Int J Clin Exp Pathol 2015;8(10):13590-13595
www.ijcep.com /ISSN:1936-2625/IJCEP0015058

*Case Report*

# Chromophobe renal cell carcinoma, eosinophilic variant with papillary growth: a case report

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Received August 25, 2015; Accepted September 25, 2015; Epub October 1, 2015; Published October 15, 2015

**Abstract:** We report the case of an 80-year-old man who presented with pathologically diagnosed chromophobe renal cell carcinoma composed of eosinophilic cells with partial papillary growth. The patient had a 2.5 cm diameter renal mass incidentally detected by abdominal ultrasound examination. Laparoscopic left partial nephrectomy was performed under a diagnosis of left renal tumor. Histopathology demonstrated uniform eosinophilic cuboidal cells growing with a partially papillary pattern: differential diagnosis of oncocytoma, papillary renal cell carcinoma, or oncocytic papillary renal cell carcinoma was necessary. Immunohistochemical staining with anti-monoclonal antibody 31 and -CD82 antibody, and choroid iron staining, were positive. Cytogenetic analysis by comparative genomic hybridization showed gains of chromosomes 1p, 9q, 19q, 20, and 21q, and losses of chromosomes 1p and q, 2q, 6q and 7q, leading to diagnosis of chromophobe RCC. We describe differential diagnosis for chromophobe renal cell carcinoma, eosinophilic variant, growing in a papillary fashion in the kidney.

**Keywords:** Renal cell carcinoma, chromophobe, eosinophilic, oncocytoma, papillary

## Introduction

Chromophobe renal cell carcinoma (RCC) is a rare variety of kidney neoplasm that represents approximately 5% of RCC. It is a clinically identified malignant neoplasm of kidney with an earlier stage and a more favorable prognosis than conventional clear-cell RCC. Chromophobe RCC was first described in 1985 by Thoenes and Colls [1], who depicted 12 cases of renal tumor consisting of chromophobe cells showing slightly opaque or finely reticular cytoplasm with hematoxylin and eosin staining. There are three different variants of chromophobe RCC. First, the classic type, which has more than 80% pale cells, is associated with necrosis and sarcomatoid changes potentiating high growth and metastases. Second, the eosinophilic variant, which consists of more than 80% eosinophilic cells, shares certain characteristics with oncocytomas, and shows nested, alveolar, or sheet-like architecture with eosinophilic granularity, perinuclear clearing, and peripheral accentuation of cytoplasm. The third variant is mixed [2].

Chromophobe RCC has recently been better characterized from a molecular and genetic perspective. Genetic abnormalities of chromophobe RCC have been well described, with an incidence of 70-90% loss of chromosomes 1, 2, 6, 10, 13, 17, or 21 [3, 4]. These genetic abnormalities might inactivate the tumor suppressor gene, promoting tumorigenesis [5].

Renal oncocytoma is a benign neoplasia and consists of a pure population of oncocytes, which are well-differentiated large neoplastic cells with an intensely eosinophilic granular cytoplasm as a result of a large number of mitochondria [6]. The origins of oncocytoma and chromophobe RCC are the same, a collecting tubule [7], and the two must be differentially diagnosed clinicopathologically.

Papillary RCC is the second most common type of RCC. Two subtypes of papillary RCC have

