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Pathologic and clinical characteristics of early onset renal cell carcinoma☆

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Summary The majority of renal cell carcinomas (RCCs) occur within the 7th decade of life, uncommonly arising in adults ≤46 years. We reviewed the clinicopathologic features of early onset RCC and evaluated the role of immunohistochemistry (IHC) in potentially identifying diagnoses of newly recognized RCC subtypes that may have been previously misclassified. A retrospective review was performed from 2011–2016 for cases of RCC. Early onset RCC was defined as ≤46 years of age. Clinicopathologic findings and hematoxylin and eosin (H&E) slides were reviewed on early onset RCC patients. IHC was performed on all cases previously diagnosed as unclassified or papillary. Clinicopathologic findings were compared to a control group of RCC patients >46 years over the same time period. We identified 98/598 (16.4%) early onset RCCs. The median age in the early onset RCC and control group was 38.4 and 62.8 years, respectively. The early onset RCC group contained 33/96 (34.3%) females and 63/96 (65.6%) males, including 52/96 (54.2%) whites, 39/96 (40.6%) African Americans, 4/96 (4.2%) Hispanics, and 1/96 (1%) Asian. Nonwhites were significantly more likely to develop early onset RCC ($P = .004$). Early onset RCCs included 52% clear cell, 28.6% papillary, 8.2% unclassified, 5.1% chromophobe, 3.1% clear cell papillary(CCP), and 3 other rare tumors. Six unclassified and 26 papillary RCCs had tissue available for IHC. Two of 6 (33.3%) unclassified RCCs were reclassified (1 CCP, 1 Xp11 translocation). One of 26 (3.8%) papillary RCCs was reclassified as CCP. Early onset RCCs were more likely to occur in nonwhites ($P = .004$), be lower stage ($P = .03$), and undergo partial nephrectomy ($P = .002$). Few unclassified and papillary tumors were reclassified with IHC.

1. Introduction

Renal cell carcinoma (RCC) accounts for roughly 90% of all malignant kidney tumors and an estimated 2% to 3% of all primary malignancies worldwide [1]. In the United States, RCC represents 3% to 6% of adult malignancies with 64 000

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new cases annually [2]. Despite the increased incidence, there has been an improvement in survival over the last 50 years. This trend is attributed to therapeutic advances and earlier detection of tumors via imaging [3]. RCC is twice as common in men as women, and according to the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) registry, the majority of RCC cases occur within the 6th and 8th decades of life with a median age at diagnosis of 64 years [2]. In general, the disease is rare in children and uncommon in adults under 46 years of age [4].

RCC encompasses a diverse spectrum of histological subtypes, with clear cell RCC being the most common, followed by papillary RCC. Unclassified RCCs comprise approximately 5% of tumors in large series [5,6]. A growing number of RCCs are being identified in association with inherited germline mutations, many of which were previously classified as papillary or unclassified subtypes. Several recently recognized RCC subtypes with a genetic link include Xp11 translocation RCC (associated with *TFE3* gene fusions), hereditary leiomyomatosis and RCC-associated RCC (associated with *fumarate hydratase* gene mutations), and succinate dehydrogenase (*SDH*)–deficient RCC. Hereditary RCC is now thought to account for approximately 5% to 8% of primary kidney malignancies [7]. While a younger age of onset is associated with a worse prognosis in other tumor types (eg, colon cancer), the behavior of RCC arising in younger adults is not well established [4,8,9].

Currently, data regarding the early onset RCC patient population is limited. Our aim was to investigate the clinical and pathologic characteristics within this unique subset of patients with RCC. In addition, we sought to re-review these tumors, utilizing newly available immunohistochemical (IHC) studies, to potentially identify newly recognized RCCs that may have been previously misclassified.

2. Materials and methods

An institutional review board–approved retrospective search of the surgical pathology database was performed from 2011 to 2016 for all cases of RCC. We used the age criteria for early onset RCC, as defined by Shuch and colleagues, as ≤46 years of age at the time of initial diagnosis [10]. The original hematoxylin and eosin (H&E)–stained slides were re-reviewed by a single GU fellowship–trained pathologist. The histologic subtype, grade, size, margin status, and the presence or absence of necrosis and/or sarcomatoid features were examined. Tumor grade was assigned based on the International Society of Urological Pathology (ISUP) grading criteria [11]. An in-depth retrospective chart review was performed on all early onset RCC patients, with a focus on the clinical findings. The specific clinical characteristics included gender, race, family history of cancer, laterality of tumor, comorbidities, previous medical history, known RCC risk factors, treatment modality, medications, and disease recurrence. The clinical and pathologic findings of patients in the early onset RCC group were compared to RCC patients older than 46 years of age over the same time period.

After re-review of H&E-stained slides, all unclassified and papillary early onset RCCs with tissue available underwent further IHC studies. Representative samples from each case were stained with SDHB (Abcam, Cambridge, MA, USA; 1:00 dilution), FH (Santa Cruz Biotechnology, Dallas, TX, USA; 1:200 dilution), TFE3 (Cell Marque, Rocklin, CA, USA prediluted), and cathepsin K (Abcam, 1:800). CK7 (Ventana, Tucson, AZ, USA) and CAIX (Cell) IHC stains were additionally utilized for tumors with morphology suspicious for clear cell papillary RCC.

Statistical analysis was performed using one-way analysis of variance, specifically to assess the significance of the difference in factors between the early onset and control groups. A $P < .05$ was considered significant and all tests were 2-tailed.

3. Results

We identified 598 RCCs in 576 patients. In the early onset RCC group, 98/598 (16.4%) RCCs occurred in 96 patients. The remaining 500/598 (83.6%) RCCs occurred in 480 patients older than 46 years, which comprised the control group. The clinical and pathologic characteristics of the early onset RCC group are listed in Table 1. The median age of patients in the early onset RCC group compared to our control group was 38.4 ± 7.0 years and 62.8 ± 8.7 years, respectively. There were 33/96 (34.3%) females and 63/96 (65.6%) males in the early onset group. In the control group, there were 176/480 (36.7%) females and 304/480 (63.3%) males. The early onset group included 52/96 (54.2%) whites, 39/96 (40.6%) African Americans, 4/96 (4.2%) Hispanics, and 1/96 (1%) Asian. In the control group, there were 335/480 (69.8%) whites, 139/480 (30.0%) African Americans, 3/480 (0.6%) Hispanics, 2/480 (0.4%) Other, and 1/480 (0.2%) Asians. Nonwhites were significantly more likely to develop early onset RCC than whites ($P = .004$; Table 2).

The original RCC histologic diagnosis in the early onset group included 51/98 (52%) clear cell, 28/98 (28.6%) papillary, 8/98 (8.2%) unclassified, 5/98 (5.1%) chromophobe, 3/98 (3.1%) clear cell papillary renal cell carcinoma, 1/98 (1%) multilocular cystic renal cell neoplasm of low malignant potential, 1/98 (1%) acquired cystic kidney disease–associated RCC, and 1/98 (1%) well-differentiated neuroendocrine tumor. Six of eight (75%) unclassified RCCs and 26/28 (92.9%) papillary RCCs had tissue available for IHC studies. Two out of six (33.3%) unclassified RCCs were reclassified. Both tumors had clear cell and papillary features. One showed positivity for cathepsin K and TFE3, consistent with an Xp11 translocation RCC (Fig. 1). The other previously "unclassified" tumor showed strong diffuse positivity for CK7 and CAIX, which along with its morphology, was consistent with clear cell papillary RCC (Fig. 2). One of 26 (3.8%) previously