ORIGINAL ARTICLE

Isolated bilateral renal mucormycosis in apparently immunocompetent patients—a case series from India and review of the literature

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ABSTRACT

Background: Isolated renal mucormycosis (IRM) is a potentially fatal disease affecting immunocompromised hosts. IRM affecting apparently immunocompetent patients is rare, with few previous reports, mostly from India. We describe 10 cases of bilateral IRM with no underlying risk factors.

Methods: We performed a retrospective analysis of cases of IRM from our hospital information system admitted between 2009 and 2016. We analyzed the data of this cohort of IRM, including epidemiological characteristics, clinical presentation, diagnostic procedures, treatment details and outcome.

Results: In all, 10 cases of bilateral IRM were identified. All of them were males with a mean age of 24.7 years (range 10–42). Most patients were initially managed as acute bacterial pyelonephritis with acute kidney injury. A total of eight patients were diagnosed antemortem. Diagnostic clues include sepsis not controlled with broad-spectrum antibiotics and enlarged kidneys with or without hypodensities on ultrasound/computed tomography imaging. Three patients also gave a specific history of passing white flakes in their urine. Eight patients received specific antifungal therapy with amphotericin B with or without posaconazole. Three patients in whom the disease was apparently confined to the pelvicalyceal system underwent local irrigation with Amp-B. One patient underwent bilateral nephrectomy. Four patients succumbed to the disease while five patients were successfully treated. One patient was discharged against medical advice.

Conclusions: IRM is a rare, life-threatening disease associated with high mortality even in immunocompetent individuals. Typical clinical and radiological findings and a high index of suspicion may help in early diagnosis, but definitive diagnosis

requires histopathological and/or microbiological confirmation. Early and rapid diagnosis along with aggressive multidisciplinary management including initiation of specific antifungal therapy with or without surgical debridement is vital for a successful outcome.

Keywords: amphotericin B, immunocompetent, isolated renal mucormycosis, nephrectomy, posaconazole

INTRODUCTION

Mucormycosis (MM) is a rare, life-threatening invasive fungal infection caused by a group of filamentous fungi of the class Zygomycetes. Most cases are caused by those of the order Mucorales, which include genera *Rhizopus* (most common pathogen), *Mucor*, *Rhizomucor*, *Absidia*, *Apophysomyces* and *Cunninghamella*. The terms MM and zygomycosis are used interchangeably (the term phycomycosis is also used) [1, 2]. They are vasotropic and angioinvasive, usually affecting immunocompromised patients. Renal involvement due to MM mostly occurs concurrently with disease affecting other parts of the body or as a part of disseminated disease [3, 4].

Isolated renal mucormycosis (IRM) is reported rarely in the literature and mainly as unilateral. It has been documented in few case reports, mostly from developing countries, especially from the Indian subcontinent, in patients having an underlying immunocompromised state [5–11]. IRM is liable to be missed clinically, especially in immunocompetent patients. It is an almost fatal disease if bilateral and diagnosed late, especially in the angioinvasive state [5–11]. There is a paucity of literature on the clinical behavior, management and outcome of bilateral IRM.

Here we present 10 cases of bilateral IRM affecting apparently immunocompetent patients with no underlying predisposing conditions, with the objective of comparing our data in terms of clinical behavior, management and outcome with those cases already reported in the literature. We also propose an algorithm for early diagnosis and management of these patients.

MATERIALS AND METHODS

We retrospectively collected the data of all patients admitted between 2009 and 2016 with a diagnosis of renal MM from the hospital information system (HIS) of our tertiary care center. The cases with IRM were identified as those without evidence of *Mucor* infection at other sites such as the nasal sinuses, orbits, eyes, lungs and central nervous system. Those with the disseminated disease were excluded. Patients with underlying predisposing conditions for *Mucor* infection, including diabetes mellitus, human immunodeficiency virus (HIV) infection, steroid or immunosuppressant use and known immunodeficiency disease, were excluded.

We analyzed the data of this cohort of IRM, including epidemiological characteristics, clinical presentation, diagnostic procedures, treatment details and outcome. In all the cases, routine hematological and biochemical tests, blood and urine cultures, imaging [ultrasound (US), renal Doppler or computed tomography (CT)] were done.