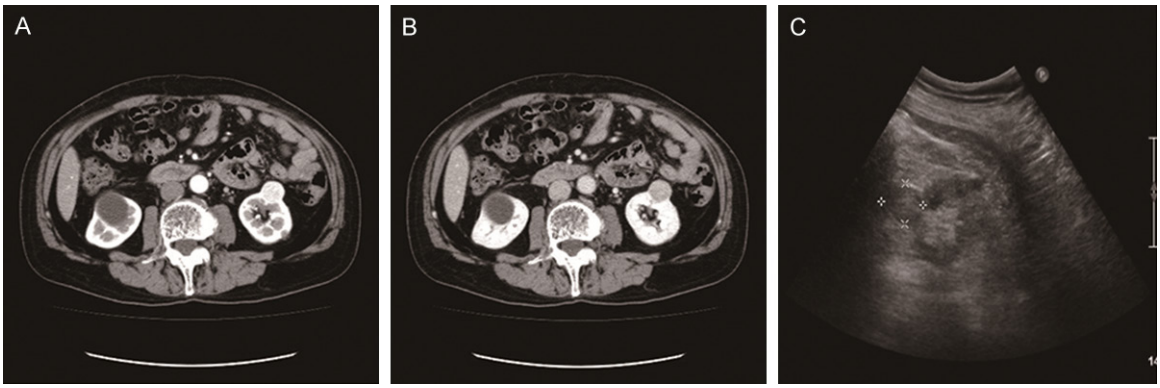


**Figure 1.** Pre-operative diagnostic imaging. The left renal tumor of 2.5 cm diameter is regularly enhanced and well-marginated at early phase (A) and contrast agent is rapidly washed out at middle phase (B). Ultrasound sonography reveals a homogenous and isoechoic mass in the left kidney (C).

been recognized-type 1 and type 2. Diagnosis is mostly based on features of papillary architecture. Cells typically display a basophilic cytoplasm, and the presence of foamy histiocytes is characteristic.

In differential diagnosis of kidney neoplasms, histopathological findings of tumors such as chromophobe RCC, oncocytoma, and papillary RCC are often confusing. In this report, we present a case of chromophobe RCC showing eosinophilic staining and papillary growth, and discuss such rare entities and the pertaining literature.

## Case presentation

An 80-year-old man was introduced to Kochi Medical School from a private hospital with incidental left renal tumor detected by abdominal ultrasound. Abdominal contrast-enhanced computed tomography (CT) revealed a left renal tumor, 2.5 cm in diameter, showing uniform contrast and well-defined margins at early phase and the contrast agent earlier washed out at middle phase, and no findings of metastases (**Figure 1A** and **1B**). Abdominal ultrasound demonstrated a regularly isoechoic solid mass in the left kidney (**Figure 1C**). All blood and urine examinations were within normal limits.

Laparoscopic left partial nephrectomy was performed under a presumed diagnosis of left RCC. The tumor was a macroscopically well-circumscribed solid mass without a fibrous capsule. The cross-sectional surface was homogenously light brown (**Figure 2A**). Histopathology of the tumor demonstrated uniform eosinophilic cuboidal cells growing tubally with a papillary pattern (**Figure 2B** and **2C**). Nuclei were centrally located and round with perinuclear halos (**Figure 2D**). Wrinkled and raisinoid nuclei, and often binucleation, were observed (**Figure 2E**). Few mitoses were identified. Bleeding and necrosis were not observed.

Positive staining with colloid iron (**Figure 2F**) and immunostaining with anti-EpCAM (MOC31) (**Figure 2G**), -CD82 (**Figure 2H**), -cytokeratin 7 (CK7), -c-kit were diffuse and anti-mitochondria was focally identified, but negative results were seen for anti-melanosome, -CA9, -RCCMa, -CD10, S100, cathepsin K, -TFE3, and alpha-smooth muscle actin (data not shown).

We examined cytogenetic abnormalities of the tumor by comparative genomic hybridization (CGH), performed according to the standard protocol with minor modifications. Briefly, genomic DNA from the tumor specimens and peripheral blood lymphocytes from the patient as control was isolated by standard techniques [8]. Reference and tumor DNAs were labeled by nick translation with rhodamine-dUTP (Amersham Pharmacia Biotech, USA) and fluorescein-12-dUTP (NEN Life Science Products, Boston, MA), respectively. Imaging analysis was performed using an Olympus BX-50 fluorescence microscope equipped with single band-pass filters for fluorescein, rhodamine, and DAPI and with a cooled CCD camera (KAF 1400; Photometrics, USA). Telomeric and heterochromatic regions were excluded from the analysis. The CGH findings demonstrated gains (green

