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Clear Cell Renal Cell Carcinoma With a Poorly Differentiated Component: A Novel Variant Causing Potential Diagnostic Difficulty

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Background

• Several variant histologic patterns of clear cell renal cell carcinoma (RCC) are well known, particularly sarcomatoid and rhabdoid features. However, we have encountered rare cases in which a high-grade adenocarcinoma not otherwise specified (NOS) pattern or urothelial carcinoma-like component would be difficult to appreciate as clear cell RCC.

Design

• We retrieved 26 tumors with histologically typical clear cell RCC juxtaposed to a high-grade non-clear cell component.

• A high-grade non-clear cell component was defined as non- sarcomatoid, non-rhabdoid areas that would be difficult to assign as renal cell in origin if viewed in isolation.

• Tumors were studied with immunohistochemistry and fluorescence in situ hybridization (FISH) or sequencing.

Results

• Median percentage of poorly differentiated component was 50% (IQR 20-70).

• All tumors showed abrupt transition from clear cell carcinoma to poorly-differentiated areas, with micropapillary (7/26; 27%), urothelial-like (10/26; 39%), and adenocarcinoma NOS features (9/26; 35%).

• Carboanhydrase IX (CA-IX) was uniformly positive in the well-differentiated component (20/20), but the poorly differentiated component showed a median positivity of 82.5% (IQR 65-100).

• The poorly differentiated component was positive for CK7 (5/19; 26%), CK20 (3/12; 25%), AMACR (7/12; 58%), PAX8 (12/15; 80%), and showed intact FH (6/6; 100%). CD20 was uniformly negative.

• Chromosome 3p loss or VHL mutation was present in 8/13 (62%), tested with either FISH (n = 9) or sequencing (n = 4).

• All tested cases were negative for TFE3 (0/11) and TFE2B (0/9) rearrangements using FISH.

• With follow-up, 5/21 (24%) patients were alive with metastatic disease and 5/21 (24%) had died of disease on follow up. One metastasis with sarcomatoid areas that would be difficult to assign as renal cell in origin if viewed in isolation.

Conclusions

• Clear cell RCC with a poorly differentiated component resembling adenocarcinoma or urothelial carcinoma is a novel source of morphologic heterogeneity that has not been previously well characterized.

• Potential pitfalls include decreased or absent CA-IX staining the high-grade component and aberrant positivity for cytokeratin 7 or 20.

• With the increasing use of renal mass biopsy and biopsies of metastatic sites for targeted therapy, pathologists should be aware of this entity and consider the possibility of clear cell RCC even for morphologically unusual tumors.