Diagnosis of IRM

Diagnosis of renal MM was established by doing urine microscopy and culture, imaging in all patients of suspected MM and renal biopsy in certain cases. Figure 3A represents the diagnostic algorithm followed by us. Repeatedly positive urine microscopy and culture established the diagnosis of renal MM. Smears of specimens were prepared for direct microscopic examination through the use of 10% potassium hydroxide and Gomori's methenamine silver (GMS) stain. Some part of the specimens were also inoculated on Sabouraud dextrose agar. Abundant, broad, sparsely septate thin-walled hyaline hyphae with irregular non-dichotomous branching characteristic of zygomycetes were found on studies of both the potassium hydroxide mounts and Grams-stained material and on this basis a diagnosis was made of zygomycosis. On the basis of the culture and microscopic characteristics, the strain was identified.

In patients with negative urinalysis but with a high index of suspicion based on imaging studies and other presenting features, a renal biopsy was performed. A histopathological diagnosis of renal MM was made based on the identification of broad, aseptate, irregular and right-angled branching fungal hyphae in renal biopsy tissue sections stained with hemotoxylin and eosin, periodic acid–Schiff, Grocott–Gomori or silver methenamine stains. Definitive diagnosis was made after tissue demonstration of fungus on histopathology, while probable diagnosis was made on the basis of only microscopy and culture positivity of fungus.

Management of IRM

Management of IRM included antifungal drugs [amphotericin B (Amp-B) with or without posaconazole] with or without bilateral nephrectomy. The choice of conventional (amphotericin deoxycholate) versus the liposomal form of Amp-B was made depending upon the renal function and cost affordability of the patients. The maximum cumulative dose of Amp-B used was 3 g. Local irrigation with conventional Amp-B through percutaneous nephrostomy (PCN) was done in patients where the disease was apparently confined to the pelvicalyceal system as suggested by imaging or in whom there was a poor response to parenteral Amp-B therapy. Posaconazole was added to Amp-B as part of the initial regimen in patients who could afford therapy and in patients with a poor response to the initial 2 weeks of Amp-B therapy. Response to therapy was assessed by the clinical response, urine microscopy and culture and imaging findings. In patients completing the Amp-B therapy, posaconazole was used as a maintenance antifungal therapy. The decision to do a nephrectomy was based on the response to antifungal therapy and the extent/type of renal involvement by the fungus. Refractory cases and cases of invasive renal MM proven by imaging and/or biopsy were considered for bilateral nephrectomy. However, the decision to perform a nephrectomy was heavily influenced by the ability of patients to afford treatment, as a bilateral nephrectomy entails lifelong renal replacement therapy, incurring significant costs and morbidity.

