

Isolated Renal Zygomycosis: Novel Diagnostic and Prognostic Criteria with Experience of a Tertiary Care Center

Saurabh S. Chipde^a Priyadarshi Ranjan^a Hira Lal^b Vivek Singh^b Ram Naval^c
Rungmei S. Marak^d Anand Prakash^e Dharmendra Bhadoria^f R.K. Sharma^f
Rohit Kapoor^g Manas Ranjan Pradhan^a Manmeet Singh^a Jatinder Kumar^a
Mohammad S. Ansari^a Anil Mandhani^a Aneesh Srivastava^a Rakesh Kapoor^a

Departments of ^aUrology and Kidney Transplant, ^bRadiodiagnosis, ^cPathology, ^dMicrobiology, ^eSurgical Gastroenterology and ^fNephrology, Sanjay Gandhi Post Graduate Institute of Medical Sciences and ^gIntern BH, Lucknow, India

Key Words

Isolated renal zygomycosis · Prognostic criteria · Radiological diagnosis

Abstract

Background: Isolated renal zygomycosis is a life-threatening infection and difficult to diagnose ante mortem due to varied presentations. Most reports in the literature are case reports. We are presenting our experience of 10 patients. **Materials and Methods:** Retrospective data of 10 consecutive patients with primary renal zygomycosis, including 2 post-transplant patients, in our tertiary care center was analyzed. Epidemiological characteristics, predisposing conditions, clinical presentation, diagnostic findings and treatment outcomes were recorded. Characteristic radiological findings were recorded. Localized disease was managed by supportive treatment or percutaneous drainage and extensive disease with unilateral or bilateral nephrectomy. Renal involvement was confirmed in all patients by histopathology. **Results:** The mean age of presentation was 35 years. Five patients who had bilateral renal involvement presented with oliguric acute renal failure, hematuria and abdominal pain.

Three had unilateral renal disease and presented with flank pain and fever. The two post-transplant patients presented with fever and graft dysfunction. Even after aggressive treatment 5 patients died, accounting for a mortality rate of 50%. **Conclusion:** Isolated renal zygomycosis can be diagnosed with typical radiological findings, combined with clinical, laboratory and histopathological features. This study describes the newer ante mortem radiological diagnostic criteria and prognostic predictors of the disease.

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Introduction

Systemic fungal infections are rare in the kidneys but when they occur they are difficult to diagnose ante mortem and mostly prove lethal. Reno-invasive fungi are associated with overt segmental vascular thrombosis due to direct hyphal invasion of the renal vessels and parenchyma [1, 2]. Rarely, *Aspergillus* infection can cause intrarenal vascular thrombosis, but it is mostly seen with angioinvasive fungi belonging to the class Zygomycetes [3, 4]. This infection has now been classified as zygomycosis

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Dr. Saurabh S. Chipde, MS, MCh
Department of Urology and Kidney Transplantation
Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS)
Lucknow 14 (India)
Tel. +91 522 249 4110, E-Mail drsaurabh07@rediffmail.com

whereas earlier term mucormycosis is no longer in the newer taxonomic classification [5]. The most common pathogenic species are *Absidia corymbifera*, *Rhizopus oryza* and *Rhizomucor pusillus* [3–6]. They are seen usually in immunocompromized patients although rarely healthy subjects may also be affected [7–9]. Isolated renal involvement is uncommon and usually kidney gets involved as a part of disseminated disease [2, 10, 11]. The isolated renal disease has mostly been described as case reports mainly from the Indian subcontinent [12–17]. In this study, we describe a series of 10 patients with isolated renal zygomycosis.

The disease has so far been a nightmare to both urologists and nephrologists. In the past it was usually diagnosed on autopsy, but now renal biopsy and radiological imaging can confirm the diagnosis. A renal biopsy report along with special stains for fungus takes around 24–48 h in processing, which the treating clinicians cannot afford. In recent times certain radiological signs in computed tomography (CT) and magnetic resonance imaging (MRI) have been described for aggressive ante mortem diagnosis of this lethal disease. In our institution, we have learned to rely on a radiological protocol for diagnosing such cases rather than waiting for the pathology report to come. This early diagnosis and aggressive treatment is important because until the fungus filled kidney, which is throwing out fungemia into the blood, is removed or drained the mortality approaches 100%.

