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Case Series

Pathology Section

Renal Cell Carcinoma Grossly Presenting as Cystic Lesions: A Series of Four Cases

NIZAM PRIYA KALITA[1], ASEEMA DAS[2], SWAGATA DOWERAH[3], SIMANTA JYOTI NATH[4], JAYASHREE DAS[5]

ABSTRACT

Kidney cancer currently ranks as the seventh most common cancer in men and the tenth most common in women. Clear-Cell Renal Cell Carcinoma (CCRCC) represents the most common malignancy of the kidney, accounting for 80% of renal carcinomas. Most CCRCC develops in patients aged over 60 years, and the incidence is slightly higher in men than in women. Partial or total nephrectomy cures the majority of patients with CCRCC. In the present discussion, the authors present cases of 4 males with RCC radiographically identified as Space Occupying Lesions (SOL) to warn clinicians that these seemingly solid lesions have a cystic component as well and may harbour underlying malignancy. Grossly, upon cutting the kidney, all four cases showed solid and cystic components, two of which were multiloculated. Histopathological Examination (HPE) revealed three cases of CCRCC and one case of cystic CCRCC. It is difficult to determine preoperatively whether a cyst is malignant based solely on imaging examinations. Regarding disease prognosis, RCC with predominantly cystic components is considered less aggressive than solid RCC. Cystic RCC (CRCC) carries an excellent prognosis following surgical treatment. Partial nephrectomy should be regarded as the preferred surgical technique in the management of CRCC. In conclusion, authors would like to highlight the fact that histopathologists need to be familiar with the different types of RCC presenting with a cystic component, as these have prognostic significance. Clinicians also need to be aware that there are certain caveats in the radiological diagnosis of cystic renal neoplasms, and histopathology may often present a different picture from the radiological diagnosis.

Keywords: Clear cell, Histopathology, Space occupying lesions

INTRODUCTION

Kidney cancer currently ranks as the seventh most common cancer in men and the tenth most common in women [1]. It arises from the renal cortex or the renal tubular epithelial cells. Currently, Clear Cell Renal Cell Carcinoma (CCRCC) represents the most common malignancy of the kidney, accounting for 80% of renal carcinomas [1]. CCRCC is a paradigmatic example of inter- and intratumour heterogeneity from morphological, immunohistochemical, and molecular viewpoints. CCRCC is the most common type of sporadic RCC in adults. Most CCRCCs develop in patients aged over 60 years, and the incidence is slightly higher in men than in women. Partial or total nephrectomy cures the majority of patients with CCRCC. However, locally advanced or metastatic (a/m) CCRCC is not amenable to surgery alone and accounts for about 20% of newly diagnosed cases, while approximately 30% of non metastatic disease will develop metastases after surgery [2]. Here, authors have considered four cases of RCC radiographically identified as solid with the aim of alerting clinicians that renal neoplasms with cystic growth patterns are typically difficult to differentiate, often requiring extensive morphological (HPE), immunohistochemical, or molecular investigations.

CASE SERIES

Case 1

A 65-year-old male was referred to the hospital with intermittent episodes of decreased urinary output for one or two days, which reversed back to normal. An ultrasonographic abnormality of the right kidney was noted during a medical check-up. On admission, various blood and biochemical tests were performed, revealing mild anaemia with a haemoglobin level of 10.4 g/dL, a total white blood cell count of 9600/mm^3, a Packed Cell Volume (PCV) of 30.6%, a Mean Corpuscular Volume (MCV) of 65 fL, a Mean Corpuscular Haemoglobin (MCH) of 20.9 pg, a platelet count of 1.2 lac/mm^3, and mildly deranged kidney function with serum creatinine at 1.4 mg/dL and serum sodium at 132.87 mmol/L.

