Case report

Sarcomatoid and rhabdoid dedifferentiation in clear cell renal cell carcinoma, a rare combo: Does that have a dismal prognosis?

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(Received: May 2023 Revised: July 2023 Accepted: August 2023)

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ABSTRACT

Sarcomatoid and rhabdoid dedifferentiation of Renal Cell Carcinoma (RCC) has long been recognized as subtypes with extremely poor prognosis and reduced progression-free survival. The overall incidence ranges from 5% to 20%. These subtypes present at an advanced stage at diagnosis and are associated with aggressive behaviour with a high recurrence rate. Promising results including complete response were observed in patients who tolerate the multi-modal treatment well. We report a case of a 75-year-old lady who underwent radical nephrectomy with renal vein thrombectomy for RCC. Histopathology confirmed clear cell carcinoma with rhabdoid and sarcomatoid differentiation. She was started on Sunitinib and followed up for 1 year. She is doing well at present with no recurrence. This case report stresses that though rhabdoid and sarcomatoid carcinoma have a dismal prognosis, the outcome is promising if detected early and offered multimodal treatment. The sRCC (sarcomatoid RCC) and rRCC (rhabdoid RCC) portend a poorer prognosis. Overall survival is slightly better with rRCC compared to sRCC. IHC (immunohistochemistry) plays an important role in diagnosing and treating these variants. The combination of the two variants further worsens the prognosis. Results are much better if the diagnosis is made early and prompt multimodal treatment is initiated.

Keywords: Sarcomatoid; rhabdoid; renal cell carcinoma; clear cell carcinoma; nephrectomy.

INTRODUCTION

Sarcomatoid RCC (sRCC) and rhabdoid RCC (rRCC) account for 5% of all cases of clear cell RCC (ccRCC) and nearly 20% of those with advanced disease (1). Studies have suggested that sRCC is associated with a bad prognosis and a median survival of less than 1 year (2).

Sarcomatoid morphology was initially described in 1968 by Farrow as "a carcinoma, intimately associated with a more pleomorphic spindle cell or giant cell malignancy resembling sarcoma" (3). Immunohistochemistry (IHC) plays a pivotal role in confirming the sRCC. While the xp11 translocations (TFE3) are uniformly negative in sarcomatoid; PAX8, CD117, p63 and CD10 are usually positive. The sRCC generally lacks copy losses at 3p21-25 as it has a distinct tumorigenesis pathway when compared to ccRCC where VHL (Von Hippel-Lindau) mutation is common (4).

In rhabdoid morphology, prominent nucleoli within the eccentrically placed nucleus are seen in sheets or clusters of epithelioid cells (5). The rRCC is diagnosed by vimentin, epithelial membrane antigen and cytokeratin positivity, while CD68, desmin, myogenin, myoglobin, and MyoD1 are negative. These variants have a higher Ki-67, p53 overexpression, and INI1 (integrase interactor1) expression (6).

Our case report emphasizes that this unusual combo need not always be lethal. A prompt diagnosis and an early appropriate treatment may yield promising results.

Case history

A 75-year-old woman presented with episodic, painless total haematuria for the last two months. She did not have any other urinary complaints. She was a known hypertensive for 30 years and diabetic for the past five years. General examination was unremarkable. On abdomen examination, a soft, non-tender mass was bimanually palpable in the right lumbar region. On evaluation, she was conscious. Her performance status was good.

Her haemoglobin was 6.8 mmol/lt. Her blood urea nitrogen was 0.38 mmol/lt and the serum creatinine was 0.04 mmol/lt. The liver function tests were normal. Urine microscopic analysis showed the presence of plenty of albumin and red blood cells. The Computed Tomography (CT) urogram suggested a well-defined, heterogeneous, predominantly hypodense soft-tissue density lesion measuring 6.5 x 8.0 x 8.6 cm involving the lower and interpole of the right kidney (Fig 1a). There was no evidence of haemorrhage or fat/calcifications within the mass. The lesion showed intense arterial enhancement (Fig 1b) with washout on venous and delayed imaging. Minimal perilesional and perinephric fat stranding was observed. A thrombus measuring 3.3 x 2.7 cm showing arterial enhancement was seen involving the