Materials and Methods

The records of 10 patients diagnosed to have renal zygomycosis over the past two years in our tertiary care center were reviewed. Epidemiological data and predisposing factors were recorded. The diagnosis was established based on the characteristic radiological features on CT/MRI and renal Doppler along with histologic findings of broad aseptate branching hyphae in renal tissue sections stained with hematoxylin and eosin, periodic acid-Schiff and Grocott-Gomori silver methenamine. Amphotericin B was given to all patients. Localized disease was managed by medical treatment with or without percutaneous drainage. Extensive disease was managed with nephrectomy. Operative data and the treatment outcomes were also analyzed.

Results

The age of these patients ranged from 17 to 45 years with a mean of 35 years. All patients were males. They were screened for chest infection and concurrent immunocompromized status. An underlying predisposing

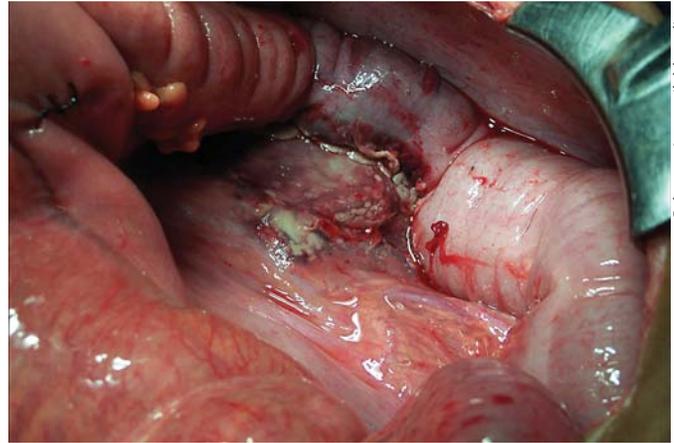


Fig. 1. The kidney wrapped in diffusely hemorrhagic perinephric fat and gangrenous colon due to thrombosis of mesocolic vessels.

condition was found in only 2 patients (taking immunosuppressants as they were renal transplant recipients). In the other 8 patients no other predisposing factor could be ascertained. All patients were tested for human immunodeficiency virus (HIV-1) infection and were found to be negative. None of the patients had a history of diabetes mellitus, iron therapy or intravenous drug abuse. Three of them presented as acute abdomen and were initially managed in the General Surgery and Gastroscopy departments; however, no clear cause was established. One of them had been to many hospitals in the region for over a month before he was finally referred to us for acute renal failure (ARF) and hematuria. Another patient attended the gastrosurgical department because of intestinal obstruction where we were called in when the mesocolon over both kidneys was observed as being very hard and sticking over the kidneys. Thrombosis of the mesocolic vessels with resultant colonic gangrene was seen at examination. Both kidneys were wrapped in diffusely hemorrhagic perinephric fat (fig. 1). At that time, the gangrenous colon was resected and a biopsy was taken from both kidneys, which later on turned out to be renal zygomycosis. The patient died on the first postoperative day.

The clinicopathological features are summarized in table 1. Five patients who had bilateral renal involvement presented with oliguric ARF and hematuria along with diffuse abdominal pain.

Fever was the commonest symptom (80%) followed by flank pain and tenderness (70%). The patients had been ill for an average of 15 days (range 7–24 days) before confirmation of the diagnosis. Among the 5 patients with

Table 1. Isolated renal zygomycosis: patient characteristics, management and outcome

