

## Papillary necrosis with invasive fungal infections: a case series of 29 patients

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### Abstract

**Background.** Renal papillary necrosis (RPN) is associated with a number of comorbid conditions. However, it has been rarely reported in patients with fungal infections of the kidney.

**Methods.** We analyzed medical records of our hospital for the last two decades and identified 29 patients with fungal infections and RPN.

**Results.** Among the 29 patients, there were 24 men and 5 women. The median (range) age at presentation was 31.2 years (2 days–73 years). Three patients (10%) were kidney transplant recipients. The remaining had varied co-existing medical conditions that included diabetes mellitus in 16 (55%) and septicemia in 4 (14%). Clinical features at presentation were fever and oliguric kidney failure in 17 patients and loin pain accompanied by passage of fleshy material per urethra in 11 (38%). Diagnosis was made ante-mortem in 17 (59%) patients. Twenty patients (69%) had infection limited to the kidneys, while in the rest, it was disseminated. Kidney involvement was bilateral in 17 patients (59%). Urinalysis showed pyuria in 23 (79%) and microhematuria in 8 (28%) patients. Fungal infections included candidiasis (69%), aspergillosis (21%) and zygomycosis (10%). Of the 17 patients in whom the diagnoses was made ante-mortem, 12 survived and 5 died. Overall mortality was observed in 48% of cases.

**Conclusions.** We herein report a series of patients with RPN associated with fungal infections of the kidney. Presentation varies from asymptomatic urinary tract infection to severe kidney failure with poor outcome. High index of suspicion is necessary to reduce the associated high mortality in these patients.

**Keywords:** candidiasis; diabetes mellitus; fungal infections; renal papillary necrosis

### Introduction

Renal papillary necrosis (RPN) is an ischemic infarction of the inner zone of the medulla especially involving the papillae. Urinary tract infection, diabetes mellitus, urinary tract obstruction, analgesic abuse and sickle-cell disease are common conditions that predispose to RPN [1–3]. Isolated reports of association with vasculitides, alcohol abuse, liver disease and kidney transplantation have been described [4, 5]. In a study of 165 patients with RPN, urinary tract infection accounted for ~40% of the cases [5].

Invasive fungal infections of the genitourinary tract are being increasingly recognized due to the improved survival of patients who are immunosuppressed [6–8]. Renal mycosis may present with varied kidney manifestations from asymptomatic involvement to acute kidney injury [8, 9]. RPN associated with candidiasis [10, 11], aspergillosis [12], zygomycosis [6], cryptococcosis [13] and

histoplasmosis [14] occurring either as an isolated condition or in association with other comorbid conditions has been described earlier as case reports. In the present study, our aim was to describe the clinico-pathological features of patients with RPN associated with invasive fungal infections of the urinary tract.

### Materials and methods

We reviewed the medical records of all patients admitted to our center over the last two decades to identify documented cases of RPN associated with invasive fungal infections of the urinary tract. Pertinent information obtained from the medical records included clinical presentation, comorbid conditions, hematology, urinalysis, biochemical values and microbiological cultures, fungal serology, imaging and histopathological reports. Invasive fungal infections referred to deep-seated opportunistic

fungal infections identified by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [15]. Histological diagnosis of RPN due to fungal invasion consisted of examining the kidney tissue obtained at biopsy or autopsy or the sloughed material passed per urethra. These tissue sections were stained by the hematoxylin and eosin as well as silver-methanamine (Grocott-Gomori) stains and the identification of the fungi was based on the typical morphological features of the molds and the filamentous fungi. Radiological suspicion of RPN was made in some patients on the basis of findings consistent with 'definite RPN' [16]. However, it was corroborated with histological evidence as well.

## Results

Among the 29 patients with evidence of RPN, there were 24 males and 5 females with a median age of 31.2 years (range 2 days–73 years). Three patients (10%) were kidney transplant recipients. Among the other 26, diabetes mellitus was a co-existing condition in 16 patients (55%) including 13 patients with type-2 diabetes mellitus and 3 patients with type-1 diabetes mellitus (Table 1) and 4 patients (14%) had evidence of septicemia. Two patients had no other significant disease (Cases 27 and 28). The remaining four patients had other comorbid conditions as mentioned in Table 1.

