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Original contribution

Renal cell carcinoma, unclassified with medullary phenotype: poorly differentiated adenocarcinomas overlapping with renal medullary carcinoma☆,☆☆,★

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Summary Renal medullary carcinoma (RMC) is a highly aggressive renal cell carcinoma arising in the collecting system and requiring careful correlation with status of sickle cell trait. A panel of international experts has recently proposed provisional diagnostic terminology, *renal cell carcinoma, unclassified, with medullary phenotype*, based on encountering an extraordinarily rare tumor with RMC morphology and immunophenotype in an individual proven not to have a hemoglobinopathy. Herein, we extend this observation to a cohort of 5 such tumors, morphologically similar to RMC, lacking SMARCB1 expression by immunohistochemistry, but each without evidence of a hemoglobinopathy. The tumors arose in 4 men and 1 woman with a mean age of 44 years, occurring in 3 left and 2 right kidneys. Clinically, aggression was apparent with involvement of perinephric adipose tissue in all 5 cases, nodal metastasis in 4 of 5 cases, and death of disease in 4 of 5 cases within 3-27 months. Histologic sections showed poorly differentiated adenocarcinoma, often with solid and nested growth patterns, as well as infiltrative glandular, tubulopapillary, cribriform, or reticular growth. Rhabdoid and sarcomatoid cytomorphology was seen in a subset. All tumors showed PAX8 nuclear positivity and SMARCB1 loss, with OCT3/4 expression in 4 of 5 cases. In summary, this first series of renal cell carcinoma, unclassified, with medullary phenotype documents tumors

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with morphologic, immunophenotypic, and prognostic features of RMC occurring in individuals without sickle cell trait. Although greater biologic and molecular understanding is needed, the available evidence points to these cases representing a sporadic counterpart to sickle cell trait–associated RMC.

1. Introduction

Renal medullary carcinoma (RMC) is a highly aggressive renal cell carcinoma (RCC) known to occur in young individuals with sickle cell trait or disease. RMC was first reported by Davis et al [1] as the seventh sickle cell nephropathy in 1995 and has been regarded variably as a distinct entity [2] or subtype of collecting duct carcinoma (CDC) [2-6] in subsequent classifications. Histologically, RMCs are high-grade renal epithelial neoplasms with features of a poorly differentiated adenocarcinoma, though most distinctively showing cribriform adenoid cystic–like or reticular microcystic growth patterns, reminiscent of yolk sac tumor, associated with a desmoplastic, inflamed stroma. Morphologic distinction of RMC from CDC is often difficult, necessitating clinicopathologic correlation with regard to age, race, and evidence of hemoglobinopathy [7]. The presence of a hemoglobinopathy by clinical history; hemoglobin electrophoresis; or, at a bare minimum, in the opinion of some, histologic identification of drepanocytes in tissue sections is often considered a general prerequisite for this diagnosis. Notably, however, even the most recent 2012 International Society of Urological Pathology Vancouver classification of RCC does not explicitly state whether the presence of a hemoglobinopathy is an obligate diagnostic criterion for RMC [8].

In recent years, convergent molecular and clinicopathologic phenomena have conspired to lend further confusion to the nosology of these high-grade adenocarcinomas related to the distal nephron. First, RMC has been determined to reproducibly harbor alternations in the *SMARCB1* gene, including loss of heterozygosity [5], hemizygous deletions [9], and even loss of chromosome 22 [10]. Very recent data have also identified balanced translocations involving the *SMARCB1* locus in 4 of 4 tested cases of RMC [11], a mechanism that may explain the several prior observations of hemizygous loss of *SMARCB1* in these tumors. The prevalence of this phenomenon, as well as its specificity to RMC among RCCs (as opposed to the growing spectrum of tumors showing loss of SMARCB1 expression) [12,13], remains to be studied. Reproducible loss of SMARCB1 (INI1) expression by immunohistochemistry (IHC) has proven to be a useful adjunct for RMC diagnosis [6]. However, prior reports have also suggested that a small subset of CDCs may have loss of SMARCB1 expression [14], challenging the notion that RMC should be defined by SMARCB1 expression per se rather than the clinical scenario of sickle cell trait or disease, as originally defined. Moreover, an emerging group of fumarate hydratase (FH)–deficient RCCs [15] typically associated with hereditary leiomyomatosis–RCC syndrome [16] has also been shown to frequently demonstrate CDC-like morphology [15,17] such that the WHO classification specifically recommends their exclusion when evaluating high-grade RCCs in the RMC/CDC differential [2] by use of IHC and, preferably, genetic counseling and testing.

Given these concerns, when presented with a case showing RMC morphology and immunophenotype (ie, loss of SMARCB1 expression) arising in an individual proven not to harbor sickle cell trait, we approached an international panel of 20 experts regarding the diagnostic criteria they use for RMC and how they would approach such a case in a context of rigorous exclusion of hemoglobinopathy [18]. Strikingly, no consensus was reached regarding the necessity for evidence of sickle cell trait or disease as an obligate criterion for RMC diagnosis, with similar numbers specifically endorsing requirement of sickle cell trait for RMC (~44%) and willingness to consider the diagnosis of RMC based on morphology and immunophenotype alone (~56%) even if hemoglobinopathy were excluded. Indeed, we note that this subset of tumors could be viewed diagnostically in at least 2 different ways. One could classify these as variants of CDC or unclassified renal cell carcinoma that demonstrate an RMC phenotype, including morphology, loss of SMARCB1, and expression of OCT3/4 (POU5F1), holding the clinical criterion of hemoglobinopathy as paramount only for RMC. Alternatively, one could very reasonably argue that it is the morphology, immunophenotype, and/or molecular aberration that are paramount and that such a carcinoma should be designated as RMC based on these features alone (ie, even in the absence of a hemoglobinopathy), presuming that these features are likely reflective of the underlying biology.

In the end, the panel of experts surveyed, although lacking consensus prospectively, was able to agree to propose the provisional term *renal cell carcinoma, unclassified, with medullary phenotype* (RCCU-MP) for such tumors with appropriate cytomorphology, loss of SMARB1 expression, and the absence of a hemoglobinopathy while additional experience accrued. This provisional term and its diagnostic scenario, though not adopted as a formal category of RCC, is described in the RMC chapter of the 2016 WHO classification of kidney tumors [2]. Certainly, much study will be needed prospectively to characterize these tumors, define their spectrum, and determine how they would be best classified and clinically managed.

Herein, we aim to present the first piece of this puzzle. We describe clinical and morphological features of 5 carefully characterized cases of RCCU-MP, cases that appear morphologically typical for RMC and show loss of SMARCB1 by IHC but do not have any evidence of hemoglobinopathy by history, laboratory findings, or histology.