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Original Articles

Xp11 Translocation Renal Cell Carcinoma (RCC): Extended Immunohistochemical Profile Emphasizing Novel RCC Markers

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Abstract

Xp11 translocation renal cell carcinoma (RCC) harbor various *TFE3* gene fusions, and are known to underexpress epithelial immunohistochemical (IHC) markers such as cytokeratin and EMA relative to usual adult type RCC; however, their profile in reference to other IHC markers that are differentially expressed in other subtypes of RCC has not been systematically assessed. Few therapeutic targets have been identified in these aggressive cancers. We created 2 tissue microarrays (TMA) containing five 1.4-mm cores from each of 21 Xp11 translocation RCC (all confirmed by TFE3 IHC, 6 further confirmed by genetics), 7 clear cell RCC (CCRCC), and 6 papillary RCC (PRCC). These TMA were labeled for a panel of IHC markers. In contrast to earlier published data, Xp11 translocation RCC frequently expressed renal transcription factors PAX8 (16/21 cases) and PAX2 (14/21 cases), whereas only 1 of 21 cases focally expressed MiTF and only 5 of 21 overexpressed p21. Although experimental data suggest otherwise, Xp11 translocation RCC did not express WT-1 (0/21 cases). Although 24% of Xp11 translocation RCC expressed HIF-1α (like CCRCC), unlike CCRCC CA IX expression was characteristically only focal (mean 6% cell labeling) in Xp11 translocation RCC. Other markers preferentially expressed in CCRCC or PRCC, such as HIG-2, claudin 7, and EpCAM, yielded inconsistent results in Xp11 translocation RCC. Xp11 translocation RCC infrequently expressed Ksp-cadherin (3/21 cases) and c-kit (0/21 cases), markers frequently expressed in chromophobe RCC. Using an H-score that is the product of intensity and percentage labeling, Xp11 translocation RCC expressed higher levels of phosphorylated S6, a measure of mTOR pathway activation (mean H score=88), than did CCRCC (mean H score=54) or PRCC (mean H score=44). In conclusion, in contrast to prior reports, Xp11 translocation RCC usually express PAX2 and PAX8 but do not usually express MiTF. Although they may express HIF-1α, they only focally express the downstream target CA IX. They inconsistently express markers associated with other RCC subtypes, further highlighting the lack of specificity of the latter markers. TFE3 and Cathepsin K remain the most sensitive and specific markers of these neoplasms. Elevated expression of phosphorylated S6 in Xp11 translocation RCC suggests the mTOR pathway as an attractive potential therapeutic target for these neoplasms.