Presenting symptoms and signs included fever and oliguric kidney failure in 17 patients (59%), loin pain in 12 (41%), passage of fleshy material per urethra in 11 (38%), dysuria in 10 (35%) and gross hematuria in 4 patients (14%). Among 17 patients with oliguric kidney failure, the mean serum creatinine was  $4.4 \pm 3.2$  mg/dL ( $391.9 \pm 291.2$   $\mu$ mol/L). Elevated blood glucose was present in 13 patients (45%) with 4 patients (14%) having diabetic ketoacidosis.

Urinalysis revealed pyuria in 23 patients (79%), proteinuria in 17 (59%) microscopic hematuria in 8 (28%) and ketonuria in 5 patients (17%). Thirteen patients had positive urine culture; bacteria in 10 patients (34%) and fungi in 3 (10%). Fungal infections included *Candida tropicalis* in two and *Candida albicans* in one. All three patients with positive urine fungal cultures also grew the same fungi in the blood.

Fungi were identified from the histopathological sections of the kidneys in 15 (52%) patients, 12 on autopsy (Figure 1) and 3 on biopsy (Figure 2), or from examination of the sloughed tissue passed in urine in 11 (38%) (Figure 3) and from the tissue removed during nephrostomy in 2 patients (7%). In the remaining one patient, fungi were identified in aspirated pus from renal abscess with computerized tomography showing the classical 'ring sign'. Twenty patients (69%) had fungal infection limited to the kidney, whereas it was disseminated in the remaining nine patients (31%). Kidney involvement was bilateral in 17 patients (59%), unilateral in 9 patients (31%) and there was involvement of the transplant kidney in the remaining 3 patients (10%).

Diagnosis of RPN was made ante-mortem in 17 (59%) patients. The ante-mortem diagnosis was based on the sloughed papillae in 13 patients (11 sloughed through the urethra, 2 sloughed through the percutaneous nephrostomy drain). Among the 17 patients in whom the diagnosis was made ante-mortem, RPN was suspected

based on radiological evidence in 10 patients. However, a definitive diagnosis of RPN was possible in only two patients who had 'ring shadow' on nephrostogram with the demonstration of fungal profiles in aspirated pus from the renal abscess (Case 15), or renal biopsy (Case 29). However, of the 12 patients in whom confirmation of diagnosis of RPN was made at autopsy, ante-mortem suspicion was possible in only 2. Overall, 14 (48%) of the patients died.

## Discussion

This study describes a group of patients with evidence of fungal infections of the kidney and papillary necrosis. To our knowledge, this series is the largest report describing the association between fungal infection and RPN. Friedrich [17], in 1877, described RPN for the first time in a patient with benign prostatic obstruction. Since then, RPN has been shown to be associated with multiple comorbid conditions. The role of urinary tract infection as a causative factor for RPN is important. In the study from the Mayo clinic [5], urinary tract infection was evident in 67 (41%) patients. The most common organisms cultured in this large series were *Escherichia coli*, *Candida* and *Klebsiella*. The role of urinary tract infection in RPN may vary from the primary initiating factor to an accompanying condition of little etiological importance. However, it is undoubtedly a frequent accompaniment [1, 6]. Diabetes mellitus is associated with RPN in 22–72% of cases [1, 5, 18]. In autopsies of patients with diabetes, RPN was found in 4.4% [19]. Several studies have however emphasized that multiple etiological factors contribute to RPN [1, 5]. In concordance with these studies, the majority of our patients also had multiple well-defined risk factors for papillary necrosis.

