

# Journal of Nephropathology



## Chromophobe renal cell carcinoma with clear cell features; a case report with review of literature

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### ARTICLE INFO

*Article type:*  
Case Report

*Article history:*  
Received: 5 March 2020  
Accepted: 12 November 2020  
Published online: 5 December 2020

*Keywords:*  
Renal cell carcinoma, Renal cell carcinomas, Nephrectomy

### ABSTRACT

Renal cell carcinoma (RCC) accounts for 3.0% of all malignant lesions of the human body. The World Health Organization (WHO) has classified renal malignant epithelial tumors as-clear cell, papillary, chromophobe and collecting duct RCCs and benign tumors as oncocytoma and angiomyolipoma. Chromophobe RCC is a distinct and rare variant of RCC. It shows equal preponderance in males and females and most commonly presents in the 6th decade of life. Because of overlapping clinical and microscopic features in different variants of RCC and considering the significant implications of the subtypes in the prognosis and treatment of these tumors, the histological classification of RCCs is extremely important. Here we report a case of a 56-year-old male, who presented with urinary complaints of hematuria, and was diagnosed as chromophobe RCC with clear cell features on histopathology and radiographic imaging.

### *Implication for health policy/practice/research/medical education:*

Considering the significant implications of the subtypes in the prognosis and treatment, the histological classification of renal cell carcinomas (RCCs) is extremely important. Subtypes of RCC have overlapping clinical and histological features. The practicing histopathologists should be well aware of different subtypes of RCC to make the accurate diagnosis for better treatment outcome.

*Please cite this paper as:* Ara A, Shahin S, Akhtar K, Siddiqui SA, Saleem M. Chromophobe renal cell carcinoma with clear cell features; a case report with review of literature. J Nephropathol. 2021;10(x):exx. DOI: 10.34172/jnp.2021.xx.

### Introduction

Renal cell carcinomas (RCCs) are the seventh most common histological type of cancer in the western world and have shown an increasing prevalence (1,2). The incidence of clear cell RCC (70-90%), papillary RCC (10%-15%) and chromophobe RCC is 3-5%, based on 2016 WHO classification of renal tumors (3). Chromophobe RCC is presumably derived from the intercalated cells of the collecting duct system. Chromophobe RCC is a rare variant of RCC but it presents at an earlier stage and has a better prognosis than conventional RCC. Chromophobe RCC was first described in 1985 by Thoenes et al (4). Most commonly, the tumor is identified accidentally on imaging and rarely due to urological symptoms. Here we present a case of a 56-year-old male, who presented with urinary complaints of hematuria and was diagnosed

as chromophobe RCC with predominating clear cell features.

### Case Report

A 56-year-old male presented to the surgery outpatient department with chief complaint of hematuria for the last three months. There was no history of fever, pain abdomen, weight loss, hypertension or any other systemic chronic illness. Family history of renal carcinoma was not significant. On physical examination the abdomen was soft, painless with no evidence of any peritoneal mass lesion. The routine hematological and biochemical tests were within normal limits. The abdominal ultrasound revealed a solid mass on the left renal pole. CT scan was performed, which showed a left solid homogenous renal tumor of 5×4 cm in size.

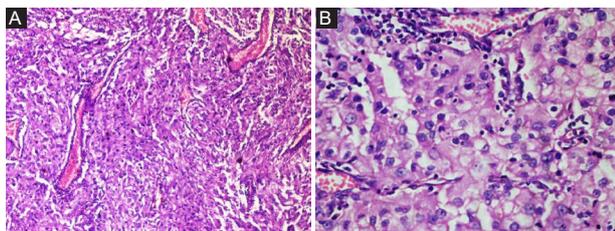
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The patient was operated and the nephrectomy specimen was sent for histopathology. Grossly, the tumor was 5×5 cm in size, light brown to tan in color, well-circumscribed, solid with cystic areas, soft to firm in consistency with smooth outer surface. On microscopic examination, characteristic nesting arrangement of the tumor cells was seen. The tumor cells had sharply defined borders and abundant pale granular to acidophilic cytoplasm with perinuclear clearing. Foci of large polygonal cells with abundant dense eosinophilic cytoplasm were also seen at places (Figures 1A and 1B). Immunorexpression of chromophobe RCC component showed diffuse cytoplasmic positivity for CK7 (Figure 2A) and the clear cell foci showed CD10 membranous positivity (Figure 2B). Our patient was administered immunotherapy, (Soratinib 400 mg twice daily) and is doing well after 12 months postoperative follow up period.

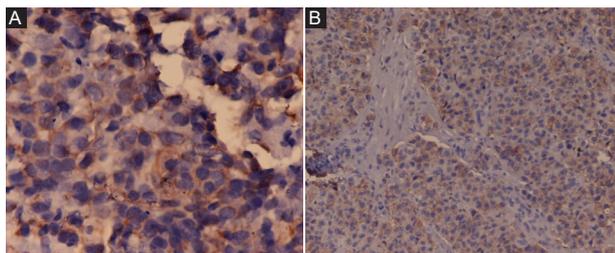
### Discussion

According to the 2016 WHO classification of renal tumors; several histological RCC subtypes are recognized. The most common subtype of RCC is clear cell (75%-90%), followed by papillary (10%-15%), chromophobe (3-5%) (3,5).

