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Collecting Duct Carcinoma Versus Renal Medullary Carcinoma

An Appeal for Nosologic and Biological Clarity

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Collecting duct carcinoma was recognized as a distinctive type of renal cell carcinoma in 1986 by Fleming and Lewi[1,2] on the basis of a description of 6 cases of high-grade, invasive adenocarcinoma, arising in the renal collecting system and showing characteristic tubulopapillary growth associated with prominent stromal reaction.[2–4] Review of published series of collecting duct carcinomas shows a male predominance of ~2:1, a laterality favoring the right kidney of ~2:1, and an aggressive clinical course with survival of ~50% at 3 years.[5–7] Recent efforts have addressed the difficulty of distinction of collecting duct carcinoma from urothelial carcinoma of the upper tract, including by the use of immunohistochemistry.[8,9] To encourage uniformity in this diagnosis, the newly reported International Society of Urological Pathology (ISUP) Vancouver Classification[10] emphasizes diagnostic criteria, including the following: "(1) at least some of the lesion involves the medullary region; (2) there is a predominant formation of tubules; (3) a desmoplastic stromal reaction should be present; (4) cytologic features are high grade; (5) growth

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pattern is infiltrative; and (6) there is an absence of other typical renal cell carcinoma subtypes or urothelial carcinoma."

Renal medullary carcinoma was first described by Davis et al[11] in 1995, on the basis of an observation of 34 cases arising, with a single exception, in individuals with sickle cell trait. Recent series confirm that this poorly differentiated adenocarcinoma occurs most frequently among the young, with the mean age in the third decade, marked male predominance (> 2:1), right-sided laterality (> 2:1), high stage at presentation, including nodal or visceral metastasis in >50% of cases, and exceptionally poor survival.[7,12–14] Evidence of sickle cell trait, disease, or related hemoglobinopathy, whether by history taking, hemoglobin electrophoresis, or histologic identification of drepanocytes, is apparent in the vast majority of cases.[7,12–16] Histologic studies have characterized the high-grade, poorly differentiated appearance of the invading glands in medullary carcinoma, which frequently show a reticular and cribriform appearance and infiltrative growth eliciting desmoplasia and stromal inflammation; a subset of cases may also show rhabdoid cytomorphology or tubular/tubulopapillary architecture.[7,14,16] Renal medullary carcinomas show immunohistochemical loss of expression of the nuclear transcriptional regulator SMARCB1 (INI1), encoded on chromosome 22.[16–19] Molecular studies have correlated this finding to loss of heterozygosity[16] or hemizygous deletions[19] at the *SMARCB1* locus, although loss of chromosome 22 has also been observed.[12] Recent data suggest that acquisition of expression of the stem cell marker, POU5F1 (herein, OCT3/4), may also be diagnostically helpful.[15] For that matter, infrequent cases of sickle cell trait–associated renal carcinoma, showing amplification of the kinase *ABL*,[20] have been identified, as have cases with fusions between the kinase, *ALK*, and the gene *VCL*,[21–23] which are considered an "Emerging/Provisional New Tumor Entity" under the ISUP Vancouver Classification. Although authors have postulated a relationship between renal medullary carcinoma and collecting duct carcinoma,[2,3,7] the question of whether or not the specific clinical setting of sickle cell trait or disease is requisite to make the diagnosis was not addressed in the ISUP Vancouver Classification of Renal Neoplasia itself[10] or at the consensus conference[24] held concurrently at the 2013 Meeting of the United States and Canadian Academy of Pathology.