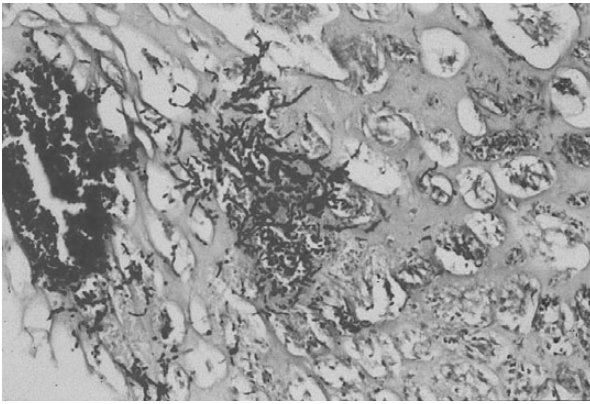
The association of RPN with various fungal infections has been documented earlier as isolated case reports [2, 10, 17]. Chiew [10] reported a case of RPN due to *Candida* in a woman with diabetes. *Candida* infections associated with RPN have also been reported in a patient with Hodgkin's disease [20] and with fungal bezoar in a patient with AIDS [21]. In an autopsy series of 42 patients with visceral candidiasis, Tomashefski and Abramowsky [11] identified RPN in 21% of the patients. Accurate ante-mortem diagnosis could not be made in any of them. Unusual presentations of RPN associated with *Candida* includes mycetoma (fungal balls) [22], bilateral involvement with anuria [23] and emphysematous pyelonephritis [24]. Infection with *Candida glabrata* pyelonephritis has also been reported [25]. One of our patients with RPN had mucormycosis. An association of renal mucormycosis and RPN has been reported only once [6]. There have also been rare reports of RPN due to *Candida* infection in a transplant recipient [26]. This condition usually results from acute or chronic rejection of the allograft [27].

The gold standard for the diagnosis of RPN is the demonstration of necrosed papillae in the material passed per urethra. Imaging studies may also assist in the diagnosis. Plain radiograph may show a curvilinear or ring-like calcification up to 5–6 mm in diameter, indicating a calcified sloughed tissue. Antegrade pyelography performed after draining of the obstructed urinary tract or extraction of debris through the nephrostomy tube may also help in the diagnosis of RPN [28]. However, recently ultrasonography [29] or multiphasic helical CT have been utilized

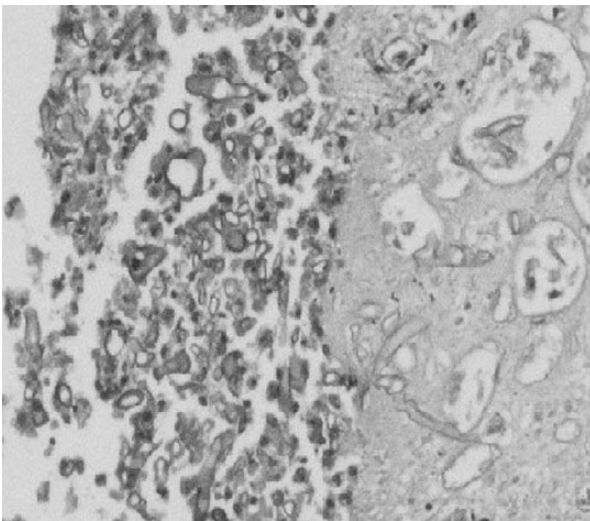
**Table 1.** Characteristics of patients with fungal infections of kidney and RPN

