Human Pathology (2017) 66, 152–158

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

GATA3 as a valuable marker to distinguish clear cell papillary renal cell carcinomas from morphologic mimics☆,☆☆

Jose G. Mantilla MD[a,*], Tatjana Antic MD[b], Maria Tretiakova MD, PhD[a]

[a]Department of Pathology, University of Washington Medical Center, Seattle, WA 98105, USA
[b]Department of Pathology, University of Chicago Medical Center, Chicago, IL 60637, USA

Received 20 April 2017; revised 7 June 2017; accepted 29 June 2017

Keywords:
Renal cell carcinoma;
GATA3;
Clear cell papillary renal cell carcinoma;
Genitourinary pathology;
Renal neoplasms;
Immunohistochemistry;
Tissue microarray

Summary Clear cell papillary renal cell carcinoma (CCPRCC) is a low-grade, indolent neoplasm with no reported cases of death from disease or metastasis. These lesions can show clinical, morphologic, and immunophenotypic overlap with several aggressive forms of renal cell carcinoma (RCC), including clear cell RCC, translocation RCC, and papillary RCC with cytoplasmic clearing. Given the difference in behavior, it is important to reliably separate these entities. We retrospectively reviewed 47 tumors from 45 patients with morphologic features of CCPRCC. All cases were stained against cytokeratin 7 (CK7), carbonic anhydrase IX (CAIX), and GATA3. Cases inconsistent with CCPRCC were reclassified. In addition, we stained tissue microarrays with 103 typical clear cell RCCs and 62 papillary RCCs, each in triplicate. Twenty-five cases were morphologically and immunophenotypically consistent with CCPRCC; all of them showed diffuse CK7 expression and cup-like reactivity with CAIX. Of these, 19 (76%) showed strong nuclear reactivity for GATA3. Although some non-CCPRCC neoplasms showed at least partial CK7/CAIX coexpression, none were immunopositive for GATA3. All background normal kidneys studied showed GATA3 expression in the distal tubules, collecting ducts, and retention cysts of the distal nephron. On follow-up, none of the patients with CCPRCC had recurrences or metastasis. Sensitivity and specificity for GATA3 staining in the diagnosis of CCPRCC were 76% and 100%, with positive and negative predictive values of 100% and 74%. In conclusion, GATA3 is specific and sensitive for CCPRCC and can be used for accurate distinction from its main mimickers. Coexpression of GATA3 and CK7 in most CCPRCC provides evidence of their origin from distal nephron.

1. Introduction

Clear cell papillary renal cell carcinoma (CCPRCC) is a recently described, relatively uncommon renal neoplasm characterized by an indolent biological behavior, with a tendency to locally recur, but no documented cases of aggressive behavior or metastatic disease [1]. Although originally described in

☆ Presented in an abstract form at the annual meeting of the United States and Canadian Academy of Pathology, San Antonio, TX, March 4-10, 2017.
☆☆ Disclosures: None.
* Corresponding author at: 1959 Pacific St, Box 357470, Seattle, WA 98195.
E-mail address: mantilla@uw.edu (J. G. Mantilla).

http://dx.doi.org/10.1016/j.humpath.2017.06.016
0046-8177/

individuals with end-stage renal disease (ESRD), it has been also seen in otherwise healthy kidneys [1-3]. Its typical morphologic features are those of a well-circumscribed lesion composed of tubules and papillary structures lined by cuboidal to columnar cells with clear cytoplasm and low-grade nuclei showing characteristic linear alignment with apical distribution resembling endometrium in secretory phase or "piano keys".

The most important morphologic differential diagnoses of CCPRCC are low-grade clear cell renal cell carcinoma (CCRCC), papillary renal cell carcinoma (PRCC) with prominent cytoplasmic clearing, and MiTF/TFE-family translocation-associated carcinomas, which can be very aggressive neoplasms with a tendency to metastasize even several years from the original time of diagnosis. Therefore, accurately distinguishing between indolent CCPRCC and these more aggressive tumors is of vital importance in terms of treatment and long-term prognosis [4]. In cases in which the morphologic features are not clear to distinguish CCPRCC from these more aggressive neoplasms, combined immunoreactivity with cytokeratin 7 (CK7) and carbonic anhydrase IX (CAIX), along with negativity for TFE3, P504S, and CD10, can aid in the recognition of CCPRCC [5,6]. However, there is significant overlap between the morphologic and immunophenotypic features of CCPRCC and other recently described subtypes of RCC, including those characterized by monosomy 8 and/or TCEB1 loss, renal adenomyomatous tumors (RATs), tuberous-sclerosis associated RCCs, and unclassified RCC. This constitutes an important diagnostic pitfall, which can lead to unnecessarily aggressive treatment [6,7].