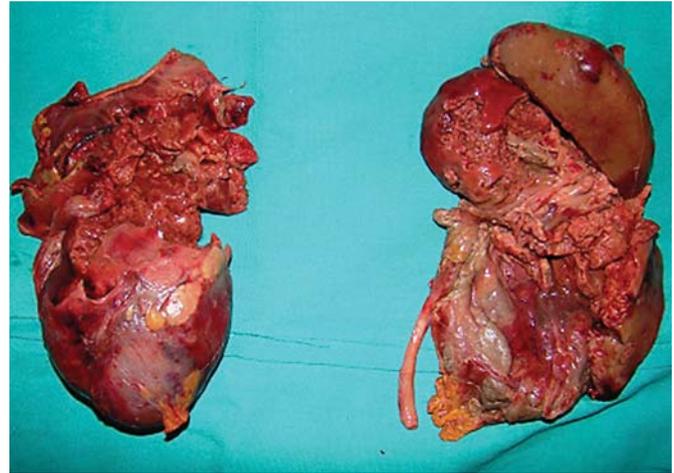
Case No.	Age/sex	Side	Risk factor	Clinical features	Diagnosis	Pathology	Management	Outcome
1	34/M	B/L	none	ARF, sepsis, acute abdomen, altered sensorium	urine for fungus, USG, CT, MRI, biopsy	renal zygomycosis	bilateral nephrectomy, conventional amphotericin B, dialysis	died on second post-operative day
2	32/M	B/L	none	acute abdomen, intestinal obstruction with sepsis	intraoperative biopsy during explorative laparotomy for intestinal obstruction	renal zygomycosis	biopsy, nothing was done for the kidney as the diagnosis was not established ante mortem	died on first postoperative day
3	43/M	U/L	none	fever, flank pain, flank discoloration	USG, MRI, biopsy	renal zygomycosis	nephrectomy, conventional amphotericin B, serial wound debridements and dressings with amphotericin B	severe malnourishment, could not afford treatment, discharged against medical advise
4	45/M	B/L	none	fever	CT scan – early changes, urine smear positive for zygomycosis	not done	liposomal amphotericin B (total dose: 2 g)	survived
5	38/M	U/L	none	fever, flank pain	CT scan, USG	renal zygomycosis	nephrectomy, conventional amphotericin B	survived
6	17/M	U/L	none	bilateral flank pain, high-grade fever, vomiting, passage of white flakes in urine	USG – bilateral hydronephrosis with echogenic particulate material in right pelvicalyceal system and upper ureter	PCN placed, thick pus drained, smear showed zygomycete	PCN, amphotericin B 40 mg/day	survived, asymptomatic after 3 months
7	32/M	B/L	none	right flank pain, fever, dysuria, pyuria	USG/CT – bilateral nephromegaly with multiple renal abscesses	bilateral PCN, pus drained showed zygomycete	bilateral PCN, amphotericin B for 3 months	survived
8	36/M	B/L	none	fever, bilateral flank pain, ARF, sepsis	CT – bilateral nephromegaly with nonenhancement	renal zygomycosis	dialysis, amphotericin B	died before surgery
9	18/M	U/L	renal transplant recipient	fever, sudden graft tenderness and syncope	color Doppler/MRI showed renal artery thrombosis	renal artery thrombus showed mycotic pathology	graft nephrectomy done	died 1 month after graft nephrectomy
10	45/M	U/L	renal transplant recipient	fever, graft tenderness, ARF	color Doppler/MRI showed pseudoaneurysm of renal artery with thrombosis	mycotic aneurysm	graft revascularization done with synthetic graft	died after 6 weeks of surgery with septicemia and ARF

B/L = Bilateral; U/L = unilateral; ARF = acute renal failure; USG = ultrasonography; CT = computed tomography; MRI = magnetic resonance imaging; PCN = percutaneous nephrostomy.



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Fig. 2. Edema and flank discoloration.



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Fig. 5. Gross specimen showing enlarged kidney with areas of necrosis.



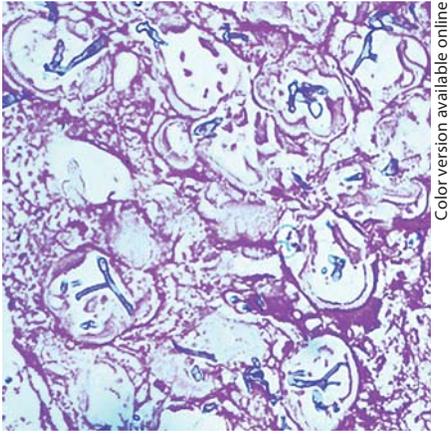
Fig. 3. Contrast-enhanced CT showing enlarged nonenhancing kidney with low-attenuated areas suggesting intrarenal abscesses and perinephric collections.



Fig. 4. Magnetic resonance imaging showed hypointensity in right kidney and a characteristic restriction in the T₂-weighted image.

bilateral renal involvement, 2 had renal failure (mean serum creatinine 8.9 ± 2.2 mg%) with anuria requiring dialysis, while 3 patients had normal serum creatinine. Other laboratory features included pyuria and hematuria in 30% of the patients. One patient presented with fever, flank pain, edema and flank discoloration (fig. 2). Radiological findings were available in 9 patients. Ultrasonography performed in 7 patients revealed enlarged kidneys in all and a perinephric collection in 3 of them. Contrast-enhanced CT was carried out in 5 patients and it confirmed enlargement of the kidneys with reduced or absent contrast excretion with the majority having, in addition, multiple low attenuation areas in the parenchyma (fig. 3). Magnetic resonance imaging showed hypointensity in the affected kidney and a characteristic restriction in the T₂-weighted image due to the large amounts of iron necessary for the growth of these fungi (fig. 4). The radiological differential diagnosis in these patients included acute severe pyelonephritis and focal bacterial nephritis.