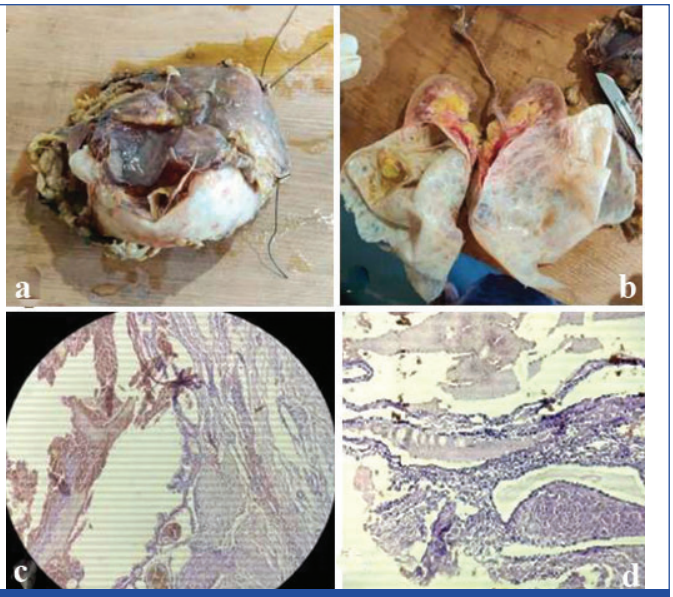
Ultrasonography examination revealed an isoechoic SOL (solid) in the right renal midpole. The renal midpolar SOL was sonographically benign, and a diagnosis of angiomyolipoma was offered. Further imaging with a Computed Tomography (CT) scan demonstrated a heterogeneous, strongly enhancing mass at the mid-posterior right renal parenchyma with a small exophytic component, suggestive of Renal Cell Carcinoma (RCC). No sizable lymphadenopathy was noted.

The patient underwent right-sided radical nephrectomy, and the specimen was sent for histopathological examination. The specimen was formalin-fixed. Grossly, the cut section of the kidney was solid and cystic, with a cyst measuring 10×8×4.5 cm in the inferior pole. Another cyst measuring 1.5×1×1 cm was noted within the wall of the larger cyst [Table/Fig-1a,b]. Haematoxylin and Eosin (H&E) stained sections from different areas of the cyst wall showed an alveolar architecture of neoplastic cells admixed with a network of thin-walled blood vessels and focal areas of haemorrhage and necrosis [Table/Fig-1c,d]. Individual cells were clear cells with centrally placed round to oval nuclei with inconspicuous nucleoli. Immunohistochemical staining showed that these cells were positive for cytokeratin. The findings were consistent with CCRCC, International Society of Urological Pathology (ISUP)/World Health Organisation (WHO) Grade-1, Stage-pT2bNx.

The patient is currently well and has no clinical or radiological signs of recurrence after two months of follow-up, both through phone conversations and regular outpatient examinations.

Case 2

A 45-year-old male was admitted to the Urology Department of the hospital on November 18, 2022, due to itching and generalised oedema (anasarca). A well-defined solid cystic lesion in the upper pole of the kidney, showing intense enhancement, was detected by CT [Table/Fig-2a] during his hospitalisation. He also had a medical



[Table/Fig-1]: (a & b) Grossly, the cut section of the kidney is solid and cystic; (c & d): In biopsy specimen of the cyst wall, Histopathological staining shows clear cells with small nuclei forming alveolar or small cell nest structures (H&E, 4X).

history of hypertension for 5 to 6 years, which was well-controlled by long-term management with antihypertensive medications (Tab amlodipine 5 mg). Blood and biochemical investigations were performed, revealing a haemoglobin level of 12.1 g/dL, total count of 9900/mm^3, and platelet count of 3.2 lacs/mm^3. However, the renal function test (S.creatinine-1.6 mg/dL, S.urea-7.61 mg/dL), liver function test (total protein-4.81 gm/dL, albumin-1.72 gm/dL, A:G ratio-0.55, sodium-132.38 mmol/L), and thyroid function tests (free T3-3.1, free T4-13.3) showed some abnormalities. The patient underwent right radical nephrectomy, and the specimen was received in the Department of Pathology. Grossly, the cortex appeared thinned out in the upper pole of the right kidney. A well-demarcated mass measuring 4.5×3.5×3 cm was noted in the superior pole. The cut-section of the mass was solid and cystic, with areas of haemorrhage, and the cystic area was multiloculated, separated by septa [Table/Fig-2b]. The inferior pole appeared normal. H&E stained sections from the solid foci of the growth showed neoplastic cells arranged in nests, admixed with a network of blood vessels and cystic spaces. Individual cells in the nests were round to polygonal, with round nuclei, dispersed chromatin, inconspicuous nucleoli, and clear to pale eosinophilic cytoplasm [Table/Fig-2c]. Some of the cystic spaces were also lined by a single layer of tumour cells with abundant clear cytoplasm, small nuclei without nucleoli. Stained sections from the cystic part of the growth showed a large area of stroma with myxoid degeneration and a cyst lined by neoplastic cells with clear to pale eosinophilic cytoplasm, dispersed chromatin, and inconspicuous nucleoli. The ureter, renal artery, and renal vein were free from infiltration by malignant cells. The picture was consistent with CCRCC ISUP/WHO Grade-1, Stage-pT1bNx.