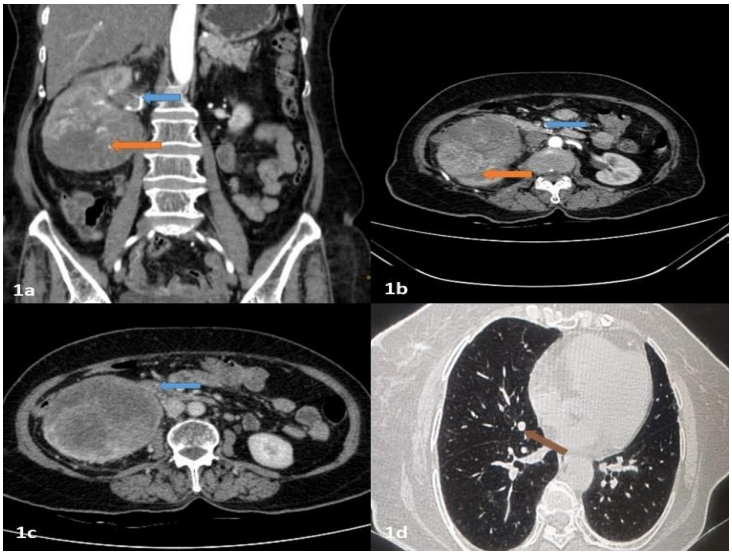

Fig. 1a. Coronal section arterial phase showing tumour in lower polar and interpolar region (orange arrow) and thrombus enhancement (blue arrow). **Fig. 1b.** Transverse section arterial phase with heterogeneous tumour (orange arrow) showing enhancement as well as thrombus (blue arrow). **Fig. 1c.** Thrombus showing enhancement involving the right renal vein up to its drainage into the infrarenal IVC. **Fig. 1d.** High-resolution CT Thorax suggested well-healed COVID-19-related pneumonia with a perifissural nodule in the medial segment of the right middle lobe (brown arrow).

right renal vein up to its drainage into the infrarenal IVC (Fig 1c). High-resolution CT Thorax suggested well-healed COVID-19-related pneumonia with multiple tiny random nodules in both lungs (Fig 1d).

She was posted for right open radical nephrectomy (RN) with renal vein thrombectomy. The tumour was adherent to the hepatic flexure and duodenum, and multiple collaterals were found around the mass. The renal artery and vein were single. The postoperative period was uneventful, and she was discharged on the third day after surgery.

A gross examination of the tumour revealed a unifocal mass of size 8.5 x 8.1 x 6.2 cm involving the lower pole and interpolar region (Fig. 2a). Histologically, the tumour cells were positive for vimentin, PAX8 and negative for WT1, CK7, CK20, ALK, HMB45, CD10, TFE3 and Ki67 (Fig. 2b). The presence of prominent nucleoli within the eccentrically placed nucleus in a cluster of epithelioid cells that are stained for vimentin (Fig. 2c) with higher Ki67 was suggestive of rRCC (Fig. 2d). In addition, the presence of spindle cells with PAX8 staining positive (Fig. 2e) and TFE3 staining uniformly negative suggested sRCC (Fig. 2f). She was referred to medical oncology for adjuvant therapy. She started on Sunitinib 50 mg once daily for two weeks with a one-week interval.

