Early Occurrence of Two Distinct Histological Types of Renal Cell Carcinoma in End-stage Renal Disease Patient on Haemodialysis

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ABSTRACT

Background: The occurrence of renal cell carcinoma is a well-known complication in end-stage renal disease on haemodialysis. Various histological types of renal cell carcinomas are observed in these patients and varies with the duration of haemodialysis. Though the synchronous association of two renal cell carcinomas in the patients are known, the existence of such dual renal tumours in the patient on dialysis is extremely rare and unheard in the English literature. Moreover, tubulocystic renal cell carcinoma is rarely reported in this setting.

Case Report and Discussion: We describe an unusual early synchronous occurrence of two tumours with distinct histology i.e. Papillary renal cell carcinoma (PRCC, type I) and Tubulocystic renal cell carcinoma (TC-RCC) in a patient with end-stage renal disease on haemodialysis for a duration less than a year. Though exact etiological factors peculiar to the occurrence of these tumours are not known, increased oxidative stress occurring in end-stage renal disease patient on haemodialysis might play an important role in carcinogenesis.

Conclusion: Renal cell carcinoma with more than one histological type may occur exceedingly early without any symptoms in these patients. Radiologists and urologists should be aware of it for early diagnosis and prompt treatment. Pathologists should also be more cautious while grossing and pick the sub-centimetric primary or secondary tumours that may have an impact on patient survival.

Keywords: Haemodialysis, End Stage Renal Disease, Tubulocystic Renal Cell Carcinoma, Papillary Renal Cell Carcinoma, Collision Tumours

Background

Renal cell carcinoma (RCC) is potentially fatal complication in a patient with End-stage renal disease (ESRD) on haemodialysis and its occurrence is 3-24-fold greater than in the general population and directly proportionate to the duration of haemodialysis.¹² Though exact pathogenesis is not well understood, many studies highlight oxidative stress as the critical inducer of carcinogenesis in the ESRD patients.¹³ Different histological types of RCCs are observed in the ESRD patients and vary with the duration of dialysis. Clear cell RCC, papillary RCC, clear cell papillary RCC are the most common histological types that occur in patients with less than 10 years duration of dialysis whereas Acquired Cystic disease-associated RCC occurs most commonly in patients with longer duration of dialysis.¹⁴

The synchronous association of two renal cell carcinomas in the patients are known and the commonly observed one include papillary RCC and chromophobe RCC. The existence of such dual renal tumours in the patient on dialysis is extremely rare and unheard in the English literature. We describe an unusual early synchronous occurrence of two renal tumours with distinct histological subtype i.e. Papillary renal cell carcinoma (PRCC, type I) and Tubulocystic renal cell carcinoma (TC-RCC) in a patient with ESRD on hemodialysis for a duration less than a year.

Case study

A 49-year-old gentleman, with a history of uncontrolled hypertension, visited general OPD, PGIMER (Chandigarh, India) with complaints of anasarca and breathlessness for one month, and on evaluation, he was diagnosed as stage V chronic kidney disease. Maintenance haemodialysis was initiated twice a week for renal dysfunction, and symptoms were subsiding subsequently. He was kept on regular follow up and remained asymptomatic. KUB ultrasonogram carried out at the end of 9 months, after initiating hemodialysis, revealed Ceus-Bosnaik 4 lesions in the left kidney which raised suspicion of occurrence of a carcinoma. Further, non-contrast computed tomography (NCCT) of the abdomen revealed multiple hypodense lesions in the left kidney which raised suspicion of occurrence of a carcinoma. The specimen was sent for histopathological examination.