Results

We found 21 cases of MM with renal involvement in our HIS. In all, 12 patients had IRM and of them, 10 were diagnosed with bilateral disease. No underlying predisposing conditions were identified in all 10 cases.
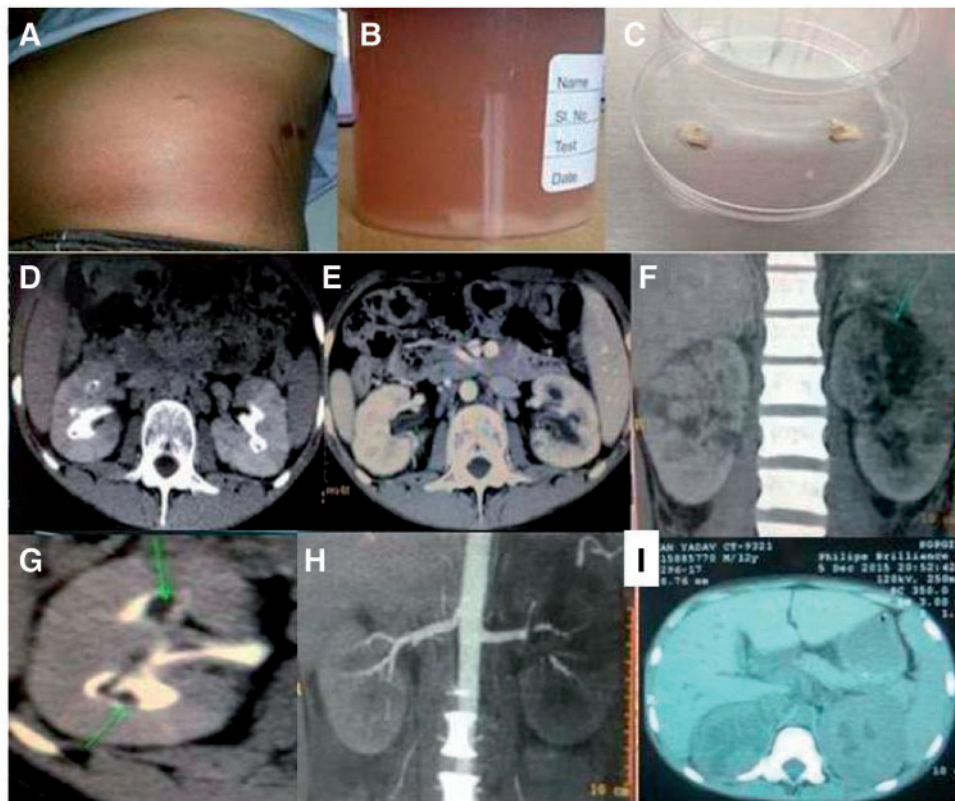
FIGURE 1: Clinical findings in IRM patients. (A) Patient's abdomen shows erythema and subcutaneous edema of the flank region. (B) Urine sample: gross hematuria with white flakes containing papillary tissue and fungus settled at the bottom. (C) Mucor bezoars passed in the urine of an IRM patient complaining of abdominal colics. (D) Non-contrast CT of the abdomen in the coronal plane at the level of the kidneys shows bilateral bulky kidneys with parenchymal hypodensities. (E) Contrast CT of the abdomen in the axial plane at the level of the kidneys shows bilateral bulky kidneys with enhancing thickening of the wall of the renal pelvis. (F) Contrast CT of the abdomen in the coronal plane shows bilateral bulky kidneys with multiple nonenhancing areas with preserved normal subcapsular parenchyma (Rim sign). (G) Contrast CT of the abdomen (excretory phase) in the coronal plane shows the right kidney demonstrating a filling defect in the calyceal system. (H) CT angiography (reformatted in the coronal plane) shows normal main renal arteries with attenuated segmental branches in the region of nonenhancing areas suggestive of vasular invasion. (I) Noncontrast CT of the abdomen shows bilaterally enlarged kidneys with irregular, nonhomogeneous, hypodense areas within the renal parenchyma and perinephric fat stranding.
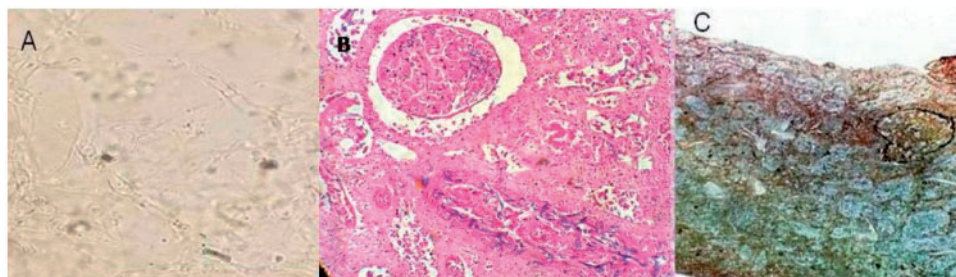

FIGURE 2: (A) Urine cytopathology shows broad, ribbon-like fungal hyphae. (B) Extensive cortical necrosis of the renal parenchyma with broad, ribbon-like fungal hyphae (hematoxylin and eosin, ×200). (C) Broad, aseptate hyphae with right-angle branching in necrosed renal parenchyma (chromic acid silver methenamine stain, oil immersion).

Demographic profile

The ages of the patients ranged from 10 to 42 years (mean 24.7). All were male, hailed from a rural community and belonged to the low socioeconomic strata. None of the patients had any predisposing conditions such as diabetes mellitus, HIV infection or malignancy and were apparently immunocompetent. However, a separate search for immunodeficiency disorders was not performed.