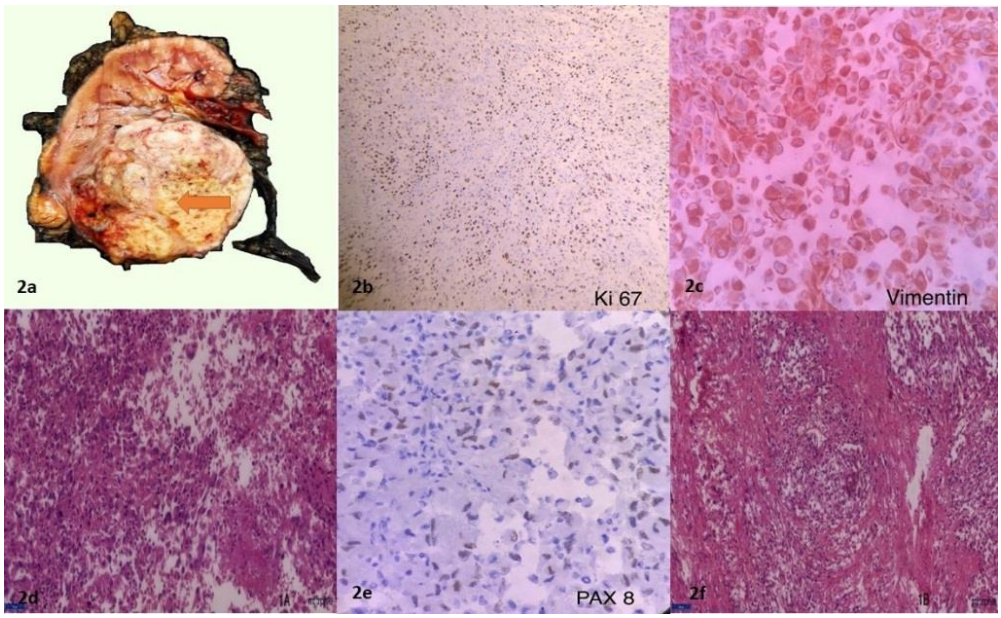

Fig. 2a. Gross specimen picture showing the tumour (orange arrow) being mainly lower polar and interpolar infiltrating thus compressing renal parenchyma. **Fig. 2b**. IHC showing KI67 staining suggestive of rhabdoid RCC. **Fig. 2c.** IHC showing vimentin staining suggestive of rhabdoid RCC. **Fig.2d**. RCC with rhabdoid features (eccentrically placed nucleus is seen in the sheets or cluster of epithelioid cells), H&E staining with 10X magnification. **Fig. 2e**. IHC showing PAX8 staining suggestive of sarcomatoid RCC. **Fig. 2f**. RCC with sarcomatoid features showing spindle cells, Hematoxylin and Eosin (H&E) with 40X magnification.

The patient was followed up every six weeks with a complete blood count, liver function test, renal function test, LDH and regular charting of blood pressure. An 18-FDG PET-CT was done after one year which showed no recurrence. She tolerated Sunitinib well and targeted therapy was continued for one year.

DISCUSSION

Sarcomatoid or rhabdoid differentiations are considered as grade 4 according to WHO/ISUP classification and sRCC has a significantly worse cancer-specific survival (CSS) when compared to other grades. Isolated rRCC was not associated with increased mortality.

A. Sarcomatoid differentiation

Nephrectomy and adjuvant therapy

The sRCC is rarely amenable for Nephron-Sparing Surgeries (NSS). RN is preferred over NSS as these tumours are locally advanced at presentation and show infiltration in pre-operative imaging. As there is more chance of local recurrence, RN provides a better outcome (7).

Patients on Sunitinib as adjuvant treatment had a longer median duration of Disease-Free Survival (DFS) compared to the placebo group. The S-TRAC trial conclusively proves the efficacy of Sunitinib in patients with a higher-stage disease with or without lymph node involvement (8). On the other hand, the ASSURE trial showed no improvement with either Sunitinib or Sorafenib in DFS or Overall Survival (OS) when compared to placebo (9). The PROTECT trial recommends that Pazopanib is not a useful adjuvant therapy following resection of locally advanced RCC (10).

Targeted therapy

Metastatic ccRCC responds well to VEGF (Vascular Endothelial Growth Factor) inhibitors but their response in sRCC remains poor to date. Though sRCC has poor DFS and OS, anti-VEGF agents remain a valid option. Golshayan *et al.*, reported a 19% Partial Response (PR) rate to VEGF-targeted agents including Sunitinib, Sorafenib, or Bevacizumab in mRCC associated with sarcomatoid dedifferentiation. Results were better in ccRCC with a lower percentage of sarcomatoid changes (11).

In a subgroup analysis comparing the metastatic sRCC with metastatic non-sRCC, after administration of mTOR inhibitors, Voss *et al.,* observed that there was shrinkage of tumour in 32% of cases, but most patients succumbed to the disease (12).

Immunotherapy and radiotherapy

Noguchi *et al.,* suggested the use of Nivolumab in metastatic sRCC. He observed a significant clinical improvement with increased tolerance to the drug (13). High-dose Interleukin-2(IL-2) showed a good response initially in metastatic inoperable RCCs but failed to show long-term benefits (14). The use of monotherapy with interferon-a (IFN-a) or combination therapy with IFN-a, IL-2 and 5-fluorouracil (5-FU) in metastatic sRCC had no significant improvement in overall survival (1).

A combination of adjuvant local radiation with chemotherapy (vincristine, adriamycin, cyclophosphamide and actinomycin D) has been found to be not so beneficial. Sano *et al.,* observed that his patient showed a transient response but eventually succumbed to progressive brain metastases after 8 months (15).

B. Rhabdoid differentiation

Treatment

Kapoor *et al.,* suggested the role of Sorafenib after cytoreductive nephrectomy for mRCC with rhabdoid differentiation after disease progression following one-month chemotherapy with doxorubicin and gemcitabine (16). McKay observed a better overall response rate (ORR)with PD-1/PDL-1in patients with ccRCC and sRCC with or without rRCC. This ORR is higher than responses observed with targeted therapies in sRCC (17). Wynja observed a poor response with pazopanib in a patient with rRCC. The patient showed a complete response after the completion of 4 cycles of Nivolumab (18).

Our report is an anecdotal observation. Other IHC studies like PDL-1, PD-1, and p53 expression might help to pursue novel treatment modalities if there is a failure to respond or recurrence. A longer follow-up period might give us a better understanding of the course and progression of the disease.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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