Nephrectomy was performed in 5 patients out of which 2 had undergone bilateral nephrectomies. On gross examination, the kidneys were found to be swollen with areas of infarction and necrosis (fig. 5). In histopathology, the kidneys showed large areas of infarction with vascular thrombosis. Irregularly shaped, broad (10–20 mm in diameter), nonseptate and right-angle-branching hyphae pointed towards zygomycotic infection (fig. 6). Thrombi occluding the lumen of main renal artery and vein were identified grossly in 3 cases, 2 of which were the post-transplant patients. In 1 case gross necrosis of the renal and liver undersurface was found, studded with multiple



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Fig. 6. Microscopic image of irregularly shaped broad, nonseptate and right-angle-branching hyphae.

tiny tubercles. Microscopic examination revealed multiple areas of infarction and necrosis, multiple microabscesses as well as granulomas with Langerhans and foreign body giant cells. Culture identification was possible in 7 of our patients. *Rhizopus arrhizus* and *Apophysomyces elegans* were identified in these. Amphotericin B was administered intravenously in doses of 1 mg/kg/day for 3–60 days (average 24 days) with an average total dose of 1.5 g. Among 10 patients 5 died and one was discharged against medical advice because of poor finances. The follow-up of patients ranged from 3 to 8 months.

Discussion

Our experience confirms the devastating outcome of renal zygomycosis as described earlier [1, 3, 5]. Zygomycetes are opportunistic organisms with ubiquitous distribution in soil, decaying organic matter and air [4, 5]. They have minimal intrinsic pathogenicity but are known to initiate an aggressive and often fatal infection in certain conditions such as diabetic ketoacidosis, lymphoproliferative disorders, renal failure and viral hepatitis [3–5]. The list of predisposing conditions continues to grow, the latest additions being desferrioxamine therapy for iron/aluminum overload in dialysis patients [6] and intravenous drug abuse particularly in those with HIV infection [15–18]. The four main presentations of zygomycosis described in man are the rhinocerebral, pulmonary, gastrointestinal and disseminated forms [5]. Infection of single organs such as bone, heart and kidney also rarely occurs.

The rhinocerebral form is most frequently found [3, 4]. Renal involvement occurs as part of disseminated zygomycosis in 22% of the cases [10], but isolated renal disease has been documented usually as single case reports [12–17]. The drug abuse has been experimentally linked to the development of isolated zygomycosis in the brain as well as in the kidney [18, 19]. In contrast, the majority of our patients had previously been healthy. Of the 6 cases with renal zygomycosis analyzed recently, 2 were unilateral and 4 bilateral [12]. In our series, unilateral and bilateral cases were found in equal number. Bilateral disease has often been mistakenly treated as rapidly progressive glomerulonephritis or acute pyelonephritis [1, 13]. Renal failure is usually the result of near total occlusion of the renal arteries and/or their branches as also documented in our patients. Both small and large arteries exhibit hyphal invasion and consequent thrombosis leading to massive cortical and medullary infarction [1, 13–15].

While there have been only isolated cases of zygomycosis reported from other parts of India [20–23], robust data has been analyzed by Chug et al. [24] but the most cases were diagnosed post mortem after the autopsy. Real life ante mortem diagnosis is still a challenging task because autopsies are performed very infrequently at other centers in the country. Whereas the infection has been reported to occur mostly in immunocompromised patients in the west, the majority of our patients were healthy individuals. The presentation of renal zygomycosis in some of our patients was fever, flank pain, gross hematuria and pyuria. These symptoms would be consistent with a diagnosis of acute pyelonephritis. But these patients paradoxically may show unusual radiographic findings on ultrasonography and CT [24–26]. The characteristic CT findings in renal zygomycosis have been previously reported [24] which include enlarged nonenhancing kidneys with absent contrast excretion and low-attenuation areas suggesting intrarenal abscesses and perinephric collections. The diagnostic value of CT has been stressed by some authors who described the areas of low attenuation with diminished enhancement as a ‘diffuse patchy nephrogram’ [12, 25]. Confirmation of the diagnosis of zygomycosis depends on obtaining tissues for microscopic examination and culture. Histology must be aggressively sought even in situations where other infectious agents have been isolated [10]. Demonstration of irregularly shaped, broad (10–20 mm in diameter), nonseptate and right-angle-branching hyphae amidst a neutrophilic infiltrate is important for the diagnosis of zygomycosis [3]. These fungi are easily seen on routine HE and PAS stains but silver methenamine is the most useful.