We were spurred to revisit this issue by a case we reviewed in consultation, of a high-grade adenocarcinoma, confined to the left kidney without metastasis at the time of resection, which arose in a white female in her twenties confirmed to have normal hemoglobin by electrophoresis. The morphology was of a high-grade, widely infiltrative adenocarcinoma, centered in the collecting system, with variable, tubular, nested, and cribriform architecture, sclerosing to myxoid stromal reaction, and perineural invasion (Figs. 1A–D). The lesion had expression of keratins and PAX8, consistent with a renal primary (not shown). Nuclear expression of SMARCB1 was uniformly lost, whereas OCT3/4 showed a subset of positive nuclei (Figs. 1D–F). As the World Health Organization[4] and ISUP classifications[10] do not address how to classify such a case, we informally surveyed a panel of 20 experts, leaders, and prior collaborators in kidney tumor pathology as to their diagnostic approach to such a case. We asked how they would diagnose such a case, and we asked whether a relevant hemoglobinopathy was an obligate diagnostic criterion for medullary carcinoma or whether immunomorphology was sufficient for the diagnosis.[11] We tabulated deidentified responses, revealing the following breakdown by diagnosis: renal medullary carcinoma (30%), collecting duct carcinoma (15%), renal cell carcinoma, unclassified (15%), ambiguous/descriptive diagnosis (30%), or insufficient experience (10%). Eighteen colleagues addressed our query regarding whether, to them, sickle cell trait was generally a required diagnostic criterion, with 44% in the affirmative, and 56% in the negative. We conclude that a consensus does not exist as to whether evidence of sickle cell trait or disease is a required criterion for renal medullary carcinoma diagnosis.

We submit that either position is eminently arguable. The trend in pathology is increasingly to guide or sometimes establish diagnosis by molecular status, a development reflected by the ISUP Vancouver Classification that defines entities such as Xp11 or t(6;11) translocation renal cell carcinomas by translocation status or hereditary leiomyomatosis renal cell carcinoma syndrome–associated renal cell carcinoma by *fumarate hydratase* mutation status.[10] Whether collecting duct and medullary carcinomas are a spectrum, with the medullary variant at the more aggressive end, has been extensively debated.[2,3,7,11,25,26] Thus, it is very reasonable to consider defining renal medullary carcinoma as a variant of collecting duct carcinoma showing loss of expression of SMARCB1[9,16,17,19] or even induction of OCT3/4[15] by immunohistochemistry.

In contrast, the argument to separate renal medullary carcinoma from collecting duct carcinoma and define it by the clinical setting dates back to the original Davis et al[11] description, literally as a "sickle cell nephropathy," deliberately separating it from collecting duct carcinoma. This observation continues through larger series[12,16] and interinstitutional clinicopathologic comparisons of these carcinomas,[7] verifying the aggressiveness of renal medullary carcinoma. Against definition of renal medullary carcinoma by loss of SMARCB1 nuclear immunoreactivity, recent experience identifies focal/weak expression of this marker in 2/6 collecting duct carcinomas in 1 study[9] and complete (15%) or decreased (another 15%) expression, with no difference in survival by SMARCB1 expression, in another cohort of 20 cases of collecting duct carcinoma.[25] Our recent case, which would be renal medullary carcinoma by a SMARCB1 expression loss criterion or collecting duct carcinoma by clinical setting criterion, underscores the problem. Our case occurred in a patient of the less frequent sex and laterality of kidney for either tumor type, while showing lack of the locally advanced or metastatic disease at presentation more characteristic of medullary carcinoma.

