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 diagnosis 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
Renal papillary necrosis with fungal infections

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 septicaemia. 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 ± 3.2 mg/dl (391.9 ± 291.2 μmol/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 15 (52%) macroscopic 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 computed 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, Tomasheski 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
| Number | Age/gender | Presenting features | Underlying diseases | Culture, blood (B)/urine (U) | Serum creatinine mg/dL (μmol/L) | Kidney imaging | Kidney involvement | Diagnosis | Outcome |
|--------|------------|---------------------|--------------------|-----------------------------|---------------------------------|----------------|-------------------|-----------|---------|
| 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 | Disseminated | Autopsy | Died |
| 5      | 40 M       | Septicemia | Type-2 diabetes | Type-1 diabetes, sepsis | 7.6 (671.4) | Not available | Isolated | Autopsy | Died |
| 6      | 45 M       | Fever, flank pain, oliguria | Type-2 diabetes | Type-1 diabetes | 9.3 (872.1) | Not available | Isolated | Autopsy | Died |
| 7      | 20 M       | Fever, flank pain, DKA, anuria, FMPU | Type-2 diabetes | E. coli (U) | 7.8 (689.5) | PCS-dilated | Isolated | Sloughed papilla | Alive |
| 8      | 36 F       | Fever, flank pain, dysuria, | Type-2 diabetes | E. coli (U) | 3.8 (335.9) | PCN-dilated | Isolated | Sloughed papilla (PCN) | Alive |
| 9      | 38 M       | Urine retention, acute renal failure | Type-2 diabetes | K. pneumonia (U) | 7 (618.8) | PCS-dilated | Disseminated | Autopsy | Died |
| 10     | 62 M       | Oliguria, dysuria, FMPU | Type-2 diabetes, 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 | C. tropicalis (B) Enterococcus (B) Klebsiella (B) | 1.6 (141.4) | PCS-dilated | Disseminated | Autopsy | Died |
| 12     | 50 M       | Fever, flank pain, anuria, FMPU | Type-2 diabetes, sepsis | C. tropicalis (PCN) E. coli (U) K. pneumoniae (B) | 7.9 (698.3) | US- and CT-dilated PCS, Renal abscess | Not available | Sloughed papilla | Died |
| 13     | 1/12 M     | Diarrhea, acute renal failure | Hemolytic uremic syndrome Bell's palsy, steroid use | C. albicans (U) | 2.5 (221) | Not available | Disseminated | Autopsy | Died |
| 14     | 48 F       | Dysuria, FMPU | Immune deficiency | C. tropicalis (B) Enterococcus (B) Klebsiella (B) | 1.5 (132.6) | PCS-dilated | Isolated | Sloughed papilla | Alive |
| 15     | 48 M       | Flank pain, dysuria recurrent FMPU | Type-2 diabetes, sepsis | C. tropicalis (B) E. coli (U) | 4.3 (380.1) | PCS-dilated | Isolated | Sloughed papilla | Alive |
| 16     | 32 F       | Fever, flank pain, oliguria, dysuria | Type-2 diabetes | E. coli (U) | 2.4 (212.1) | US-pyonephrosis CT-abscess with ring sign | Isolated | Sloughed papilla | Died |
| 17     | 52 M       | Flank pain, dysuria, FMPU | Type-2 diabetes | E. coli (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 | K. pneumoniae and E. coli (U) | 3.5 (309.4) | No abnormality | Isolated | Sloughed papilla | Alive |
| 20     | 73 M       | Fever dysuria | Bilateral kidney stones | Enterococcus faecalis (U) | 4.5 (397.8) | PCS-dilated | Isolated | Sloughed papilla (PCN) | Alive |
| 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 | E. coli (U) | 1.9 (167.9) | Kidney size increased NA | Disseminated | Autopsy | Died |
| 23     | 1 M        | Fever, diarrhea | Hemolytic uremic syndrome | Not available | 3.5 (308) | Not available | Disseminated | Autopsy | Died |
| 24     | 45 M       | Fever, flank pain, FMPU | Type-2 diabetes | Not available | 10.3 (910) | Bilateral kidney abscesses NA | Isolated | Sloughed papilla Biopsy | Alive |
| 25     | 25 M       | Fever, hematuria allograft dysfunction | Kidney transplant | Pseudomonas (U) | 10 (884) | Bilateral kidney abscesses NA | Isolated | Sloughed papilla Biopsy | Alive |
| 26     | 40 M       | Flank pain, FMPU | Type-2 diabetes | Not available | 1.5 (132.6) | NA | Isolated | Sloughed papilla | Alive |
| 27     | 25 M       | Fever, flank pain, anuria, hematuria | None | Not available | 7 (618.8) | NA | Disseminated | Autopsy | Died |
| 28     | 55 M       | Fever, flank pain, FMPU | None | Not available | 1.3 (114.9) | US-filling defect | Isolated | Sloughed papilla Biopsy | Alive |
| 29     | 59 M       | Fever, dysuria allograft dysfunction | Kidney transplant | Pseudomonas (U) | 2.0 (176.8) | CT-transplant kidney abscesses | Isolated | Sloughed papilla Biopsy | Alive |
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 Aspergil lus 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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