Number	Age/ gender	Presenting features	Underlying diseases	Culture, blood (B)/urine (U)	Serum creatinine mg/dL ( $\mu$ mol/L)	Kidney imaging	Kidney involvement	Diagnosis	Outcome
<b>Candidiasis</b>									
1	32 M	Diarrhea, fever, gastrointestinal bleed, DKA	Type-1 diabetes	Not available	1 (88.4)	Not available	Disseminated	Autopsy	Died
2	2/365 F	Jaundice, ARDS, gastrointestinal bleed	Prematurity	Not available	0.8 (70.7)	Not available	Disseminated	Autopsy	Died
3	19 M	Gastrointestinal bleed, liver failure	Hepatitis	Not available	4 (353.6)	Not available	Disseminated	Autopsy	Died
4	45 M	Acute renal failure, Increased blood glucose	Type-2 diabetes	Not available	10.7 (945.8)	Not available	Isolated	Autopsy	Died
5	40 M	Septicemia	Type-2 diabetes	Not available	7.6 (671.8)	Not available	Isolated	Autopsy	Died
6	45 M	Fever, flank pain, oliguria	Type-1 diabetes, sepsis	<i>C. albicans</i> (B) <i>Enterococci</i> (B)	9.3 (872.1)	PCS-dilated	Isolated	Autopsy	Died
7	20 M	Fever, flank pain, DKA, anuria, FMPU	Type-1 diabetes	<i>C. tropicalis</i> (U)	7.8 (689.5)	PCS-dilated	Isolated	Sloughed papilla	Alive
8	36 F	Fever, flank pain, dysuria	Type-2 diabetes	<i>E. coli</i> (U)	3.8 (335.9)	PCN-dilated PCS	Isolated	Sloughed papilla (PCN)	Alive
9	38 M	Urine retention, acute renal failure	Type-2 diabetes	<i>K. pneumonia</i> (U)	7 (618.8)	PCS-dilated	Disseminated	Autopsy	Died
10	62 M	Oliguria, dysuria, FMPU	Type-2 diabetes, alcoholism	Not available	5.5 (486.2)	Not available	Isolated	Sloughed papilla	Died
11	2/12 M	Fever, dysuria, flank pain	Immune deficiency	<i>C. tropicalis</i> (B) <i>Enterobacter</i> (B) <i>Klebsiella</i> (B)	1.6 (141.4)	PCS-dilated	Disseminated	Autopsy	Died
12	50 M	Fever, flank pain, anuria, FMPU	Type-2 diabetes, sepsis	<i>C. tropicalis</i> (PCN) <i>E. coli</i> (U) <i>K. pneumoniae</i> (B)	7.9 (698.3)	US- and CT-dilated PCS, Renal abscess	Isolated	Sloughed papilla	Died
13	1/12 M	Diarrhea, acute renal failure	Hemolytic uremic syndrome	Not available	2.5 (221)	Not available	Disseminated	Autopsy	Died
14	48 F	Dysuria, FMPU	Bell's palsy, steroid use	<i>C. albicans</i> (U)	1.5 (132.6)	PCS-dilated	Isolated	Sloughed papilla	Alive
15	48 M	Flank pain, dysuria recurrent FMPU	Type-2 diabetes	<i>C. tropicalis</i> (B) <i>E. coli</i> (U)	4.3 (380.1)	PCS-dilated	Isolated	Sloughed papilla	Alive
16	32 F	Fever, flank pain, oliguria, dysuria	Type-2 diabetes	<i>E. coli</i> (U)	2.4 (212.1)	US-pyonephrosis CT-abscess with ring sign	Isolated (Aspirate- <i>C. Albicans</i> )	Aspirate-candida, CT-Abscess with ring sign	Alive
17	52 M	Flank pain, dysuria, FMPU	Type-2 diabetes	<i>E. coli</i> (U)	1.5 (132.6)	PCS-dilated	Isolated	Sloughed papilla	Alive
18	40 F	Fever, dysuria, FMPU	Type-2 diabetes	Not available	1.2 (106.1)	Not available	Isolated	Sloughed papilla	Alive
19	49 M	Fever, dysuria, oral thrush	Kidney transplant, post-transplant diabetes mellitus	<i>K. pneumoniae</i> and <i>E. coli</i> (U)	3.5 (309.4)	No abnormality	Isolated	Biopsy	Alive
20	73 M	Fever dysuria	Bilateral kidney stones	<i>Enterococcus faecalis</i> (U)	4.5 (397.8)	PCS-dilated	Isolated	Sloughed papilla (PCN)	Alive
<b>Aspergillois</b>									
21	56 M	FMPU	Type-2 diabetes	Not available	1.2 (106.1)	NA	Isolated	Sloughed papilla	Alive
22	18 M	Fever, flank pain	Septicemia	<i>E. coli</i> (U)	1.9 (167.9)	Kidney size increased	Disseminated	Autopsy	Died
23	1 M	Fever, diarrhea	Hemolytic uremic syndrome	Not available	3.5 (308)	NA	Disseminated	Autopsy	Died
24	45 M	Fever, flank pain, FMPU	Type-2 diabetes	Not available	10.3 (910)	Bilateral kidney abscesses	Isolated	Sloughed papilla	Alive
25	25 M	Fever, hematuria allograft dysfunction	Kidney transplant	<i>Pseudomonas</i> (U)	10 (884)	NA	Isolated	Biopsy	Alive
26	40 M	Flank pain, FMPU	Type-2 diabetes	Not available	1.5 (132.6)	NA	Isolated	Sloughed papilla	Alive
<b>Mucormycosis</b>									
27	25 M	Fever, flank pain, anuria, hematuria	None	Not available	7 (618.8)	NA	Disseminated	Autopsy	Died
28	35 M	Fever, flank pain, FMPU	None	Not available	1.3 (114.9)	US-filling defect	Isolated	Sloughed papilla	Alive
29	59 M	Fever, dysuria allograft dysfunction	Kidney transplant	<i>Pseudomonas</i> (U)	2.0 (176.8)	CT-transplant kidney abscesses	Isolated	Biopsy	Alive