Clinical features

Table 1 summarizes the epidemiological and clinical characteristics of all patients with bilateral IRM. All patients except one presented with fever, flank pain, sepsis and acute kidney injury (AKI). This patient (patient 3; Table 1) presented with acute abdomen, sepsis and AKI. In all, six patients were oliguric and dialysis dependent while the remaining four had non-oliguric (patients 1, 4, 5 and 10) renal failure. An initial clinical diagnosis of bacterial pyelonephritis was made in eight patients and hence treated with broad-spectrum antibacterial agents. Antibacterial agents were withdrawn after confirmation of fungal infection. A total of eight patients were diagnosed antemortem. Diagnostic clues pointing to a fungal etiology in these patients were sepsis not controlled with broad-spectrum antibiotics and enlarged kidneys with or without hypodensities on
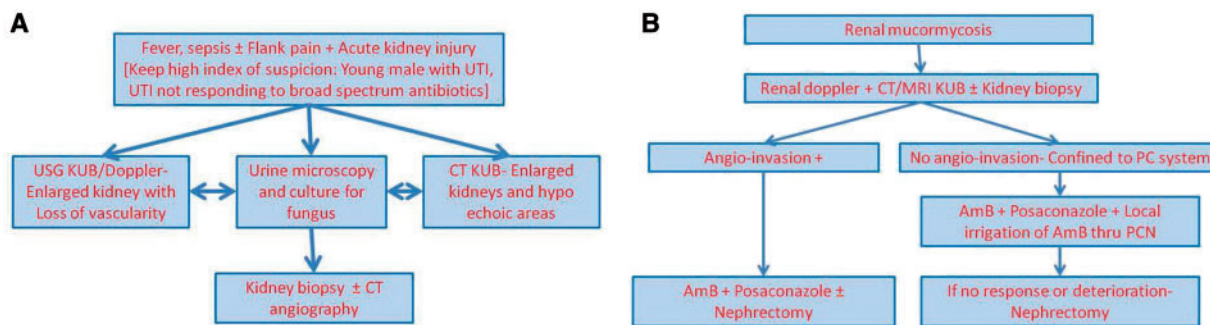
FIGURE 3: Algorithmic approach to the **(A)** diagnosis of IRM **and (B)** management of IRM. KUB, kidney ureters bladder; MRI, magnetic resonance imaging. AmB, Amphotericin; CT, computerized tomography; KUB, kidney ureter bladder; MRI, magnetic resonance imaging; PCN, percutaneous nephrostomy; USG, Ultrasound.

Table 1. Epidemiological and clinical characteristics of patients with bilateral IRM

Patient number	Age (years)/ gender	Background/ socioeconomic strata	Clinical features	Clinical diagnosis	Clue to diagnosis	Urine microscopy
1	32/M	Rural/low	Fever, flank pain, sepsis, AKI	Bacterial PN	B/L ↑ in kidney size	*Rhizopus*
2	34/M	Rural/low	Fever, flank pain, sepsis, AKI	Bacterial PN	B/L ↑ in kidney size with infarction	Anuric
3	34/M	Rural/low	Fever, acute abdomen, anuria, peritonism with ascites and sepsis	Intestinal perforation	PM diagnosis on histopathology	Not done
4	32/M	Rural/low	Fever, flank pain, sepsis, AKI	Bacterial PN	B/L ↑ in kidney size	*A. elegans*
5	24/M	Rural/low	Fever, flank pain, hematuria, white flakes in urine	Bacterial PN/ papillary necrosis	White-colored urine mixed with blood and fungal hyphae, B/L ↑ in kidney size	*Rhizopus*
6	10/M	Rural/low	Fever, flank pain, sepsis, AKI	TMA/DIC	PM diagnosis on histopathology	Not done
7	42/M	Rural/low	Fever, flank pain, sepsis, AKI	Bacterial PN	B/L ↑ in kidney size with infarction	Anuric
8	18/M	Rural/low	Fever, flank pain, sepsis, AKI, MODS	Bacterial PN	B/L ↑ in kidney size with hypodensities	*A. elegans*
9	24/M	Rural/low	Fever, flank pain, sepsis, AKI	Bacterial PN	White-colored urine with fungal hyphae, B/L ↑ in kidney size	*Rhizopus*
10	14/M	Rural/low	Fever, flank pain, white flakes in urine	Bacterial PN	White-colored urine with fungal hyphae and bezoars, B/L ↑ in kidney size	*A. elegans*

B/L, bilateral; DIC, disseminated intravascular coagulation; MODS, multiorgan dysfunction syndrome; PM, postmortem; PN, pyelonephritis; TMA, thrombotic microangiopathy; ↑, increased.