Given the indolent (and possibly completely benign) nature and wide clinical and morphologic differential diagnosis of CCPRCC, it is of utmost importance to accurately diagnose these tumors to prevent unnecessary therapy as well as to provide patients and clinicians with adequate prognostic information. In this study, we evaluate the utility of GATA3, a widely expressed transcription factor that is crucial to the development of the collecting system [8], as an immunohistochemical marker for the diagnosis of CCPRCC and in contrast to those entities in its differential diagnosis.

2. Materials and methods

2.1. Case selection

With prior approval from the institutional review boards from both institutions, records from the Anatomic Pathology Laboratory Information Systems were reviewed, identifying 47 tumors with histologic features suggestive of CCPRCC (ie, low-grade neoplasms with a tubulopapillary architecture, abundant clear cytoplasm, and apically oriented nuclei) in 24 resection specimens and 1 needle core biopsy. Cases with the morphologic features of CCPRCC that also showed positive membranous and cytoplasmic staining for CK7 and cup-like staining with CAIX, performed as described below, were classified as CCPRCC. The remainder of cases, in which the morphologic, immunophenotypic, or cytogenetic findings were inconsistent with CCPRCC, were reclassified accordingly. In cases with overlapping features, additional immunohistochemical stains, including CD10, P504S, 34βE12, Vimentin, and TFE3, were performed to clarify the diagnosis.

Clinical and demographic characteristics of all patients were recorded, as well as tumor size and follow-up information, including the presence or absence of recurrent disease, metastasis, and death of disease or due to other causes. The length of follow-up was variable, ranging between 1 and 60 months (median, 23 months).

In addition, 103 cases with a diagnosis of classic CCRCC and 62 with a diagnosis of PRCC were stained for GATA3 in tissue microarray using the technique described below, with each case represented in triplicate for comparison.

2.2. Immunohistochemical stains

The immunostaining was performed in a College of American Pathologists-certified diagnostic immunohistochemistry laboratory, according to the standardized protocol as previously described [9]. In brief, the unstained 4-μm sections were deparaffinized on the automated immunostainer (Bond III; Leica Biosystems, Nussloch, Germany). Three applications of a proprietary Bond Dewax solution were followed by 3 applications of 100% ethanol and then 3 applications of Bond Wash solution. Antigen retrieval was performed on Bond III using ER2 buffer (pH 9.0) for 20 minutes. After rinsing and endogenous peroxidase blocking, a post-primary IgG linker was applied followed by several rinses with the Bond Wash solution and a deionized water rinse. The slides were incubated for 15 minutes with mouse monoclonal antibodies against CK7 (clone OV-TL, Dako, Glostrup, Denmark, M7018, dilution 1:100), CAIX (clone TH22, Leica Biosystems, cat. #NCL-L-CAIX, dilution 1:25), or GATA3 (clone L50-823, Biocare Medical, Pacheco, CA, cat. #PM405AA, ready to use). After multiple rinses with Bond Wash solution, a polymer anti-mouse or anti-rabbit poly-HRP-IgG was applied, and slides were incubated for 8 minutes with polymer detection reagent (Bond Polymer Refine Detection Kit, Leica). This was followed by multiple rinses, reacted with 3,3′-diaminobenzidine (DAB) tetrahydrochloride chromogen for 10 minutes, and counterstained with hematoxylin for 5 minutes.

3. Results

Forty-seven cases were identified in 45 different patients, of which 25 (in 24 patients) were morphologically and immunophenotypically consistent with CCPRCC, including 1 patient with synchronous bilateral CCPRCC. The remaining 22 cases were reclassified as follows: 8 CCRCCs with