry and correlated with Grade Groups, as well as with the presence of chronic inflammation and peritumoral glandular atrophy.

Results: Increased AMACR expression (93.9% of cases) and increased Ki-67 index (>20% in 29.3% cases) were significantly correlated with high Grade Groups ($p<0.001$). Loss of NKX3.1 expression increased from Grade Group 1 to Grade Group 4, followed by a lower frequency in Grade Group 5, indicating a non-linear association with histopathological grade (p for trend <0.001). The concomitant presence of chronic inflammation and glandular atrophy was associated with high Grade Groups and with a significantly higher Ki-67 index ($p=0.001$ and $p<0.001$). Triple staining (AMACR/p63/HMWCK) showed no discordant cases in distinguishing ADK from benign lesions that mimic prostate cancer.

Conclusions: The extended immunohistochemical profile (AMACR, NKX3.1, Ki-67) provides valuable biological information correlated with tumor aggressiveness. Integrating these markers into the preoperative evaluation, along with standard histopathological evaluation and the peritumoral microenvironment, may contribute to a more accurate risk stratification. However, these findings are correlative, and their clinical applicability requires validation through further prospective studies.

Keywords: prostate cancer, AMACR, NKX3.1, Ki-67, risk stratification, immunohistochemistry