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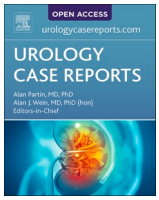

Oncology

Synchronous bilateral papillary renal cell carcinoma in the native kidneys after 10 Years of renal transplantation: Report of a case and review of the literature

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ABSTRACT

A case of synchronous bilateral native kidneys papillary RCC is presented in a 48 year old patient who underwent a living donor kidney transplant 10 years prior. He was on regular immunosuppressant therapy. Despite the long term follow-up, bilateral cystic and exophytic masses were incidentally found on CT scan. Subsequent bilateral open radical nephrectomy revealed papillary RCC in both kidneys.

1. Introduction and literature review

In spite of the fact that, renal transplantation has improved both the quality of life as well as life expectancy of patients with chronic kidney disease on dialysis, but still these doesn't match the figures of general population. One of the major contributing factor, is that these patients have tendency to develop malignancies. The overall number reaches about 2–4 folds when compared to general population, and with regard to renal malignancy, this may reach about 15 fold.[1–3] This is suggested to occur as a result of the immunosuppressant's, which is used extensively in renal transplant patients. The most common type of tumours in renal transplant patients, are skin cancer and non-Hodgkin's lymphoma, with renal cell carcinoma represent about 5 % of tumour detected in transplant patients.[4] As well there is some report of 100 fold increase risk of native kidney malignancies, doublet et al.[5] Post-transplant kidney malignancy almost always arises in the native kidneys, with only few reports its development in the allograft.[6–8] Polycystic kidney disease is one of the major factors associated with the development of renal cell carcinoma,[9] it is found in about 70–90 % in the surgical autopsy biopsies post surgically.[10] The loss of tubules, induce the growth of cysts and compensatory hyperplasia within the kidney, which is regulated by growth factors and firing of proto-oncogenes.[11,12] The renal tumours arising in the polycystic kidneys, tend to be of papillary type.[13,14]

This case report describes one of the most rare cases, a post kidney transplant native kidneys bilateral RCC, occurring simultaneously after ten years post living donor kidney transplantation.

The case is of 48 years male, presented with incidentally discovered bilateral native kidneys masses on follow up CT scan of the abdomen. He underwent living donor renal transplant 10 years back. The intra-operative findings, was bilateral renal masses, with the histopathology examination concluded bilateral papillary RCC.

2. Case presentation

2.1. History of present illness

The 48-year-old male presented with a three-month history of gradual weight loss, noticed by both himself and his wife. A CT of the abdomen revealed bilateral native kidney masses, with no signs of distant metastases. He was previously diagnosed with end-stage renal disease of unknown etiology and underwent a living kidney donor transplant a decade ago. He was on a regimen of immunosuppressant drugs included Tacrolimus, Mycophenolate Mofetil, and Prednisolone. Additionally, he had been managing systemic hypertension since 2005 with amlodipine 5 mg once daily. There was no family history of chronic kidney disease or polycystic kidneys, but a positive history of hypertension on his mother's side. Furthermore, his sister had a history of uterine malignancy, for which she underwent hysterectomy-bilateral oophorectomy.

The physical examination showed a weight of 59 kg with a BMI of 19. Abdominal palpation revealed a soft lax abdomen with no tenderness, a palpable right loin mass that is hard, mobile, and bimanually palpable and ballotable. The left scrotum exhibited Grade IV testicular varicocele, which is persistent on standing up and during the Valsalva manoeuvre.

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Laboratory tests: Table 1.

2.2. Imaging studies

-CT urography scan showed, bilateral multiple radiolucent cystic lesions, some of them with solid elements and contrast enhancement . Some of the cysts graded as Bosniak 2A, some are 5. Both kidneys are atrophied with features consistent with CKD (Fig. 1).

-Other metastatic work up (including chest CT scan), had showed no evidence of distant metastases.

2.3. Operative findings

The patient was previously informed and consented for the surgical procedures and potential complications. The surgery was performed under general anaesthesia in a supine position with a midline laparotomy incision. A laparotomy check was conducted to look for metastases, including liver and lymph nodes palpation. Both kidneys were identified, and the procedure began with the right kidney, with mobilization of the right hemi colon and duodenum kocherisation. A radical nephrectomy and regional lymphadenectomy were carried out. The same steps were then repeated on the left kidney. The transplanted kidney was located, examined, and found to be grossly normal. Specimens were collected for histopathology examination, and the patient was referred to the oncology department for further treatment and monitoring.