US/CT imaging. In all, three patients also gave a specific history of passing white flakes in their urine. A postmortem diagnosis of renal MM was made in two patients.

Investigations

Table 2 summarizes the imaging characteristics, management and outcomes. US of the kidneys was done in all patients, while other imaging studies, including renal Doppler, CT scan or magnetic resonance imaging, were done in all but two patients. In all, three patients had focal areas of loss of vascularity on renal

Doppler imaging suggestive of infarction, which were later confirmed by CT imaging. A thick pelvicalyceal system and ureters without suggestion of infarction on CT imaging were seen in four patients, suggestive of confinement of infection up to the pelvicalyceal system. Urine for fungal microscopic examination, culture and sensitivity was sent in six patients and was positive repeatedly for *Mucor*. Of the remaining patients, urine examination for fungus could not be performed, as the diagnosis was not suspected in two patients who had a stormy course culminating in death and two patients were anuric. The organism on fungal culture was identified in three patients as

Table 2. Imaging characteristics, management and outcome of IRM in immunocompetent patients

Patient number	US abdomen	Doppler study	CT abdomen/MRI	Management	FU	Outcome
1	B/L ↑ in kidney size	Normal	B/L ↑ in kidney size, thick PC system	Amp-B (2.8 g), posaconazole (4 months), bilateral instillation of Amp-B via PCN	61 months	Survived
2	B/L ↑ in kidney size, with hypodensities	Focal loss of vascularity	B/L ↑ in kidney size, hypodensities, infarcts	Amp-B bilateral nephrectomy	10 days	Mortality
3	B/L ↑ in kidney size, ascites	Not done	Not done	Laparotomy, antimicrobial only	4 days	Mortality
4	B/L ↑ in kidney size, mild HDN	Normal	B/L ↑ in kidney size, thick PC system	Amp-B (2.5 g), posaconazole (4 months) and bilateral instillation of Amp-B via PCN		Survived
5	B/L ↑ in kidney size	Normal	B/L ↑ in kidney size, focal PN	Amp-B (3.2 g), posaconazole (6 months)	26 months	Survived
6	B/L ↑ in kidney size	Not done	Not done	Broad-spectrum antibiotics	7 days	Mortality
7	B/L ↑ in kidney size with hypodensities	Focal loss of vascularity	B/L ↑ in kidney size, hypodensities, infarcts	Amp-B (3 g), posaconazole (2 weeks)	–	DAMA
8	B/L ↑ in kidney size with hypodensities	Focal loss of vascularity	B/L ↑ in kidney size, hypodensities, infarcts	Amp-B (200 mg)	5 days	Mortality
9	B/L ↑ in kidney size	Normal	B/L ↑ in kidney size	Amp-B (3 g), posaconazole (3 months)	6 months	Survived
10	B/L ↑ in kidney size	Normal	B/L ↑ in kidney size, thick PC system	Amp-B (2.8 g), posaconazole (4 months), bilateral instillation of Amp-B via PCN	3 month	Survived

B/L, bilateral; DAMA, discharged against medical advice; FU, follow-up; HDN, hydronephrosis; MRI, magnetic resonance imaging; PC, pelvi-calyceal system; PN, pyelonephritis; ↑, increased.

Apophysomyces elegans and in three as *Rhizopus*. An antemortem diagnosis of renal MM was made in all but two patients, in whom the diagnosis could only be confirmed postmortem. Kidney biopsy was done in 8 of 10 patients and 2 of these were postmortem. Histopathological demonstration of fungus was made in 4 of 10 patients. The histopathological findings of patients 2, 3, 6 and 8 were suggestive of acute cortical necrosis along with ghost outlining of cellular architecture and broad, aseptate hyphae with right-angle branching in necrosed renal parenchyma. The histopathological findings of patients 1, 4, 5 and 10 were suggestive of acute tubular necrosis along with interstitial infiltrates, but fungus could not be demonstrated.