Histopathological Examination

Gross Findings: The left nephrectomy specimen measured 12.5x6x5cm with attached perinephric fat (Fig 1A). The
capsular aspect was intact and there was no evidence of tumour extension. The cut surface revealed a multi-focal tumour distributed throughout the kidney. All the lesions were well-circumscribed and ranged in size from 0.7 to 4 cm in maximum dimensions. The largest nodule showed predominantly necrotic areas at the centre (70-80%) with firm grey-white solid areas at the periphery. The rest of the nodules were solid, grey-white, and firm. Besides, at the junction of the middle and lower portion of the kidney, a distinct well-circumscribed multi-loculated cystic lesion measuring 1 cm in maximum dimension was identified, which is 0.5 cm away from the nearest solid nodule. Renal sinus, pelvic calyceal region and uretero-vascular resection margins were not involved by tumour.

**Light Microscopy:** Histopathological examination shows two distinct well-demarcated tumours, one with predominant papillary configuration and an another with tubulo-cystic pattern (Fig 1B). Most of the solid nodules show papilae lined by single-layered tumour cells and sheets of foamy macrophages in their fibrovascular core (Fig 1C). They displayed round to oval nuclei with intermediate degrees of nuclear pleomorphism, vesicular chromatin, and prominent nucleoli (Grade 3, WHO/ISUP 2016 grading system). The cytoplasm was moderate and eosinophilic in the majority; however, in some foci, it appeared clear. Extensive necrosis, cholesterol cleft formation, and collections of hemosiderin-laden macrophages were noted in the sections from the largest tumour nodule. No rhabdoid or sarcomatoid or giant cell transformation was observed. These neoplastic cells had shown expression for pan-keratin, Keratin 7, PAX8, AMACR (Fig 1E), Keratin 8/18, and Keratin 19 on immunohistochemistry. Considered together, observed features were those of papillary renal cell carcinoma, type I.

Microscopic examination of a distinct cystic lesion observed on gross examination showed a well-circumscribed cystic tumour with variable-sized tubules lined by flattened to cuboidal epithelial cells (Fig 1D). At places, the Hobnail pattern of lining was also noted. No significant nuclear atypia was evident. The surrounding stroma was fibrotic with sparse inflammatory cells. On immunohistochemistry, the neoplastic cells had shown expression for pan-keratin, PAX8, AMACR (Fig 1F), Keratin 8/18, and Keratin 19. CD10 and Keratin 7 immunostains were patchy and focal, respectively. Considering the uniqueness of gross and microscopic findings along with immunoprofile outcome, the diagnosis of tubulocystic renal cell carcinoma was entertained. The markers that include Keratin 20, c-kit, CA-IX, TFE3, HMB45, and Melan-A were negative in both the neoplasms. There was no evidence of lymph-vascular space emboli or perineural invasion. The intervened renal parenchyma showed predominantly sclerosed glomeruli with accompanied atrophic tubules and marked interstitial fibrosis. Thyroidisation of tubules was noted. Simple cortical cysts were also present. Significant hypertension-induced changes were observed in the form of circumferential and nodular hyalinosis in the arterioles and marked fibro-intimal hyperplasia with mucoid degeneration in the arteries. Surprisingly, the focus of papillary adenoma was also appreciated in one of the sections.

Postoperatively, the nephrologists advised the patient to continue with hemodialysis. He was continuing well on the last follow-up.