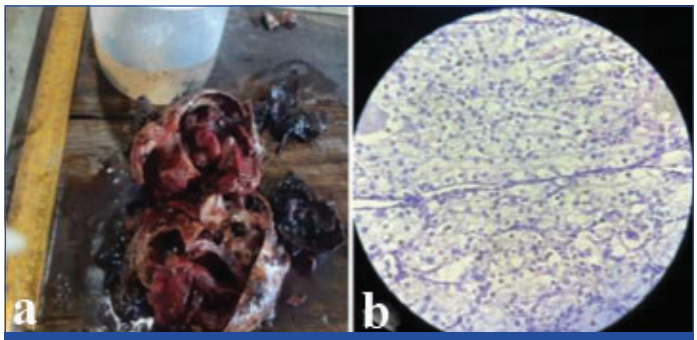
[Table/Fig-2]: (a) A well-defined solid and cystic lesion in upper pole of right kidney detected by CT; (b) Cut section of the mass is solid and cystic, the cystic area is multiloculated separated by septa; (c) In biopsy from solid area. Histopathological staining shows clear cells with small nuclei forming alveolar or small nest structures admixed with a network of blood vessels (10X).

The patient has been doing well for the past five months and comes to the Outpatient Department (OPD) of urology for routine follow-up examinations.

Case 3

A 68-year-old male was referred to the hospital with microscopic haematuria and an ultrasonographic abnormality in the left kidney during a medical check-up. On admission , no abnormalities were found during the physical examination. The ultrasound examination revealed a 50 mm cyst in the lower pole of the left kidney. The patient underwent a left radical nephrectomy, and the specimen was sent for histopathological examination.

Grossly, the kidney measured 18×12×6 cm in size. The cut section was entirely cystic with some solid foci (3.5×3 cm) near the cortex. The cystic area was multiloculated with areas of haemorrhage and blood clot [Table/Fig-3a]. Sections stained with H&E from the solid area near the cortex showed neoplastic cells arranged in tubules and solid nests, admixed with a network of blood vessels. The individual cells were round to polygonal with round nuclei, dispersed chromatin, prominent nucleoli, and clear to pale eosinophilic cytoplasm [Table/Fig-3b].

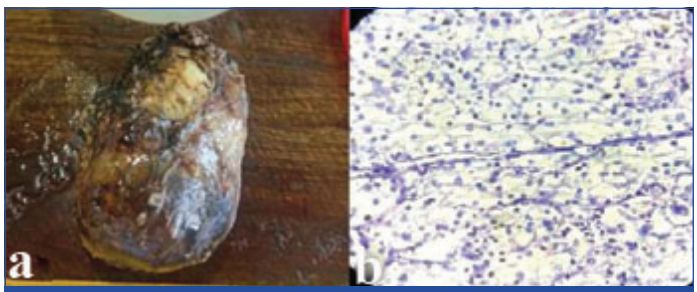


[Table/Fig-3]: (a) Cut section of the growth is friable with areas of haemorrhage; (b) In biopsy from solid area. Histopathological staining shows clear cells with small nuclei forming alveolar or small nest like structures (40X).

A section from the cyst wall showed multi-layered neoplastic cells with clear cytoplasm lining the cyst wall. Sections from the ureter, renal artery, renal vein, perinephric pad of fat, and Gerota's fascia were free from infiltration by malignant cells. The findings were consistent with CCRCC ISUP/WHO Grade-3, Stage-pT2bNxMo. The patient has been on routine follow-up without any signs and symptoms of recurrence.

Case 4

A 54-year-old male was referred to the Department of Urology with complaints of abdominal distension, irregular bowel habits, and dark-coloured urine for one month, as well as abdominal pain for two weeks. Ultrasound findings revealed an ill-defined heterogeneous isoelectric SOL (solid mass) with cystic areas and calcified foci within. There was a 5.1×6.5 cm mass located in the lower pole of the left kidney, which showed vascularity on colour Doppler study. Upon admission, blood investigations were conducted, revealing anaemia, deranged liver function test, and a slight increase in serum creatinine. CT scan of the abdomen and pelvis revealed a relatively well-defined heterogeneously enhancing SOL measuring approximately 5.6×6.4×7.4 cm. The SOL originated from the lower pole of the left kidney and exhibited a few hypoattenuating areas suggestive of necrosis, as well as a calcific focus, indicating RCC