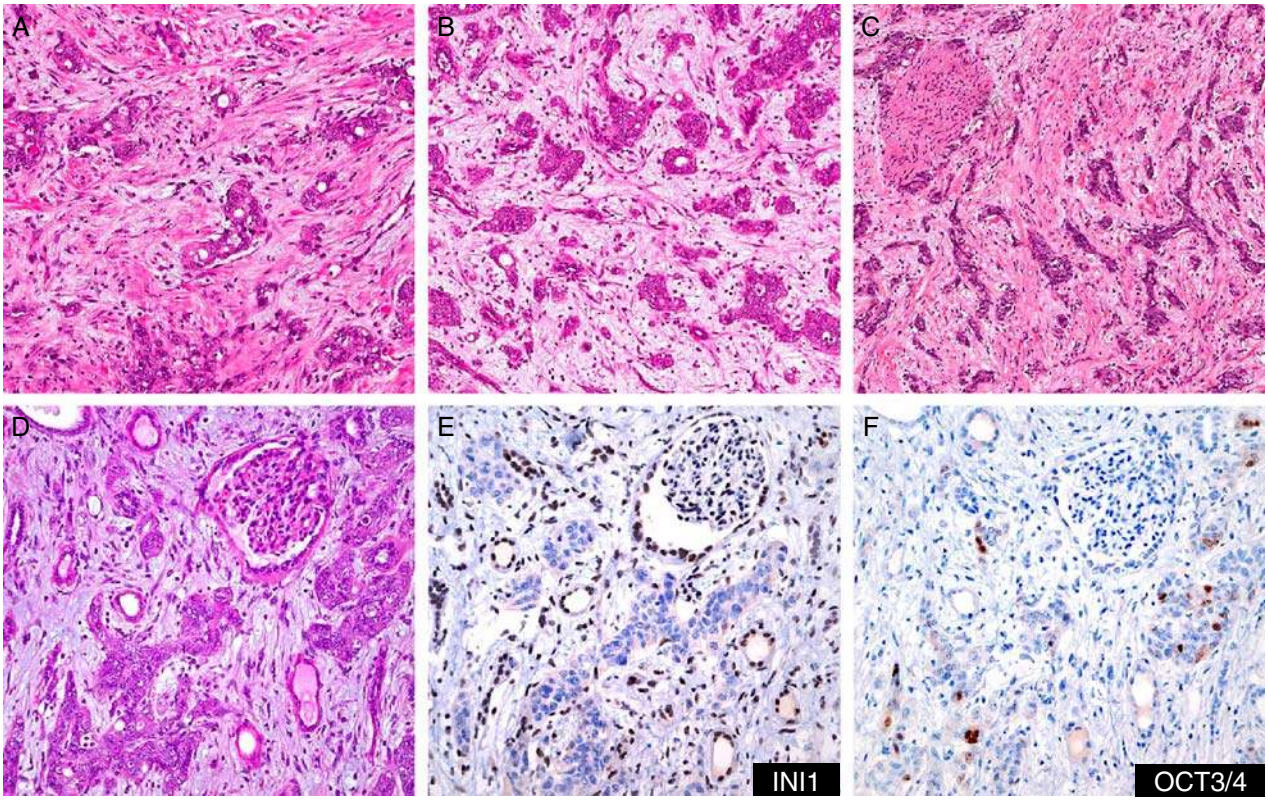

FIGURE 1. Morphology and immunophenotype of the index case. A–C, Representative micrographs showing a poorly differentiated adenocarcinoma with tubular and cribriform morphology and inflamed desmoplastic stroma (A), with myxoid change (B), and perineural invasion (C, upper left). D–F, Micrograph and paired immunostains of a focus of carcinoma invading cortical renal parenchyma adjacent to glomerulus. SMARCB1/INI1 expression is lost while scattered nuclei show OCT3/4 positivity.

Thus, we propose that nearly 30 years after recognition of collecting duct carcinoma and 20 years after renal medullary carcinoma, it is time to begin to address this conundrum, even if provisionally, in advance of revision of the World Health Organization "Blue Book."[4] Although further studies are necessary to understand the relationship between these cancers, we recommend that *collecting duct carcinoma* be defined as proposed in the ISUP Vancouver Classification and outlined above.[10] For *renal medullary carcinoma*, we propose that it be defined as originally proposed by Davis and colleagues, on the basis of both appropriate histology *and* evidence of sickle cell trait or disease, preferably including hemoglobin electrophoresis. Finally, to address the dilemma of cases of high-grade renal adenocarcinomas showing morphology, immunophenotypic, or molecular features characteristic of medullary carcinoma but in a patient without evidence of hemoglobinopathy, we propose the term *unclassified renal cell carcinoma with medullary phenotype*. With this diagnosis, we recommend inclusion of comments with respect to the (1) clinical setting, that is, lack of evidence of sickle cell disease, trait, or related hemoglobinopathy, and (2) description of features that are present (morphology, eg, cribriform, myxoid, reticular, rhabdoid; immunohistochemistry, including any data for OCT3/4, SMARCB1, or even ALK; and molecular, including increasingly available genetic or sequencing data). This approach will allow prospective accrual of these data points and will help patients, clinicians, and researchers understand our diagnoses going forward. With emerging technologies as tools, coupled with standardized terminology, we may be able to achieve meaningful definitional criteria regarding these tumors when we revisit "*Vancouver*."

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