Management

Specific treatment was possible in eight patients, including antifungal therapy (Amp-B with or without posaconazole) with or without local irrigation through PCN of the pelvicalyceal system and ureters with Amp-B. In all patients, a conventional form of Amp-B was used. Posaconazole was used as an adjuvant therapy to Amp-B in two patients (patients 5 and 10). Maintenance antifungal therapy with posaconazole was given in two patients

(patients 4 and 9). Local irrigation with Amp-B, in collaboration with urologists, was done in three patients in whom MM was thought to be confined to the pelvicalyceal system and ureters with no evidence of angioinvasion. Bilateral nephrectomy was done in patient 2 (Table 2) and was planned in patient 5 (Table 2). However, patient 5 was subsequently discharged against medical advice because of the inability to afford hemodialysis and a poor response to antifungal therapy.

Outcome

In all, 4 of 10 patients succumbed to the disease due to severe sepsis and multiorgan dysfunction syndrome. One patient was discharged against medical advice on financial grounds. The remaining five patients who survived were followed up (range 3–61 months) and did not have subsequent relapse of the disease.

DISCUSSION

To our knowledge, this is the first detailed and largest report of bilateral IRM in apparently immunocompetent patients. This

Table 3. Comparison of different case series/reports of IRM in immunocompetent patients

Case series	n	Age range	Sex (n)	Antemortem	Renal involvement (n)	Therapy (n)	Mortality, n
Gupta et al. [30][a,b]	7	9 mo–57 yrs	M (7)	4	U (1), B (6)	Amp-B (3), Amp-B and nephrectomy (2), untreated (2)	6
Chakrabarti et al. [13][a,b]	3	10–70 yrs	M (3)	3	U (1), B (2)	Amp-B and surgical drainage or PCN (3)	1
Chugh et al. [14][a]	3	17–37 yrs	M (1) F (2)	3	U (2) B (1)	Amp-B and nephrectomy (3)	2
Marak et al. [15][a]	2	17–32 yrs	M (2)	2	U (1) B (1)	Amp-B and PCN (2)	2
Jianhong et al.[24][b]	3	3 mo–14 yrs	M (2) F (1)	3	U (3)	Amp-B (1), Amp-B and surgical drainage (1), Amp-B and nephrectomy (1)	0
Pahwa et al. [31][a]	1	30 yrs	M (1)	1	U (1)	Nephrectomy (1)	0
Kumar et al. [32][a]	1	39 yrs	M (1)	1	U (1)	Amp-B and endoscopic removal of fungal bezoars (1)	0
Nayagam et al. [33][a,b]	1	18 mo	M (1)	1	U (1)	Amp-B and nephrectomy (1)	0
Thomas et al. [34][a]	1	41 yrs	M (1)	1	U (1)	Amp-B and nephrectomy (1)	0
Paonam et al. [35][a]	1	24 yrs	F (1)	1	B (1)	Amp-B and surgical debridement (1)	1
Goel et al. [28]	1	45 yrs	M (1)	1	U (1)	Amp-B and nephrectomy (1)	0
Singh et al. [36][a]	1	18 yrs	M (1)	1	B (1)	Amp-B and nephrectomy (1)	1
Pickles et al. [37]	1	18 yrs	M (1)	1	U (1)	Amp-B and nephrectomy (1)	0
Singh et al. [38][a]	1	22 yrs	M (1)	1	U (1)	Amp-B and nephrectomy (1)	0
Our case series[a,b]	10	10–42 yrs	M (10)	8	B (10)	Amp-B (9), untreated (1), surgery (1), PCN (3)	5

B, bilateral; DAMA, discharged against medical advice; F, female; M, male; mo, months; U, unilateral; yrs, years.
[a]Reports from India.
[b]Included children.