[Table/Fig-4]: (a) Grossly the kidney is solid with a growth in the upper pole; (b) Histopathological staining shows clear cells arranged in small nests and alveolar pattern admixed with a network of blood vessels (10X).

involvement in the left kidney. Grossly, the cut section of the kidney showed a solid growth measuring 5×5.5×4.5 cm in the upper pole [Table/Fig-4a], with the cortex appearing thinned out. However, the lower pole appeared normal. The cut section of the growth was friable with areas of haemorrhage. The H&E stained section from the growth in the upper pole revealed neoplastic cells arranged in nests and an alveolar pattern with cystic degeneration [Table/Fig-4b]. The individual cells were uniform, large with pale cytoplasm and distinct cell membrane, round nuclei, and prominent eosinophilic nucleoli. The picture was consistent with CCRCC, ISUP-Grade 2, Stage pT1bNx. The patient is currently doing well and has been regular with his follow-up routine check-ups at the Urology OPD. All cases are summarised in the table provided in [Table/Fig-5].

Case no.	Age	Gender	Chief complains	Investigations	Provisional diagnosis (radiological)	Histopathological diagnosis	Follow-up details
Case 1	65 years	Male	Decreased urinary output	Anaemia deranged KFT	Renal Cell Carcinoma (RCC)	Cystic Clear Cell Renal Cell Carcinoma (CCRCC) ISUP/ WHO Grade-1 Stage-pT2bNx	After 2 months of follow-up no signs of recurrence
Case 2	45 years	Male	Itching generalised oedema	Normal CBC deranged KFT, LFT and thyroid function	Angiomyolipoma	CCRCC ISUP/WHO Grade-1 Stage-pT1bNx	No signs of recurrence
Case 3	68 years	Male	Incidental finding detected during routine checkup.	Microscopic haematuria	Renal cyst	CCRCC ISUP/WHO Grade-3 Stage-pT2bNxMo	No signs of recurrence
Case 4	54 years	Male	Abdominal distension Irregular bowel habits dark coloured urine pain abdomen	Anaemia deranged LFT ↑ S. creatinine-1.7mg/dL	Cystic lesion with a calcified foci and necrosis suggestive of RCC	CCRCC ISUP/WHO Grade-2 Stage-pT1Nx	No signs of recurrence

[Table/Fig-5]: Summary of the four cases.
*CBC: Complete blood count; KFT: Kidney function test; LFT: Liver function test

DISCUSSION

Clinically, the evaluation of cystic renal masses primarily depends on the Bosniak classification system [3,4]. The Bosniak classification of renal cysts is as follows:

- Category I: Non enhancing cyst - A benign cyst is characterised by a smooth border without any calcification or echoes in the cyst (anechoic). It has a thin wall without any septations, calcification, or solid component. There is no risk of malignancy, and no follow-up is needed.
- Category II: Less than 3 cm benign cyst with a few thin septations or fine calcification. No follow-up is needed.
- Category IIF: Greater than 3 cm benign cyst with a few thin septations or fine calcification. "F" refers to follow-up with imaging in six months.
- Category III: Cysts with irregular walls or thick septations with cystic masses. Enhancement is seen. About 60% of the cysts have the risk of malignant transformation.
- Category IV: Bosniak III criteria+enhancing soft tissue components adjacent to but independent of the wall or septum. Malignancy risk is around 90%.

According to the guidelines [5], Bosniak Category I and II renal cysts are considered radiologically benign, requiring no further evaluation or follow-up. Categories III and IV include a certain extent of malignant cystic disease, which may require adequate treatment. A recent meta-analysis also revealed that the likelihood of cancer in histopathological analysis of a cystic renal mass of Category IIF or below is low [6]. However, it is not always accurate.

In the current cases, for example, the radiologically benign renal cystic lesions (Bosniak Category I) were finally demonstrated to be RCC. Therefore, it is difficult to preoperatively determine whether a cyst is malignant solely based on imaging examinations. The basic mechanisms by which RCC presents as a renal cyst can be classified into the following types [7]: (1) intrinsic cystic growth as a multiloculated fluid-filled mass; (2) intrinsic cystic growth as a unilocular fluid-filled mass (cyst adenocarcinoma); (3) cystic necrosis (pseudocyst); and (4) origin from the epithelium of a pre-existing simple cyst.

