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Original contribution

Renal cell carcinoma in kidney allografts: histologic types, including biphasic papillary carcinoma ☆

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Summary Kidney transplant recipients are at increased risk for malignancy, with about 5% incidence of cancer in native end-stage kidneys. Carcinoma in the renal allograft is far less common. Prior studies have demonstrated a propensity for renal cell carcinomas (RCCs) of papillary subtypes in end-stage kidneys, and perhaps in allograft kidneys, but most allograft studies lack detailed pathologic review and predate the current classification system. We reviewed our experience with renal carcinoma in kidney allografts at 2 academic centers applying the International Society of Urological Pathology classification, informed by immunohistochemistry. The incidence of renal allograft carcinoma was about 0.26% in our population. Of 12 allograft carcinomas, 6 were papillary (50%), 4 were clear cell (33%), 1 was clear cell (tubulo)papillary, and 1 chromophobe. Two of the papillary carcinomas had distinctive biphasic glomeruloid architecture matching the newly named "biphasic squamoid alveolar" pattern and were difficult to classify on core biopsies. The 2 cell types had different immunophenotypes in our hands (eosinophilic cells: RCC−/CK34betaE12+ weight keratin +/cyclin D1+; clear cells: RCC+/cytokeratin high molecular weight negative to weak/cyclin D1−). None of the patients experienced cancer recurrences or metastasis. Our study confirms the predilection for papillary RCCs in kidney allografts and highlights the occurrence of rare morphologic variants. Larger studies are needed with careful pathologic review, which has been lacking in the literature.

1. Introduction

Transplant recipients are at increased risk for malignancy, most often attributed to immunosuppression [1-5]. Kidney cancer is increased 5- to 15-fold compared with the general population [1-5], and 1.4- to 4-fold compared with patients listed for transplant [1,4]. Historic registry data reported that kidney cancer accounted for 5% of malignancies in transplant recipients, with 90% of those cancers arising in native kidneys and 10% in the kidney allograft itself [6-9]. Although tumors in native end-stage kidneys are far more common, a recent comprehensive literature review identified 201 reported renal allograft tumors and calculated an incidence of 0.18% [10]; single-center studies have reported 0.2% to 0.5% incidence [7-9,11-15]. The rates can be compared with an estimated 1.5% in the dialysis population [8,16-19].

Special histologic subtypes of renal cell carcinoma (RCC) recently described in end-stage native kidneys include acquired cystic disease–associated RCC and clear cell (tubulo)papillary carcinoma [16,20-22]. Studies of renal carcinomas arising in allograft kidneys have generally reported a higher-than-expected rate of papillary carcinomas, but

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these have not included rigorous characterization of tumor subtype, or have preceded widespread recognition of clear cell (tubulo)papillary carcinoma and other variants [5,10,23]. We reviewed our experience with renal epithelial tumors in kidney allografts at 2 academic institutions with attention to contemporary subclassification, assisted by immunohistochemistry.

2. Materials and methods

2.1. Patients and cases

This study received institutional review board approval. The pathology files of Oregon Health & Science University and Stanford University (2000-2015) were searched for kidney allograft specimens containing RCC, including biopsies, partial nephrectomies, and allograft nephrectomies. Urothelial tumors, angiomyolipomas, and vascular lesions were excluded. Slides were reviewed by 2 renal/genitourinary pathologists with attention to tumor subtype, as classified by the updated International Society of Urological Pathology (ISUP) Vancouver/2016 World Health Organization classification [21,22] and ISUP grade [24]. A representative tissue block was selected for additional immunostaining as described below. Additional tumor and transplant parameters were abstracted from the pathology report and medical record (tumor size, time since transplant, patient age, cause of end-stage renal disease, allograft function, serum creatinine, follow-up).

2.2. Immunohistochemistry

Four-micron unstained paraffin sections were prepared and stained with routine methods on Ventana (Ventana, Tucson AZ), or Leica Bond (Leica, Buffalo Grove, IL) autostainers with the following antibodies: AMACR (13H4, α-methylacyl-coenzyme A racemase; Biocare, Concord, CA), CD10 (clone 56C6; Cell Marque (Rocklin, CA) or Leica), cytokeratin 7 (CK7; clone OV-TL 12/30; Cell Marque or Dako (Carpenteria, CA)), high-molecular-weight (HMW) keratin (clone 34βE12; Cell Marque), RCC (PN-15; Cell Marque), and cyclin D1 (SP4; Thermo Fisher Scientific, Waltham, MA). Antibody detection was performed with Ventana Ultraview or Leica Bond polymer-based detection kits. Stained slides were scored for the presence and distribution of positive immunostaining.

3. Results

3.1. Patients and tumors

We reviewed 12 renal carcinomas from 11 kidney allografts from our 2 academic centers. Over the last 20 years, an estimated 4200 transplants were performed combining volumes for both centers, for an incidence of RCC in allografts of about 0.26%.

The morphology and immunophenotype of renal allograft carcinomas were evaluated in 10 surgical specimens (2 with prior biopsy) and 2 biopsy specimens (Table 1). Carcinomas arose in 4 failed allografts and 6 functional allografts, with status of 1 graft unknown. Tumors in failed allografts were treated by allograft nephrectomy. Functioning allografts underwent partial nephrectomy or, in 1 patient (no. 7), core biopsies with imaging surveillance. Tumors occurred at an average of 14.7 years after transplant (range, 9-20 years).

3.2. Tumor subclassification and immunohistochemical results

Based on morphologic and immunohistochemical features, the 12 tumors were classified according to the ISUP Vancouver classification as follows: conventional clear cell carcinoma, 4; papillary, 6 (2 with distinctive biphasic morphology); clear cell (tubulo)papillary carcinoma, 1; and chromophobe, 1 (Table 1; Figs. 1 and 2).

3.2.1. Clear cell (tubulo)papillary RCC

The clear cell (tubulo)papillary carcinoma (no. 1) had small cystic areas, but was mostly occupied by clear cells with central to apically polarized nuclei lining branching tubular and focal papillary structures (Fig. 1). The following immunophenotype helped to confirm the classification: RCC−/CD10−/CK7+/AMACR−/CK 34βE12+ (Table 1).

3.2.2. Biphasic papillary RCC

Two of the papillary tumors had distinctive biphasic papillary architecture. Tumors 2 and 3 were well circumscribed, mostly encapsulated mass lesions of 4.1 and 2.3 cm, respectively. Carcinomas comprised 2 cell types arranged in an organized pattern. Islands of cells with relatively abundant eosinophilic cytoplasm loosely occupied glandular/cystic spaces with vaguely glomeruloid architecture, although rather discohesive. Emperipolesis was identified in rare eosinophilic cells. These eosinophilic "squamoid" cells were surrounded by a population of smaller cells with scant clear cytoplasm (Fig. 2) and smaller nuclei without nucleoli forming glandular/alveolar spaces of varying sizes, and rarely small papillae. Collections of foamy histiocytes were focally prominent. The immunophenotype of these 2 epithelial populations was also divergent (Table 1). In both cases, the eosinophilic cells were negative for RCC and strongly positive for both CK7 and HMW keratin (34βE12). The clear cells were positive for RCC and stained more weakly for keratins as compared with the eosinophilic cells (Table 1). Cyclin D1 was positive in the nuclei of many of the eosinophilic cells, but not in the small clear cells.

3.2.3. Papillary RCC

Of the 4 other papillary carcinomas, all contained numerous cells with clear cytoplasm. Three papillary carcinomas