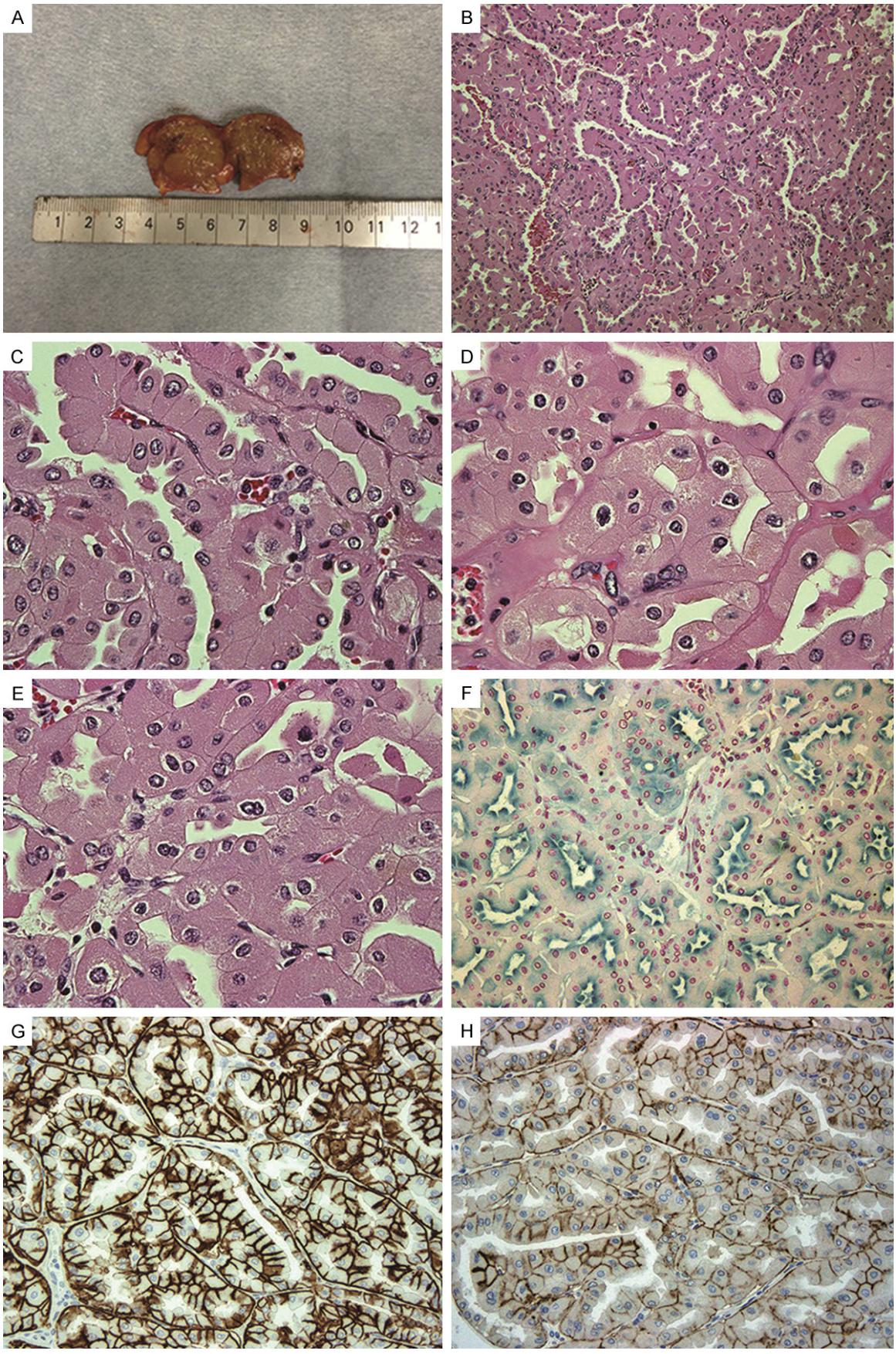
A
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**Figure 2.** Macro- and microscopic findings of surgical specimens. The tumor was macroscopically well-marginated and uniformly brown in color. Necrosis and bleeding were not identified (A). Microscopic findings with hematoxylin-eosin staining reveal uniform eosinophilic cuboidal cells with papillary growth (×40; B and ×200; C). Nuclei were centrally located and round. Wrinkled (raisinoid) nuclei, perinuclear halos, and bi-nucleated cells were observed (×200; D). Few mitoses were identified (×200; E). Colloid iron staining is positive on the luminal side of tumor cells (×200; F). Immunohistochemical staining with anti-MOC11 and CD82 are diffusely positive on the cell membrane.