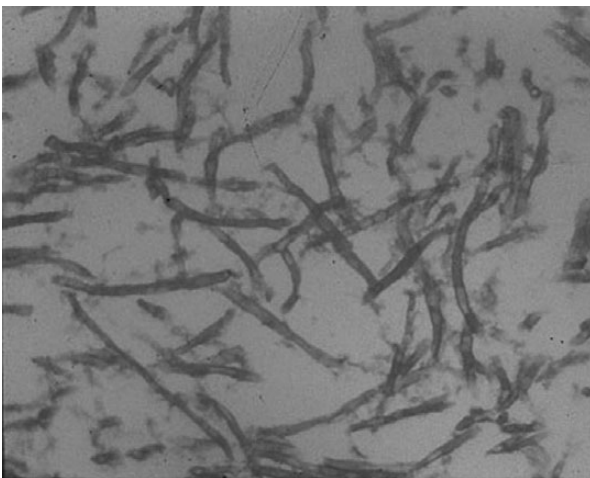




**Fig. 1.** Microsection of the kidney showing colonies of yeast and filamentous forms of *Candida* in necrosed papilla (PAS,  $\times 550$ ). A color version of this figure can be found online as supplementary data.



**Fig. 2.** Photomicrograph showing a necrotic papilla with fungal hyphae of *Mucor* in the interstitium, tubules, luminal surface and urinary space (H&E,  $\times 550$ ). A color version of this figure can be found online as supplementary data.



**Fig. 3.** High-power photomicrograph of septate hyphae of *Aspergillus*, identified in sloughed papillary tissue (PAS,  $\times 1375$ ). A color version of this figure can be found online as supplementary data.

more often for the diagnosis and management of RPN [30].

The treatment of RPN in renal mycosis includes the administration of antifungal medicines and management of associated complications. Drainage of blocked urinary system via percutaneous nephrostomy, ureteral stent placement or endoscopic retrieval of the obstructing sloughed papillae may be necessary in these patients [31]. Nephrectomy may be lifesaving if overwhelming infection is present. Besides antifungals, medical management consists of the administration of broad-spectrum antibiotics as fungal infections are often associated with bacterial infections as well. Specific antifungal therapy depends on the fungi identified in the necrotic papillae. For RPN associated with *Candida* infection, fluconazole has been found to be effective. For filamentous fungi such as *Aspergillus* and *Zygomycetes*, amphotericin-B and its lipid formulations are the drugs of choice. In addition, itraconazole has been an adjunctive therapy for renal aspergillosis and posaconazole for zygomycosis [32].

In conclusion, we report the largest series to date of RPN associated with fungal infections. It is possible, however, that besides fungal infections, associated comorbid conditions might also have contributed to the development of this condition. RPN presents with varying clinical signs and symptoms and a high index of suspicion is necessary for the ante-mortem diagnosis and management.

*Conflict of interest statement.* None declared.

### Supplementary data

Supplementary data are available online at <http://ckj.oxfordjournals.org>.

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