report highlights the life-threatening nature of *Mucor* infections even in immunocompetent individuals, in whom it rarely manifests. Most of the patients in our study had a clinical presentation akin to acute bacterial pyelonephritis and had dialysis-dependent AKI. Early diagnosis of bilateral IRM did help in salvaging half of our patients. Delayed or missed diagnosis of the angioinvasion stage might have contributed to the stormy and fatal clinical course in the other half of our patients. A few unique observations were made from our study, including bilateral IRM affected predominantly young males with low socioeconomic status and a rural background; a specific history of passing white flakes in urine was given by three patients; focal loss of vascularity on renal Doppler, corresponding renal infarcts on CT and a thickened pelvicalyceal system were common distinguishing features; four patients in whom the infection was possibly confined to the pelvi-calyceal system and ureters, as suggested by imaging and histopathology, survived with multidisciplinary care. We successfully treated 5 of 10 patients, of this nearly 100% with fatal illness [12, 13–15, 16, 17], because of a high index of suspicion learned from our previous experiences and early diagnosis.

The most common clinical presentations of MM in immunocompromised hosts include rhino-orbito-cerebral, pulmonary, gastrointestinal and disseminated forms [18, 19]. Most human infections result from inhalation of fungal sporangiospores that have been released in the air. The largest series of zygomycosis from India had 129 patients; the rhino-orbito-cerebral type was most common (44.2%) and renal involvement was seen in 14.0% of patients. About 23% of patients were apparently healthy and 35% were diagnosed postmortem [20]. The cutaneous form is most common in immunocompetent patients, followed by rhino-orbito-cerebral disease [18, 12].

Renal MM is rare and often a manifestation of disseminated disease, in which renal involvement has been reported in up to 20% of cases [4]. IRM has been reported in patients with acquired immune deficiency syndrome, intravenous drug abusers and those on corticosteroid therapy (5, 21). In contrast, IRM in immunocompetent individuals is extremely rare and the majority of cases have been reported from the Indian subcontinent and China [22–24]. However, the majority of the cases of IRM reported from India were apparently immunocompetent, in contrast to cases reported from China who possessed risk factors for developing MM. The number of such cases has shown an increasing trend over the past three decades. It is presumed to occur via seeding of kidneys during an episode of fungemia from a subclinical pulmonary focus or due to ascending infection of the urinary tract [25, 26]. Renal parenchymal necrosis results from angioinvasion of fungal hyphae, leading to vascular thrombosis and infarction. *Mucor* hyphae may also invade the glomeruli and tubules, sometimes with associated giant cell reaction and granuloma formation [27]. Clinically, patients with IRM present with fever, flank pain, tenderness, hematuria, pyuria and renal failure, which are usually the result of near total occlusion of the renal arteries or their branches, similar to our patients [6, 28, 29].

Table 3 summarizes the various case series/reports in the literature on IRM. To date ~12 cases of bilateral IRM have been described in literature. Our case series included 10 immunocompetent patients with bilateral IRM. One of these was a 10-year-old child and the remaining cases were adults, and all of them were males. All patients presented with oligoanuric renal failure and six were dialysis dependent. Most of our patients were treated initially in lines of sepsis-/pyelonephritis-induced AKI. Specific therapy was possible in

only eight patients in whom the diagnosis was suspected clinically and confirmed subsequently. Bilateral nephrectomy was planned in two patients and was possible in only one. In our case series, *A. elegans* was identified in three patients and *Rhizopus* in three patients. A total of five patients were successfully treated.

Gupta *et al.* [30] described 9 cases of IRM out of 18 cases of renal MM, most of whom were male and 7 were immunocompetent. In all, four were diagnosed by antemortem kidney biopsy, one by postmortem kidney biopsy and two by autopsy. A total of six patients had bilateral renal involvement and all of them presented with severe irreversible renal failure and died. Only one patient was successfully treated, who had unilateral disease and had undergone nephrectomy. Specific infective species were identified in 2 of the 18 patients, with *Rhizopus arrhizus* and *A. elegans* [30].

Chakrabarti *et al.* [13] described three cases of IRM and two had bilateral disease. All three patients were diagnosed by microscopic examination and culture of drained pus. Only one had histological confirmation on autopsy. The remaining two had a successful outcome. Nephrectomy was not done in any of them.