Chromophobe RCC usually presents in the 6th decade of life with equal preponderance in both genders (6,7). Our patient was 56 years of age. Most patients are diagnosed in stages 1 and 2 (8,9). Renal vein invasion is seen in only



**Figure 1.** (A) Photomicrograph shows nesting arrangement of the tumor cells, with sharply defined cell borders and abundant pale granular to acidophilic cytoplasm with perinuclear clearing. Foci of large polygonal cells with abundant dense eosinophilic cytoplasm also seen at places (H&E 10×). (B) High power of Figure A.



**Figure 2.** (A) Immunorexpression of chromophobe RCC component showed diffuse cytoplasmic positivity for CK7 IHC (×40). (B) On Immunorexpression, the clear cell foci showed CD 10 membranous positivity (IHC CD10, ×10).

5.0% of cases (7). As this neoplasm is silent in nature, the clinical symptoms of chromophobe RCC are rare. The triad of hematuria, abdominal or lower back pain and flank mass is present in a small percentage of patients with chromophobe RCC (6,7). Our patient presented with complaints of gross hematuria with no other clinical signs and symptoms. In the advanced stage of this neoplasm, pyrexia, cachexia and weight loss can also be seen (9,10).

Microscopically there are three different variants of chromophobe RCC. First, the classic type, which has more than 80.0% pale cells, is associated with necrosis and sarcomatoid changes potentiating infiltrative growth and metastases. Second, the eosinophilic variant, which consists of more than 80.0% eosinophilic cells, with nested, alveolar or sheet-like architecture with granular eosinophilic cytoplasm, perinuclear clearing and peripheral accentuation of cytoplasm. The third variant is mixed (9,10). In our case, histopathology showed nests of tumor cells with abundant pale granular to acidophilic cytoplasm and perinuclear clearing. Foci of large polygonal cells with abundant dense eosinophilic cytoplasm were also seen.

Of these three types of chromophobe RCC, usually the classic type arises as a diagnostic possibility when dealing with a renal tumor with cytoplasmic clarity. The perinuclear cytoplasmic clearing seen in chromophobe RCC is due to the presence of numerous 160 to 300 nm cytoplasmic vesicles that displace the remaining organelles to the periphery of the cell (9,10). The typical growth pattern of sheets of cells separated by incomplete vascular septae in chromophobe RCCs can be a useful finding in distinguishing these tumors from classic RCCs, which classically have thin blood vessels that completely envelope nests of tumor cells (8-10).

Imaging studies show that chromophobe carcinomas tend to be more homogeneous than clear cell carcinomas (10,11). These lesions are hypovascular and less intense than the clear cell variant of RCC. In our case, USG revealed a huge renal mass and CT scan showed a left solid homogeneous renal tumor of 5 × 4 cm in size.

The differential diagnosis of eosinophilic neoplasms includes 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, rhabdoid RCC, epithelioid angiomyolipoma, and unclassified RCC. In our case, uniform eosinophilic cuboidal cells grew tubally and nuclei were centrally located and round which suggests oncocytoma as first diagnosis, but findings like perinuclear halo, raisinoid nuclei and binucleation differentiate chromophobe RCC from oncocytoma. The routine hematoxylin and eosin (H&E) stain is

usually sufficient to identify histopathological subtype of RCC, but it becomes difficult to differentiate between chromophobe RCC, oncocytoma and clear cell RCC, when the tumor cells have eosinophilic cytoplasm. Hence, various markers and ultra-structural methods are required to reach an accurate diagnosis. Chromophobe tumor cells show a strong positive reactivity for CK7, CK8, CD117 (c-kit) and EMA with negative reaction for CD10, inhibin and vimentin in immunohistochemical (IHC) study (12). These IHC markers help to arrive at a correct diagnosis and determine the prognosis of the patient. In our case, chromophobe RCC component showed diffuse cytoplasmic positivity for CK7 and the clear cell foci was CD10 membranous positive.

Surgery is the main modality of treatment for chromophobe RCC. Till now, there are no standard guidelines of chemotherapeutic treatment for advanced chromophobe RCC (13,14). Various studies on patients have shown that mTOR inhibitors, c-Kit inhibitors and tyrosine kinase inhibitors are the treatment choices for advanced chromophobe RCC (15,16). Our patient was operated with total nephrectomy and presently under immunotherapy of sorafenib, 400 mg twice daily.

Chromophobe RCC has good prognosis and survival rates. The detection of cancer disease at an early stage is the main factor for good prognosis. Incidence of metastatic disease is observed in up to 7.0% of cases in the liver and lung (16). Median survival with metastases in chromophobe RCC is 29 months (17). Our patient is doing well after 12 months postoperative follow up period.

### Conclusion

The histological sub-typing of RCCs is of utmost importance, considering the significant prognostic and therapeutic implications of its histological variety. As the prognosis of chromophobe RCC depends upon early detection and typing of the RCC, hence the accurate microscopic examination of nephrectomy specimens is mandatory. Further research and prospective studies about chromophobe RCC can improve treatment outcome and survival.

### Authors' contribution

AA, SS and MS drafted the initial manuscript which was modified by KA. Literature review was performed by AA and KA. Microscopy findings were provided by KA and SS. Additional insight was provided by ShAS. All authors have reviewed and agreed on the final version of this manuscript prior to submission.

### Conflicts of interest

The authors declare no conflict of interest.

### Ethical considerations

Ethical issues including plagiarism, double publication, and redundancy have been completely observed by the author. The patient gave the consent for publication.

### Funding/Supported

None.

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