Sarcomatoid Variant of Renal Cell Carcinoma and a Comprehensive Exploration of Its Molecular Pathogenesis

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ABSTRACT

Renal cell carcinoma (RCC) is a common neoplasm of the kidney. A rare, highly aggressive form of RCC that can arise in any subtype of this disease is the sarcomatoid type. RCC with sarcomatoid differentiation (sRCC) has a high likelihood of metastasising and, thus, shows a poor prognosis. Signs and symptoms are mostly non-specific. Here, we report a case of a 56-year man who was misdiagnosed as a pyonephrotic kidney based on imaging and was found to have sRCC on histopathological examination. He presented to the emergency department with a complaint of long-standing left flank pain with no other associated symptoms. An ultrasound kidney, ureter, and bladder (KUB) revealed moderate hydronephrosis with thick internal echoes in the left kidney. A subscapular collection measuring 150 ml was also found. An ultrasound-guided pigtail catheter was then placed and around 300 ml of haemorrhagic fluid with necrotic tissue was aspirated. CT KUB showed a left grossly hydronephrotic kidney, measuring 13.5 × 5.3 cm, with a thinned-out cortex. A provisional diagnosis of the left pyonephrotic kidney was made, and a left nephrectomy was performed. On histopathological examination, it was diagnosed as sRCC. On a follow-up visit after one month, CT- chest abdomen, and pelvis (CAP) was performed, which revealed metastatic disease involving the lungs. This case report serves to highlight that the diagnosis of malignancy should be considered in patients who present with hydronephrotic obstructed kidneys with clots. Contrast studies and ultrasound-guided biopsy can help in preoperative diagnosis. sRCC has a rapid progression, and strict monitoring is recommended.

Key Words: *Renal cell carcinoma, Sarcomatoid component, Metastasis, Nephrectomy, Case report*.

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INTRODUCTION

Renal cell carcinoma (RCC) is a common malignant neoplasm of the kidney that, according to the GLOBOCAN data, had a global incidence of 431,288 and 175,098 deaths in 2020,[1] up from an incidence of 403,262 and 175,098 deaths reported in 2018.[2] A rare, highly aggressive form of RCC that can arise in any subtype of this disease is the sarcomatoid variant.[3] It commonly presents in patients with clear cell RCC due to the high incidence of this particular subtype, though some case series have shown that the sarcomatoid subtype has the highest frequency in the chromophobe subtype.[4,5] RCC with sarcomatoid differentiation (sRCC) has a high likelihood of metastasising and, thus, shows a poor prognosis, having a median survival of 5 to 12 months.[6]

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Studies have reported that patients with ≥25% sarcomatoid features had approximately 30% higher overall risk of all-cause mortality.[2] Signs and symptoms are mostly non-specific, with patients mostly reporting flank or abdominal pain, haematuria, and weight loss, among others.[2]

Here, the authors report a case of a 56-year man who underwent a nephrectomy with the diagnosis of pyonephrotic kidney based on imaging and was later diagnosed as sRCC on histopathological examination. This case has been reported in line with the Surgical Case Report (SCARE) Guidelines.[3]

CASE REPORT

A 56-year man presented to the emergency department with a complaint of long-standing left flank pain. There was no history of fever, haematuria, or weight loss. He worked in a textile mill and has been smoking 2 packs of cigarettes daily for the last 20 years. He had no known history of diabetes, hypertension, or other comorbidities, and his Eastern Cooperative Oncology Group (ECOG) status was 0.

On clinical examination, the left kidney was palpable, and the rest of the abdominal examination was normal. An ultrasound kidney ureter bladder (KUB) revealed moderate hydronephrosis with thick internal echoes in the left kidney. A subsca-

pular collection measuring 150 ml was also found. His right kidney and bladder showed no irregularities. An ultrasound-guided pigtail catheter was then placed, and around 300 ml of haemorrhagic fluid with necrotic tissue was aspirated. Following that, there was no further output in the drain.