2.4. Histopathology results

2.4.1. Macroscopic findings

The left kidney, multiple cysts identified, the largest about 3 cm. The kidney is below the average in size (6*4*3 cm), there is one exophytic central mass with cystic components (3*4 cm).

The right kidney also shows multiple cystic lesions, the largest about 4 cm, located in the lower pole Which is an exophytic solid lower polar mass (5*4 cm). This is surrounded by multiple cystic components.

2.5. Microscopic findings

-Left kidney:

The central component, showed cells of intermediate and small sizes, with eosinophilic cytoplasm, multiple mitotic figures, and nuclear atypia. The diagnosis is papillary multifocal RCC, Fuhrman's grade 1–2. The cysts and cystic components, some are fully capsulated, other are partially. The AJCC staging Is T1a N1M0.

-RT kidney:

The cystic lesions are well capsulated. The solid lower polar mass, also showed small size cells, eosinophilic cytoplasm, pyknosis, nuclear atypia and multiple mitotic figures. The diagnosis is papillary multifocal RCC, Fuhrman's grade 1–2, AJCC staging T1a N1M0 The tumour in both sides showed few amount of fibrotic stroma, tubules, and acini. There was no lymph vascular invasion, sacromatoid components or necrosis. The immunohistochemistry staining is positive to cytokeratin and cadherin, but negative to RCC antigen (Fig. 2).[15]

Table 1
Laboratory tests.

Test	Value	Reference range
CBC – Hemoglobin	13.5 mg/dl	13–17 mg/dl
Platelets	170.000/mcl	150.000–450.000/mcl
RFT – Creatinine	1.2 mg//dl	0.7–1.3 mg/dl
S.urea	10 mg/dl	17–43 mg/dl
LFT – ALT/AST/ALP	all within normal limit	
S.billirubin	1.5 mg/dl	0.3–1 mg/dl
PT	11 seconds	12.3–15.1seconds
APTT	28 seconds	30–40 seconds
LDH	3 IU/L	105–233 IU/L
Serum CA	8 mg/dl	8.5–10.2 mg/dl
Urine general:		
Pus cells	12	0–5
RBCS	<5	0–5