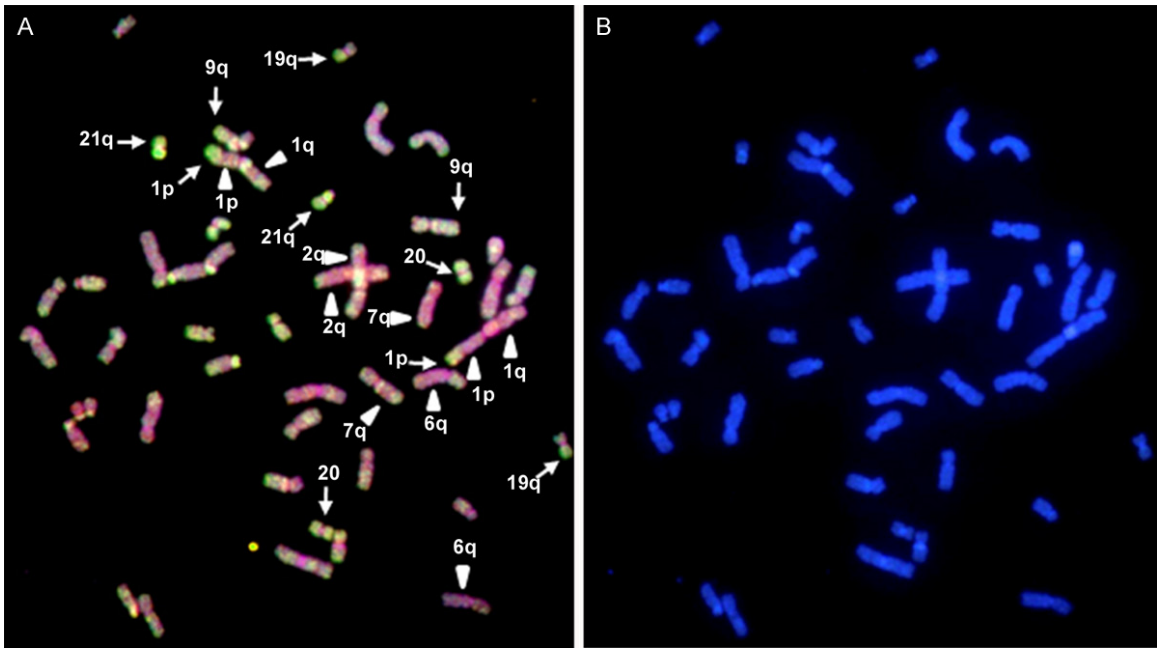


**Figure 3.** A representative CGH image of the tumor. Arrows indicate amplified locations (green signals; gain) of chromosomes 1p, 9q, 19q, 20, and 21q, and arrowheads indicate lost locations (red signals; loss) of chromosome 1p and q, 2q, 6q, and 7q (A). A counterstained with DAPI (blue signals) is for chromosome identification (B).

signals) of chromosomes 1p, 9q, 19q, 20, and 21q, and losses (red signals) of chromosome 1p and q, 2q, 6q, and 7q (**Figure 3**).

