EDITORIAL

Renal cell carcinoma associated with tuberous sclerosis complex (TSC)/mammalian target of rapamycin (MTOR) genetic alterations

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The majority of hereditary tumor syndromes involve germline mutations, which effectively inactivate tumor suppressor genes (for example *TSC1* and *TSC2*), whereby cells with a bi-allelic inactivation of such genes originate tumors in a classic tumor suppressor “two-hit” paradigm. The diverse morphologic spectrum of neoplasms found in the tuberous sclerosis complex (TSC) integrates many fundamentals of cellular biology, with the *MTOR* pathway showing frequent activation, as evidenced by expression of multiple downstream targets of *MTOR* and an increased neoplastic cell size (now well known to be a functional consequence of enhanced *MTOR* activity)¹.

While angiomyolipomas and cysts are the most common renal manifestations of TSC, ~4% of patients will develop renal cell carcinoma (RCC)². Careful morphologic studies of these RCC have permitted their subdivision into three main groups: first, RCC with clear cytoplasm, papillary architecture, and prominent smooth muscle stroma; second, RCC with granular eosinophilic cytoplasm and macrocystic architecture; and third, RCC resembling the eosinophilic variant of chromophobe RCC^{3,4}. One would predict that there should be sporadic counterparts to each of these neoplasms, effected by somatic mutations in the *TSC1/2* genes in patients who do not suffer from the tuberous sclerosis complex. Identification of such neoplasms, however, has been confounded by the fact that the *TSC1/2* genes, as well as the gene coding the downstream protein mammalian target of rapamycin (*MTOR*), are mutated secondarily in ~5% of the more common subtypes of RCC, including bonafide clear cell and chromophobe RCC cases^{5,6}. Parenthetically, these mutations may be associated with clinical response to MTOR inhibitors, emphasizing their therapeutic relevance. However, in recent years and in several studies in the current issue of *Modern Pathology*, sporadic counterparts to the hereditary tuberous sclerosis complex-associated RCC that are associated with somatic *TSC/MTOR* pathway mutations have now been described.

First, representing a somatic counterpart to group one, a RCC characterized by prominent fibromuscular bands transecting acinar and tubulopapillary architecture, and clear cells with voluminous cytoplasm and well-defined cell borders⁷ has been demonstrated to harbor somatic *TSC* or *MTOR* mutations^{8,9}. Interestingly, these neoplasms demonstrate morphologic overlap with renal tumors recently described as harboring mutations in the *ELOC* (formerly known as *TCEB1*) gene at 8q21.11, in an absence of concurrent *VHL* or chromosome 3p alterations¹⁰. These neoplasms typically label for cytokeratin 7 and carbonic anhydrase IX like clear cell papillary RCC/renal angiomyoadenomatous tumor, but in contrast also label for CD10, have voluminous cytoplasm,

and lack subnuclear vacuolization. Second, corresponding to group 2, eosinophilic solid and cystic RCC (ESC RCC), characterized by solid and cystic architecture, polygonal neoplastic cells with voluminous eosinophilic cytoplasm and basophilic cytoplasmic stippling, and frequent patchy immunoreactivity for cytokeratin 20¹¹, has been shown to harbor somatic *TSC1* or *TSC2* mutations^{12–14}. While typically indolent and presenting in adult females, this neoplasm often occurs in children¹⁵ and may rarely present with metastatic disease which in one case has dramatically responded to treatment with MTOR inhibitors. Finally, corresponding to group three, a neoplasm provisionally termed “low-grade oncocytic tumor” (LOT)¹⁶ has been described and in this issue of *Modern Pathology* demonstrated to be associated with somatic *TSC1/2* gene mutations^{17–19}. These neoplasms resemble the eosinophilic variant of chromophobe RCC in that they are composed of solid areas of low-grade oncocytic cells with perinuclear halos, which label with cytokeratin 7. In contrast, however, the neoplasm typically features transitions from solid growth to elongated cords/sheaths of neoplastic cells in edematous stroma, has fewer nuclear irregularities and less well-developed perinuclear halos, and does not label diffusely for CD117. Not surprisingly, LOT shares morphologic and biomarker overlap with a subset of eosinophilic variant of chromophobe RCC described in literature with negative CD117 expression and presence of *MTOR* mutations²⁰. Apart from the sporadic and hereditary settings, LOT have now also been reported in patients with end-stage renal disease (ESRD)²¹.

Also included among chromophobe RCC-like tumors in patients with tuberous sclerosis complex are neoplasms with hyalinized stroma, prominent nucleoli, and eosinophilic cytoplasm with prominent cytoplasmic vacuoles²². Such tumors were originally described in nonsyndromic patients on morphologic grounds under the term “high-grade oncocytic tumor”²³, given their prominent nucleoli; however, these neoplasms typically lack mitoses and have thus far have had benign outcomes. Somatic *TSC* or *MTOR* mutations²⁴ have now been found in these neoplasms (reported under the term eosinophilic and vacuolated RCC). These neoplasms are recognized as an evolving entity by both the International Society of Urologic Pathology²⁵, and Genitourinary Pathology Society²⁶, and the latter has proposed the provisional term eosinophilic and vacuolated tumor (EVT). An additional study reported in this issue of *Modern Pathology* confirms the presence of somatic *TSC/MTOR* mutations in EVT²⁷.

While remarkable progress has been made over the past decade in the delineation of *TSC/MTOR*-mutation-related renal neoplasia in both of the hereditary and sporadic settings²⁸, several questions remain to be answered. One query is whether there are other distinctive RCCs that may prove to be associated with *TSC1/2* or *MTOR* gene mutations. Along these lines, a recent report

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described *TSC2* mutations in a subset of acquired cystic disease-associated RCC²⁹. Another is how frequent are *TSC1/2* or *MTOR*-mutated RCC that do not clearly fit a given category but instead have overlapping features of ESC, LOT, and/or EVT. In addition, it is currently not very clear how *TSC* related neoplasia may be affected at the phenotypic and molecular level by aberrations involving other genes from related/unrelated pathways; for example, deletions involving *TSC2* and the adjacent *PKD1* gene have been linked to a distinct subtype of *TSC* exhibiting significant cystic kidney disease³⁰. Further studies in the upcoming few years should help further clarify this fascinating area of study with a successful definition of specific genomic insults that link aberrations in *TSC* genes with a spectrum of morphologic and clinical phenotypes.

Finally, the current National Comprehensive Cancer Network as well as American Urology Association guidelines recommend these clinical criteria for genetic risk evaluation of patients with potential hereditary kidney cancer: diagnosis at age equal to or less than 46 years, bilateral or multifocal tumors, and a first degree relative with RCC. However, specific pathologic findings (such as succinate dehydrogenase deficient or Birt–Hogg–Dubé-related tumor histology) should also trigger such evaluation. Indeed, pathologists not infrequently suggest the genetic consultation and germline testing that first establishes the diagnosis of hereditary renal neoplasia in a family following examination of a renal core biopsy or resection in a proband. The expanding spectrum of *TSC*-related renal neoplasia may further expand the pivotal role pathologists play in the initial identification of hereditary renal neoplasia.

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ADDITIONAL INFORMATION

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