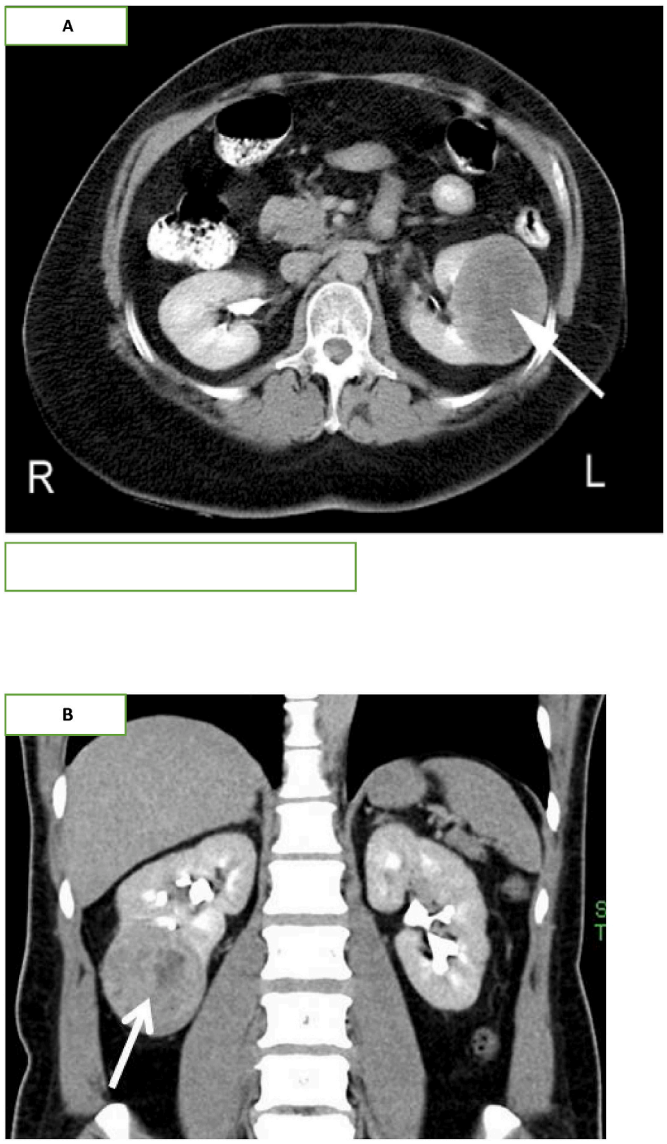

Fig. 1. Computed tomography showing multiple cysts of variable size in both kidneys. (A) Axial and (B) coronal contrast enhanced computed tomography showing enlarged kidneys multiple cysts. No tumours were identified in other organs.

3. Discussion

Papillary subtype of RCC is described to be of lower grade and indolent course [4, 5, 7–9], usually as one of the complications of CKD 9, but still it can occurs de novo 5. The microscopic features of the papillary subtype does not entitles the aggressive features of lymph vascular invasiveness, sarcomatoid features or necrosis 4.

The papillary tumour of the CKD kidneys is usually cystic and contains acini, papillae, tubules and clear cell nests. Branching tubules and clear cell ribbons are reported to be the characteristic morphologic patterns. All of these covered with single layer of tumour cells. The cytological features includes low nuclear grade,and average size cytoplasm. The nuclei are closer to the apical than the basal membrane. 4.

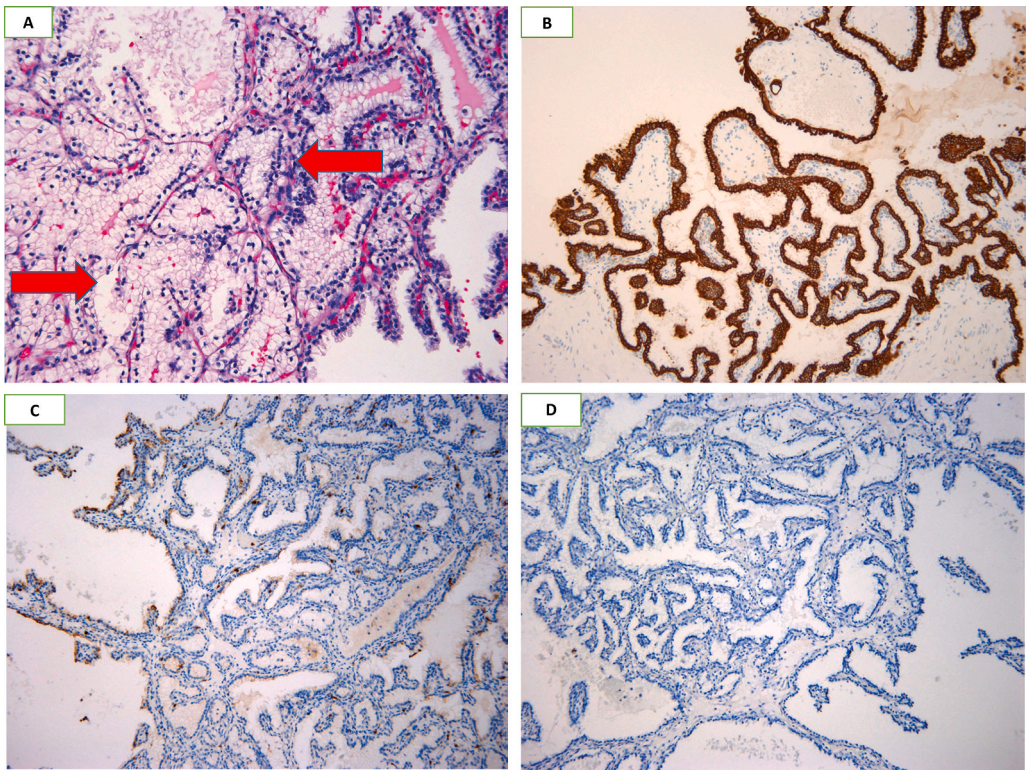

Fig. 2. Clear cell papillary renal cell carcinoma in native kidneys of a renal transplant recipient. (A) Single layers of clear cells with moderate amount of clear cytoplasm and pyknotic nuclei oriented toward the apical surfaces,H&E 400×; (B) diffuse CK7 positivity, 100×;(C) weak CD10 stain, 100×; (D) negative RCC stain, 100×.