## Conclusion

The following eosinophilic renal neoplasms require differential diagnosis: chromophobe RCC, oncocytoma, oncocytosis, hybrid oncocytic/chromophobe tumor of Birt-Hogg-Dubé syndrome, tubulocystic carcinoma, papillary RCC, clear-cell RCC with predominant eosinophilic cell morphology, follicular thyroid-like RCC, hereditary leiomyomatosis-associated RCC, acquired cystic-disease-associated RCC, Xp 11.2 translocation RCC, rhabdoid RCC, microphthalmia transcription factor translocation RCC, epithelioid angiomyolipoma, and unclassified RCC. In our case, uniform eosinophilic cuboidal cells grew tubally and nuclei were centrally located and round: these findings resemble oncocytoma. The perinuclear halo, raisinoid nuclei, and binucleation led us to diagnose chromophobe RCC differentially from oncocytoma. Immunohistochemical results contributed to the diagnosis. Anti-CK7, MOC31, and CD82 immunostaining are typically positive for chromophobe RCC but negative or focally positive for oncocytoma [9]: immunohistochemical features of our case corresponded exactly to those of chromophobe RCC. Choroid iron staining also contributed to the definitive diagnosis of chromophobe RCC (**Figure 2**).

A cytogenetic and molecular approach can distinguish these variants of RCC. The loss of chromosomes 1, 2, 6, 10, 13, 17, and 21 are promising in the diagnosis of chromophobe RCC [3, 4]. Chromosomal gains in chromophobe RCC had been mostly considered as a rare event. However, in a few recent studies using CGH, it has been found that chromosomal gains can be detected more often in chromophobe RCC than generally expected [10, 11]. Sperga et al.

reported high incidences of gains of chromosomes 4, 7, 15, 19, and 20 in chromophobe RCC: 59, 65, 54, 59, and 54%, respectively [12], in even low-grade tumors. They concluded that these chromosomal gains might be common within chromophobe RCC, irrespective of biological behavior [12]. On the other hand, cytogenetic abnormalities of oncocytoma mainly comprise loss of heterozygosity of chromosomes 1, 2, 8, 9, and 14, with low incidence. Chromosome gains have not yet been reported [13]. Thus, our cytogenetic findings showing gains of 1p, 9q, 19q, 20, and 21q, and losses of 1p and q, 2q, 6q, and 7q partially equate with previous findings, leading to the exclusion of oncocytoma and diagnosis of chromosome RCC.

Papillary growth of chromophobe RCC is very rare, with partial papillary growth reported in only 2 of 145 cases of chromophobe RCC [2]. Papillary renal neoplasms are described following differential diagnosis: papillary RCC, collecting duct carcinoma, mucinous tubular and spindle cell carcinoma, metanephric adenoma. Papillary RCC was well characterized by immunohistochemical and cytogenetic approaches. Positive immunostaining for anti-c-kit and negative for -RCCMa or -CD100 in our case definitely excluded papillary RCC [14]. Trisomy of chromosome 7 and 17, and Y missing, have been generally identified in both type 1 and 2 papillary RCC. Recently, a multiplicity of cytogenetic abnormalities of type 2 papillary RCC has been reported, such as loss of chromosome 3p printing von Hippel-Lindau tumor suppressor gene [15]. These chromosomal abnormalities were not identified in our case, so papillary RCC could be excluded. In papillary eosinophilic neoplasms, it is important to distinguish sporadic type 2 papillary RCC from microphthalmia transcription factor translocation and hereditary leiomyomatosis-associated RCC [16].

Recently, the concept of oncocytic papillary RCC has been advanced. Pathologically, this rare entity reveals papillary architectures and tumor cells resembling oncocytic cytoplasm, and round, non-overlapping, peripheralized low-grade nuclei with inconspicuous nucleoli. Positive immunohistochemical staining for vimentin, CD10, and MET; negative staining for c-kit; and typical cytogenetic characteristics with trisomy of chromosome 7 and 17, and Y missing, are typical characteristics of papillary RCC [17, 18]. Kuroda et al. reported five cases of a novel subtype of chromophobe RCC with oncocytic variant and summarized the histological characteristics in detail [19]. An evident variation in cell size, eosinophilic cytoplasms, shrunken nuclei, perinuclear halos, and distinct cell borders in chromophobe RCC with eosinophilic variant, different from oncocytic variants, led to easy and definitive diagnosis [19].

In conclusion, immunohistochemical and cytogenetic findings allowed us to diagnose chromophobe RCC. We propose a rare variant of chromophobe RCC, similar to oncocytoma, with papillary component.

## Disclosure of conflict of interest

None.

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