Based on the ultrasound findings, an impression of the pyonephrotic kidney was made and a contrast study was not done. A CT-KUB was performed, which showed a left grossly hydronephrotic kidney, measuring 13.5 × 5.3 cm, with a thinned cortex and abrupt narrowing at the pelviureteric junction (PUJ), representing its obstruction. A linear hyper-attenuating area was noted within the dilated pelvicalyceal system (HU 42), representing a clot (Figure 1). No stone was observed in the bilateral kidneys, ureter, and bladder. Moreover, the right kidney, pancreas, liver, and the remainder of the scan were normal. A renal MAG3 scan showed no functioning cortical tissue in the left kidney and good perfusion blush, followed by normal tracer uptake by the functioning cortical tissue in the right kidney, indicating normal function. Delayed images showed prompt clearance of the tracer from the pelvicalyceal system. The patient was scheduled for a left simple nephrectomy, which was performed approximately 2 months later. Intraoperatively, the kidney was densely adherent to the lateral abdominal wall, peritoneum, and adrenal gland, and necrotic tissue was seen. During dissection, the cortex was breached at mid-pole, and there was a spillage of pus and necrotic tissue. The presence of pus in the renal collecting system gave an impression of a left pyonephrotic kidney. The excised left kidney, along with its associated adrenal gland, was submitted for histopathological examination.

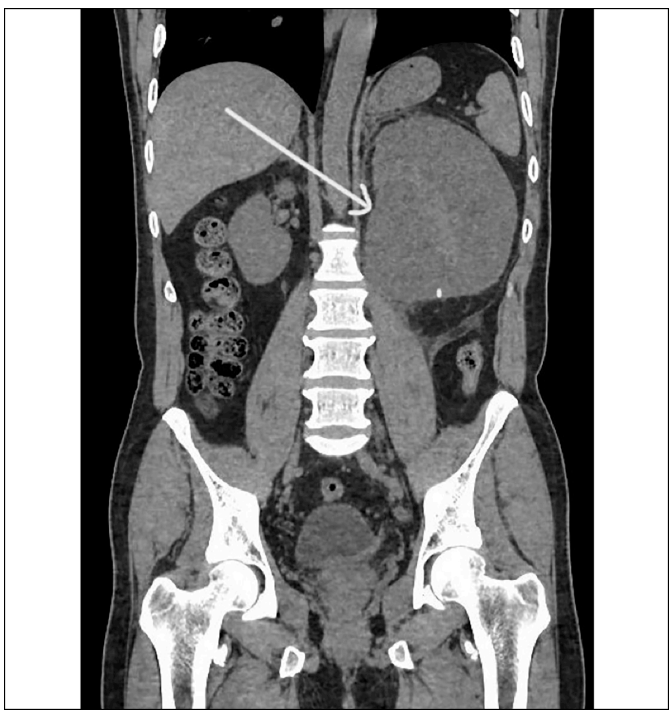

Figure 1: CT KUB showing markedly dilated hydronephrotic left kidney.

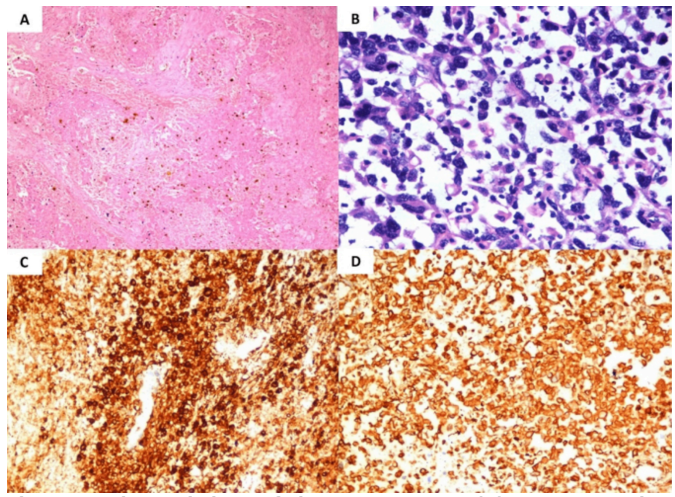

Figure 2: Histopathology of the tumour mass. (A) Low-power view showing necrotic tumour. (H&E, ×100). (B) The viable areas show a high-grade pleomorphic tumour. (H&E, ×400). (C) The tumour stained positively for CD 10. (D) The tumour also stained positively for vimentin.