Papillary RCC are usually of low pathologic stage. One study has reported 80/82 as pathologic stage 1 and the remaining 2 tumours as pathologic stage 2 [4, 5, 7–10], simillarly our case is pathologic stage 1. They also have an indolent clinical course. Another study followed-up 40 cases (mean period 28 months),and in the cases which underwent radical treatment, there was no detected disease progression or recurrence during the whole follow up period 4. Up to date our case is clear of recurrence or progression for a period of 36 months.

Other types of renal tumours may look similar,such as (multilocular cystic renal cell carcinoma (MLCRCC) and mixed epithelial and stromal tumour (MEST). MLCRCC is a variant of CCRCC with multilocular cystic growth pattern. The cysts are lined by clear cells with low nuclear grade [13, 14]. Genetically, MLCRCC also has chromosome 3p alteration 13. Although CCPRCC can have abundant smooth muscle stroma, it does not, however, have the overall characteristic morphology of MEST.

Transplants of solid organs are known to be prone to develop variety of solid organ tumours, which are usually aggressive in nature.[1] The estimation is two to three folds increase in renal transplant patients compared to general population [2, 3]. Different types of renal malignancies increase by 15-fold could be observed,[16] and of these conventional RCC is reported to be of about two thirds of the cases, while papillary is only one third.[17]

One of the major risk factors of RCC development in the native kidneys of the post-transplant recipient is acquired cystic kidney disease (ACKD). The diagnosis of ACKD is by U/S, CT or MRI.[9] The criteria of diagnosis is bilateral renal multiple cysts (at least three cysts in each kidney).[5] The pathogenesis that link the RCC development to ACKD, is thought to be, the loss of nephron induced tubular hyperplasia and cysts formation, under the influence of epidermal growth factor, hepatocyte growth factor,Bcl-2, and activation of proto-oncogene such as Jun.[11,12] The RCC histopathology types in the sporadic cases is about 19 % (papillary) Vs. 54 % in the ACKD group, in addition to that, there is a high incidence of multifocal as well as bilateral tumour in the ACKD group. Some studies has reported a percentage as high grade as 50 % in ACKD patients.[18,19] RCC which arises after organ transplantation is known of its aggressive course. This could be attributed to the immune suppression treatment.[19] Our patient was on regular follow up for up to 10 years before the apperance of the tumour, which is relatievly a long window period.

Although radical nephrectomy is recommended by many experts in the field as the main treatment, this is not supported by the enough number of evidence based studies.[18]As only one patient died in Moudouni and Neuzillet[18,19], this is not the case in the metastatic disease, in which the prognosis is poor. The treatment of metastatic disease includes surgical removal, as well as anti-tumour systemic treatment, in addition to that, the immunosuppression regimen should be modified in all patients (reducing the dose). The option of immunotherapy is also available, but in general, the use of immunotherapy is contraindicated in patient receiving immunosuppressive agents. In spite of that agents such as temsirolimus, sunitinib and sorafenib could be used safely.[18,19]

4. Conclusion

To sum up, RCC in renal transplant patients tends to has favourable parameters in regards to stage and grade, However they are most likely to be bilateral, papillary and multifocal. Metastatic RCC should be treated by surgery in form of metastatectomy. Because of the strong association between ACKD and RCC, strict follow up regimen has been advised, which is usually in the form of abdominal U/S or CT scan, according to Bosniak"s classification.[10]

-For the purpose of publishing this case report, written and verbal consent from the patient has been obtained and included in the report.

CRediT authorship contribution statement

Haytham Araibi: Writing – review & editing, Writing – original

draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

I hereby declare that I have no conflict of interest with the journal, publisher, or reviewer. This statement is directed to the chief editor in charge.

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Abbreviations And Acronyms

ACKD: acquired cystic kidney Disease
AMACR: alpha-methyl acyl-CoA racemase
BMI: Body Mass Index
Bcl-2: B cell lymphoma
CD: cellular differentiation
ccRCC: clear cell RCC
CT scan: Computer Tomography
ESRD: end stage renal dysfunction
H&E: haematoxylin and eosin
HLA: Human Leucocyte Antigen
MLCRCC: multilocular cystic renal cell carcinoma
MEST: mixed epithelial and stromal tumour
MRI: magnetic Resonance Imaging
RCC: renal cell carcinoma