Chugh *et al.* [14] found four cases of IRM; three were immunocompetent and one had bilateral disease. All three cases underwent nephrectomy in combination with antifungal therapy and two succumbed to the illness.

Two cases of IRM described by Marak *et al.*, [15] had successful outcomes without the need for nephrectomy. Of the three childhood cases of IRM described by Jianhong *et al.*, [24] one had undergone nephrectomy and all survived following therapy. Pahwa *et al.*, [31] in their single case report of IRM with no identifiable risk factors, proposed that simple nephrectomy without antifungal therapy may be sufficient in immunocompetent, afebrile, nontoxic patients with a coincidental finding of renal MM in a nephrectomy specimen.

Typical imaging findings of IRM on contrast-enhanced CT of the abdomen include enlargement of the kidneys, multiple low attenuations and nonenhancing areas in the parenchyma, reduced/absent contrast excretion and perinephric collections. Various authors have described these findings on CT as 'diffuse patchy nephrogram' [5, 25]. In the presence of suspicious radiologic findings, a biopsy is indicated to confirm the diagnosis. Diagnosis of MM is difficult, especially antemortem, due to variable clinical presentation and limitations in achieving a tissue diagnosis. The majority of cases reported in the past were diagnosed at autopsy or by a postmortem biopsy. IRM can clinically masquerade as rapidly progressive glomerulonephritis, pyelonephritis, renal abscess and acute interstitial nephritis. Hence, even in immunocompetent patients, nonresolving pyelonephritis should prompt the possibility of a fungal infection like MM. Blood and urine cultures are often negative. Examination of 24-h urine collections could increase the diagnostic yield. Radiological findings can be nonspecific. Hence definitive diagnosis relies on histopathological evidence of fungal invasion of affected tissues. A high index of suspicion is crucial for a timely diagnosis. Recently molecular diagnosis with real-time polymerase chain reaction has been suggested for early diagnosis [29].

Early initiation of therapy, which usually involves combined surgical debridement or nephrectomy and antifungal therapy, may improve the outcome. Reversal of underlying predisposing factors, if present, is also important. Drugs effective against MM include Amp-B, posaconazole and isavuconazole. The conventional Amp-B (Amp-B deoxycholate) is associated with **a** high incidence of adverse events and resistance in some cases. Lipid

formulations are especially useful in patients with renal failure and can be given at higher doses with fewer side effects. However, we have used conventional Amp-B in all of our patients.

Overall, survival for IRM is estimated to be 65% [34]. However, it is associated with nearly 100% mortality in patients with bilateral renal involvement with AKI [30]. The majority of survivors of IRM have been those with unilateral renal involvement and who received timely appropriate antifungal therapy with nephrectomy. Few case reports noted successful treatment of IRM with Amp-B deoxycholate without nephrectomy and the majority of them suffered unilateral renal disease [5, 7].

In our case series, specific antifungal therapy with Amp-B and posaconazole was given in eight patients. Local instillation of Amp-B into the pelvicalyceal system was done in three patients. Bilateral nephrectomy was done in one patient. The mortality was 50%, with four survivors and one patient discharged against medical advice.

To our knowledge this is the largest case series of bilateral IRM in the literature. A detailed description of the clinical presentation, diagnostic features and treatment outcomes contribute to the strengths of our report. However, we did not do a specific evaluation for other primary immunodeficiency syndromes in any of these patients. Hence the immunocompetent state is apparent and not absolute. This constitutes a limitation of the study and marks an area for potential research in the future.

Our experience emphasizes the need for a high index of suspicion for rapid diagnosis by imaging, microbiological and histological methods. Early initiation of systemic antifungal therapy and surgical intervention are necessary for this life-threatening condition.

CONCLUSION

IRM is a rare, life-threatening disease associated with high mortality even in immunocompetent individuals, in whom it rarely manifests. Typical clinical and radiological findings may help in rapid and early diagnosis. However, definitive diagnosis requires histopathological and/or microbiological confirmation. A high index of suspicion along with rapid diagnosis and early and aggressive multidisciplinary management, including initiation of specific antifungal therapy with or without surgical debridement, is vital for a successful outcome.

CONFLICT OF INTEREST STATEMENT

None declared, however, some of the cases have been published as individual case reports in different journals.

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