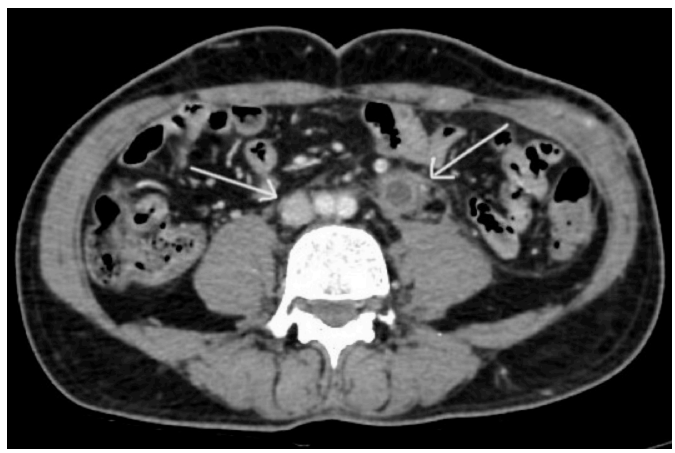

Figure 3: CT KUB showing an enhancing lymph node measuring 1.5 × 1.5 cm in the left para-aortic region, and the residual ureteric stump is also showing asymmetrical thickening and enhancement at the L5-S1 vertebral level (arrows).

Detailed gross examination revealed a tumour mass involving the cortex and protruding into the pelvicalyceal system. The tumour was additionally invading the capsule and the perinephric fat, though the adrenal gland and hilar vessels were devoid of any infiltration. Microscopic examination revealed a neoplastic lesion composed of an admixture of epithelioid, plasmacytoid, and spindle cells. There was significant nuclear pleomorphism (Figure 2A, B). Lymphovascular invasion was seen. The ureter, hilar vessels, and left adrenal gland were free of tumour masses. Immunohistochemistry showed CD10 and Vimentin positivity (Figure 2C, D). CK7, GATA3, CD99, PAX8, chromogranin, synaptophysin, HMB 45, and FLT1 were all negative. This was diagnosed as sarcomatoid RCC. Pathological staging was determined to be pT3a, pNx, and Mx.

On the follow-up visit, approximately 1 month later, a CT- chest, abdomen, and pelvis (CAP) was performed for clinical staging. When assessing the chest, multiple soft tissue nodules were noted predominantly in the superior segment of the right lung lower lobe, measuring 0.6 × 0.7 cm. A few soft tissue nodules

were also seen in the apical segment of the left upper lobe, measuring 0.2 × 0.2 cm. On examining the abdomen, soft tissue thickening was observed along the left crus of the diaphragm. An enhancing lymph node measuring 1.5 × 1.5 cm was also seen in the left para-aortic region, and the residual ureteric stump was showing asymmetrical thickening and enhancement at the L5-S1 vertebral level (Figure 3). Periureteric fat stranding was seen with thickening along the bifurcation of the aorta. His liver, pancreas, gallbladder, right kidney, and urinary bladder were normal. Furthermore, no ascites were seen. However, mild degenerative changes were noted in the left head of the femur.

Considering multiple pulmonary and para-aortic lymph node metastasis with suspicion of residual disease in the left ureteric stump, the case was discussed in a tumour board meeting. The decision was made to commence immunotherapy. Despite the initiation of immunotherapy, the patient demonstrated progressive disease. Unfortunately, he passed away approximately six months after the initial diagnosis.