Regarding disease prognosis, RCC with predominantly cystic components is considered less aggressive than solid RCC [8,9]. Furthermore, the updated WHO classification of renal tumours classifies multilocular CRCC as a cystic renal neoplasm of low malignant potential [10]. In the present series, in cases 2 and 3, although areas resembling multilocular cystic renal neoplasm of low malignant potential, which are composed entirely of variably sized cysts separated by thin septa containing clear cells, are seen, the final diagnosis of CCRCC was given due to the presence of a solid tumour nodule and microscopically observed solid area of tumour cells. Cystic degeneration of the kidney is very common among renal lesions; however, CRCC is rare, accounting for only 1% to 4% of all RCCs in previous studies [11]. CRCC carries a better prognosis than other RCCs because of its low nuclear grade and TNM stage, regardless of tumour size [12]. In our case series study, case 1 is that of CRCC with low nuclear grade, which is in accordance with other studies.

Accurate diagnosis can be challenging because clear CRCC, conventional renal cell carcinoma with cystic change, and benign renal cystic disease share similar imaging characteristics. Ultrasonography is a useful screening tool. On sonography, CRCC appears as a cystic or cystic-solid structure with thick capsule walls, hyperechoic internal septa, and heterogeneous echogenicity [13,14]. Duplex Doppler ultrasound may or may not display increased blood flow in the cyst walls. CT provides more diagnostic information than ultrasonography. On CT, CRCC presents as a cystic or mixed cystic-solid mass with thick and irregular enhancing cyst walls, with or without calcification. Thick calcification or crescent calcification holds more significance in diagnosing CRCC based on the literature. The septa are often of uneven thickness (usually >1 mm in diameter), and nodular thickening can occur at the junctions with the capsule walls [15]. Differential diagnosis for CRCC include RCC with cystic change, hereditary leiomyomatosis with a cystic renal lesion, cystic nephroma, clear cell papillary RCC, and other cystic kidney lesions. Distinguishing between these cystic tumours based on clinical, radiological, and gross features is extremely challenging and can lead to a diagnostic dilemma. RCC typically presents as a solid mass, but in 10-22% of cases, it can appear as a unilocular or multilocular cystic mass on imaging studies. Clear cell papillary RCC is typically cystic, with cyst walls lined by clear cells. However, much of the tumour usually exhibits papillary architecture, a feature not found in CRCC. It is crucial to avoid misdiagnosing CRCC as conventional clear cell RCC, which is one of the reasons we chose to present a case of CRCC. Once again, the presence of solid nodules of tumour in an otherwise CRCC would be diagnosed as CCRCC.

In the cases reported by Lai S et al., the radiological diagnosis was of a benign lesion that turned out to be RCC on histopathological examination [16]. This was also the case in two of the patients where the radiological diagnosis was of a benign lesion. Wahal SP and

Mardi K described a case of multilocular CRCC where the patient presented with flank pain and haematuria. A well-circumscribed, encapsulated multiloculated cystic mass with thin septa was observed, which microscopically showed variably sized non communicating cysts separated by septae containing tumour cells. These cells exhibited a uniform, hyperchromatic nucleus, inconspicuous nucleoli, and abundant clear cytoplasm with distinct cell borders [11]. Similar findings were observed in Cases 2 and 3 of the present series.

In a large case series of 67 CRCC cases by Chen S et al., renal CT scans were performed in 62 cases, and a possibility of CRCC was reported in only 48 cases [15]. All the cases had an excellent outcome with no evidence of recurrence or metastasis. The present cases are also doing well and remain recurrence-free to date. CRCC carries an excellent prognosis following surgical treatment. Partial nephrectomy should be regarded as the preferred surgical technique in the management of CRCC.

CONCLUSION(S)

In conclusion, authors would like to highlight the fact that histopathologists need to be conversant with the different types of RCC presenting with a cystic component, as these have prognostic significance. Clinicians also need to be aware that there are certain caveats in the radiological diagnosis of cystic renal neoplasms, and histopathology may often present a different picture from the radiological diagnosis.

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PARTICULARS OF CONTRIBUTORS:

1. Demonstrator, Department of Pathology, Assam Medical College, Dibrugarh, Assam, India.
2. Professor, Department of Pathology, Jorhat Medical College, Assam, India.
3. Associate Professor, Department of Pathology, Lakhimpur Medical College, Assam, India.
4. Associate Professor, Department of Urology, Assam Medical College, Dibrugarh, Assam, India.
5. Postgraduate Trainee, Department of Pathology, Assam Medical College, Dibrugarh, Assam, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nizam Priya Kalita,
Healthcare Polyclinic, Graham Bazar, Tiniali, Opposite Apollo Clinic,
Dibrugarh-786001, Assam, India.
E-mail: nijampriyakalita@gmail.com

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