Table 2. Rapid ante mortem diagnosis criteria for renal zygomycosis for immediate surgical treatment (nephrectomy/renal debridement)

Major criteria	Minor criteria
Diffuse unexplained abdominal/flank pain	Any predisposing factor (immunocompromized status, diabetes, HIV, intravenous drug abuse)
Positive urine smears for aseptate right angled branching hyphae	Acute renal failure/acidosis/ altered sensorium
Globular smooth enlargement of kidney on CT	Hematuria
Segmental/complete renal infarction (>2/3rd of the kidney)	Perirenal fluid on imaging
Nonvisualization of renal segmental vessels during arterial phase of contrast-enhanced CT or poor flow in color Doppler	Multiple/diffuse renal abscesses
Restriction on T ₂ -weighted image on MRI in the infarcted kidney	Pyuria
Positive renal biopsy for zygomycetes	Leukocytosis

Any three major or two major and two minor criteria should be present.

Culture identification of zygomycetes has been difficult because >90% of the patients with disseminated zygomycosis have been diagnosed at autopsy [10], so the treating clinicians should always remember to preserve the sample in saline also apart from formalin whenever they remove the renal tissue, during biopsy or nephrectomy or renal debridement. Even in ante mortem biopsy tissue, unless freshly inoculated into Sabouraud's agar and incubated at 37°C, fungal hyphae usually become nonviable due to damage to their walls or inhibition of growth if the medium contains cyclohexidine [3, 14].

Even though the frequency of zygomycosis is increasing with increasing number and improved survival of immunocompromised patients, an accurate diagnosis is often delayed because of the severe nature of the underlying disease [11, 27–29]. A high index of suspicion and knowledge of clinical manifestations is thus very important to diagnose this serious infection. If a severely ill patient with compromised host defenses develops clinical findings suggestive of acute pyelonephritis and abdominal ultrasonography shows renal enlargement with or with-

Table 3. Predictors of mortality in renal zygomycosis

Bilateral disease/solitary kidney with zygomycosis
Greater than 70% infarcted renal parenchyma
Total leukocyte count >30,000
Acute renal failure
Altered sensorium
Hematuria

out a perinephric collection, an immediate contrast CT should be carried out [12, 24]. In the presence of the characteristic findings, a biopsy is indicated to confirm the diagnosis. Successful therapy of renal zygomycosis involves a coordinated surgical and medical approach [3, 11, 29–31]. Extensive debridement of the infected and necrotic tissue, administration of amphotericin B (0.6–1 mg/kg/day up to a total of 2–3 g) and reversal of the underlying condition form the triad of therapy. There have been reports of survival following amphotericin B therapy without nephrectomy in patients with unilateral renal disease [12, 17]. Recently, the unilamellar liposomal formulation of amphotericin B has been also recommended for use in view of its lesser side effects [17, 32].

Renal zygomycosis has typical features on CT/MRI and color Doppler. In our institute, we have learnt to rely on the radiological protocol for diagnosing this condition rather than waiting for the pathological report to come. Magnetic resonance imaging showed a characteristic restriction in the T₂-weighted image due to the large amounts of iron necessary for the growth of these fungi. This finding is very rarely stressed in the literature. We can rapidly diagnose the disease based on radiological, laboratory and histopathological criteria (table 2). We also described the predictors of mortality in this disease (table 3).

Conclusion

Isolated renal zygomycosis is a rare disease with high mortality because it is difficult to diagnose and delayed treatment is fatal. It can occur in healthy individuals without any predisposing factors. The combined findings of CT/MRI/color Doppler are so characteristic that a decision to remove the kidney can be taken without waiting for the biopsy report. Even after an aggressive and early treatment the prognosis is poor.

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