DISCUSSION

Carcinomas of the kidney consist of various subtypes based on their histological and molecular attributes. These include the most common clear cell subtype, which has an incidence of approximately 75% and is responsible for the most cancer-related deaths.[7] Other subtypes include the papillary subtype (incidence ≈ 15%), the chromophobe subtype (incidence ≈ 5%), *etc*.[8] Due to the high incidence of the clear cell subtype, it is also more prone to undergo epithelial-mesenchymal transition (EMT), wherein the RCC would, on a morphological and an immunohistochemical level, contain both epithelial (carcinoma) and mesenchymal (sarcomatoid) features.[6]

The *von Hippel–Lindau (VHL)* gene plays a central role in the pathogenesis of clear cell RCC. The important function of VHL is to target and degrade hypoxia-inducible factor (HIF). HIF can activate downstream targets including GLUT1, CA9, and VEGF. Tickoo *et al*. assessed the expression of HIF in 34 cases of sarcomatoid RCCs. Sarcomatoid RCC associated with clear cell RCC maintained higher HIF pathway expression compared to that associated with non-clear cell RCC.[9] Interestingly, Oda *et al*. found that carcinomatous components had lower TP53 mutation (14%, 2/14) compared to the sarcomatoid component (79%, 11/14).[10] Malouf *et al*. analysed 26 cases of sarcomatoid RCC using genomic profiling (including 37 introns from 19 commonly rearranged genes and 3,230 exons of 236 in carcinoma). They performed genomic profiling of both sarcomatoid and carcinomatous components in three cases, two of which showed identical mutational profiles, and another case harboured commonly disrupted genes.[11] The most frequently involved genes included *TP53* (42%), *CDKN2A* (27%), *VHL* (35%), and *NF2* (19%). Ito *et al*. studied normal, carcinomatous, and sarcomatoid components of 21 cases of sarcomatoid RCC using exome sequencing.[12] They found that the carcinomatous and sarcomatoid components shared 42% of somatic single nucleotide variants (SSNVs). The sarcomatoid component demonstrated a higher overall SSNV burden and increased recurrent LOH on chromosomes 1p, 17p, 9, 10, 14, 18, and 22. The sarcomatoid and carcinomatous components shared some genes commonly found in clear cell RCC including VHL. They also found biallelic TP53 mutations in 32% of the sarcomatoid component; however, there were no TP53 mutations in the carcinomatous component. These findings provide solid evidence that both components may arise from a common progenitor or from a tiny subclone that could not be detected by the present level of resolution.[12] These discoveries are important for the postoperative management of these tumours, as immune modulation or even vaccines may be incorporated as a part of adjuvant therapy with the hope of eliminating these precursors and decreasing the chances of recurrence.

Sarcomatoid differentiation is found in approximately 5% of RCCs, making it a rare but highly aggressive form.[2,5,6] Currently, multiple case reports and case series have been documented for sRCC.[4-6] Large-scale epidemiological studies are limited due to the rarity of the lesion. Some clinical trials have also been conducted to investigate treatment efficacy and safety.[13] What separates this case from the various previously reported cases is its atypical presentation, rapid progression, and aggressiveness. At presentation, the patient simply had long-standing left-sided flank pain with no haematuria, fever, night sweats, or dyspnoea, as are frequently seen in other cases of sRCC.[2] When a CT scan was performed and hydronephrosis was noted, an initial false impression of a PUJ obstruction leading to pyonephrosis was made. On the MAG-3 scan, the kidney was nonfunctioning; hence, a nephrectomy was done. On histopathological examination of the tissue, it was discovered that the actual pathology was RCC, which can present in atypical ways such as pyonephrosis and hydronephrotic obstructed kidney. Later on, during a follow-up visit, a CT CAP was performed, which showed residual/recurrent disease in the ureter and multiple enlarged lymph nodes in the abdomen and chest, indicating a rapid recurrence and aggressive nature of the sRCC.

Patients with metastatic RCCs that have sarcomatoid differentiation have shown improvement in median overall survival and overall response rates when treated with immune checkpoint inhibitors and high-dose interleukin-2.[13] The reported median overall survival is between 5 to 12 months even with the systemic therapy.[6] In the present case, despite early initiation of immunotherapy, the disease progression was rapid, and the patient unfortunately expired six months after diagnosis. This case underscores the highly aggressive nature of sRCC and the need for ongoing research into more effective therapies.

To avoid diagnostic difficulties similar to this case, we recommend using contrast imaging. The tumour can present with pus in the renal collecting system. Additionally, intraoperative frozen sections can aid in diagnosis and alter the treatment plan. Therefore, if a patient with symptoms similar to this case comes to the clinic, contrast studies should be

conducted to rule out malignancy, and radical nephrectomy should be performed.