**Discussion**

Higher risk of renal cell carcinoma in patients with the end-stage renal disease than in the general population is attributed to the increased oxidative stress which causes several morphological and cytogenetic changes in renal tissues of dialysis patients, though the precise pathogenesis is not known. The risk of occurrence of the renal cell carcinoma is significantly correlated with the duration of dialysis, reaching up to 90% in those on dialysis for >10 years. RCC occurring in the setting of ESRD is usually multi-focal and of low tumour stage (pT1) when compared to the non-ESRD group, as observed in our case. Histological subtypes of RCC in the ESRD patients depends on the overall duration of haemodialysis. Clear cell RCC is the most common histological type observed in the ESRD patient regardless of the duration of the haemodialysis. Acquired cystic disease-associated RCC occurs most commonly in patients with longer duration of dialysis (>10 years). Papillary RCC and clear cell papillary RCC are the most common histological types reported in the patients with less than 10 years duration of dialysis. To be noted, RCC in the index case occurs within one year of initiating haemodialysis. In the English literature, the occurrence of the tubulocystic renal cell carcinoma in the ESRD patient on haemodialysis is very rarely described. A case report of bilateral tubulocystic renal cell carcinoma in a diabetic ESRD patient was reported by Kong et al. When it comes to the dual renal neoplasms in a setting of end-stage renal disease patient on haemodialysis, it is extremely rare and not been documented in the English literature. As such, the primary renal collision tumours in the general population are not rare. The known ones are papillary RCC and chromophobe RCC; collecting duct carcinoma arising concurrently with clear cell RCC; and others. Association of tubulocystic renal cell carcinoma with papillary renal cell carcinoma is not reported in
Fig. 1: A) Cut surface showing multi-focal solid tumours with friable consistency, hemorrhage, and necrosis. And also, sub-centimetric unifocal well demarcated sponge-like lesion appreciated (arrow). B) Scanner image showing well demarcated tubulocystic RCC (left) and papillary RCC (right) (H&E, x20). C) Multi-focal tumour showing characteristics papillary pattern with single layered tumour cell with foamy macrophages in sheets within the fibrovascular core (H&E, x200). D) Tubulocystic RCC depicting variable sized tubules and cystic spaces lined by neoplastic cells with ample eosinophilic cytoplasm and distinct nucleoli (H&E, x200 and Inset x400). E and F) Strong AMACR positivity is noted in both papillary and tubulo-cystic renal cell carcinoma components respectively (immunoperoxidase, x200).
ESRD patient till date. The existing theories speculate that these primary collision tumours originate from either a common precursor cell differentiating into two unrelated neoplasms or two unrelated existing cell lines proliferating simultaneously or incidental occurrence of two different unrelated neoplasms.

Tubulocystic renal cell carcinoma (TC-RCC) is a rare variant of renal cell carcinoma and recently included as a new entity in the World Health Organization classification of renal neoplasms. [10] Though it has distinct histology which displays tubules and cysts, lined by hobnail lining epithelium in a fibrotic stroma and characteristic ‘bubble wrap’ appearance on gross examination, there is some debate about its association with papillary renal cell carcinoma (PRCC) and cell of origin in the literature. [11] Since the genetic profile of TCRCC was not apparent in the initial periods, it has variably been reported to be related to other renal cell carcinomas, including papillary renal cell carcinoma and fumarate hydratase-deficient carcinoma. Recent molecular studies of tubulocystic renal cell carcinomas have demonstrated combined losses at chromosome 9 and gains at chromosome 17, as well as the loss of chromosome Y (in 5/5), and this mutational profile is very characteristic of TCRCC and distinct from other renal neoplasms. [12-13] In contrast, papillary RCC (type 1) demonstrates polysomy or trisomy of chromosomes 7 or 17 as the most frequent changes, while the mutation of MET is uncommon at least in the sporadic ones (14). Thus, the occurrence of tubulocystic RCC and papillary RCC together in the same patient must be addressed as a primary renal collision tumour as both are distinctly separate entities.

Though exact etiological factors peculiar to the occurrence of these tumours in ESRD patient is not known; however, impaired host immunity, diminished antioxidant defense mechanisms and increased synthesis of oxide intermediates are the possible mechanisms hypothesized in the literature. [5]

In conclusion, ESRD patients developing renal cell carcinomas have distinct clinical features and are usually asymptomatic. Routine follow-up with ultrasonogram is required for early identification and prompt treatment. Considering increased oxidative stress occurring in the ESRD patient, a greater number of tumours with more than one histological type may occur in these patients. So, pathologists should also be more vigilant while grossing and processing the specimen and pick the small sub-centimetric primary or secondary tumours that have an impact on patient survival.

**Abbreviations**

ESRD: End Stage Renal Disease

PRCC: Papillary Renal Cell Carcinoma

TCRCC: Tubulocystic Renal Cell Carcinoma

WHO: World Health Organization

ISUP: The International Society of Urological Pathology

KUB: Kidney, Ureters, Bladder

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**Conflict of interest**

None

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