This case report serves to highlight that the diagnosis of malignancy should be considered in patients who present with hydronephrotic obstructed kidneys with clots and pus in the renal collecting system. Contrast studies can help in preoperative diagnosis. sRCC has a rapid progression and strict monitoring is recommended.

PATIENT'S CONSENT:
Not applicable.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HB: Conceived and designed the study, conducted research, provided research materials, collected and organised the data, analysed, and interpreted the data.
HHQ: Critically reviewed and approved the final draft.
MM: Performed histopathological examination.
MN: Provided research materials, collected and organised the data.
SMF: Performed radiological investigations and provided materials.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Global Cancer Observatory. [Cited 2023]. Available from: https://gco.iarc.fr/.
2. Blum KA, Gupta S, Tickoo SK, Chan TA, Russo P, Motzer RJ, *et al*. Sarcomatoid renal cell carcinoma: Biology, natural history and management. *Nat Rev Urol* 2020; **17(12)**:659. doi: 10.1038/s41585-020-00382-9.
3. Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan A; SCARE Group. The SCARE2020 guideline: Updating consensus surgical case report (SCARE) guidelines. *Int J Surg* 2020; **84**:226-30. doi: 10.1016/j.ijsu.2020.10.034.
4. Molina AM, Tickoo SK, Ishill N, Trinos MJ, Schwartz LH, Patil S, *et al*. Sarcomatoid-variant renal cell carcinoma treatment outcome and survival in advanced disease. *Am J Clin Oncol* 2011; **34(5)**:454. doi: 10.1097/COC.0b013e3181f47aa4.
5. Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: A comprehensive review of the biology and current treatment strategies. *Oncologist* 2012; **17(1)**:46. doi: 10.1634/theoncologist.2011-0227.
6. Pichler R, Comperat E, Klatte T, Pichler M, Loidl W, Lusuardi L, *et al*. Renal cell carcinoma with sarcomatoid features: Finally, new therapeutic hope? *Cancers (Basel)* 2019; **11(3)**:422. doi: 10.3390/cancers11030422.
7. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, *et al*. Renal cell carcinoma. *Nat Rev Dis Primers* 2017; **3**:17009. doi: 10.1038/nrdp.2017.9.
8. Haake SM, Rathmell WK. Renal cancer subtypes: Should we be lumping or splitting for therapeutic decision making? *Cancer* 2017; **123(2)**:200-9. doi: 10.1002/cncr.30314.
9. Tickoo SK, Alden D, Olgac S, Fine SW, Russo P, Kondagunta GV, *et al*. Immunohistochemical expression of hypoxia inducible factor-1α and its downstream molecules in sarcomatoid renal cell carcinoma. *J Urol* 2007; **177(4)**:1258-63. doi: 10.1016/j.juro.2006.11.100.
10. Oda H, Nakatsuru Y, Ishikawa T. Mutations of the p53 gene and p53 protein overexpression are associated with sarcomatoid transformation in renal cell carcinomas. *Cancer Res* 1995; **55(3)**:658-62.
11. Malouf GG, Ali SM, Wang K, Balasubramanian S, Ross JS, Miller VA, et al. Genomic characterization of renal cell carcinoma with sarcomatoid dedifferentiation pinpoints recurrent genomic alterations. *Eur Urol* 2016; **70(2)**:348-57. doi: 10.1016/j.eururo.2016.01.051.
12. Ito T, Pei J, Dulaimi E, Menges C, Abbosh PH, Smaldone MC, *et al*. Genomic copy number alterations in renal cell carcinoma with sarcomatoid features. *J Urol* 2016; **195(4 Pt 1)**:852-8. doi: 10.1016/j.juro.2015.10.180.
13. Hanif A, Pandey M, Khan S, Attwood K, George S. Metastatic sarcomatoid renal cell carcinoma treated with immune checkpoint inhibitors. *OncoImmunol* 2019; **8(8)**:1606639. doi: 10.1080/2162402X.2019.1606639.