Renal zygomycosis: an under-diagnosed cause of acute renal failure

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Abstract

Background. Invasive zygomycosis (mucormycosis) occurs predominantly in immunocompromised patients in whom it carries a grave prognosis. While renal involvement is not so uncommon in disseminated infection, isolated renal zygomycosis is rare.

Methods and Results. Forty-five patients with systemic zygomycosis were seen over a 12-year period from January 1986 to December 1997. Among these, 18 had renal involvement, nine with disseminated disease and nine with isolated renal zygomycosis. No underlying predisposing disease was identified in the majority of patients (72%). Renal involvement was confirmed at autopsy in 13 and by ante-mortem renal biopsy in five patients. The infection involved one kidney in five patients and was bilateral in the remaining. The manifestations included fever, flank pain, haematuria and pyuria with evidence of enlarged non-functioning kidneys on computerised tomography (CT). Of those with bilateral disease, 12 (92.3%) had anuric acute renal failure. Anti-fungal therapy was given to six patients (amphotericin B in mean total dose of 1.1 g) and of these only two with unilateral disease who also underwent nephrectomy survived while all the other 16 died.

Conclusion. This study shows that renal zygomycosis has emerged as a cause of acute renal failure in the last decade since no patient with renal involvement was identified at our centre prior to 1986 even though autopsies have been done regularly in patients dying of unknown causes. Bilateral renal zygomycosis should be suspected in any patient who presents with haematuria, flank pain and otherwise unexplained anuric renal failure. Characteristic CT findings and an early renal biopsy can confirm the diagnosis and help in effective management of this serious disease.

Key words: acute renal failure; computerised tomography; mucormycosis; renal zygomycosis
and radiological findings, as well as operative notes were also analysed where available.

Infection was categorized as disseminated if one or more non-contiguous organs were involved in addition to the kidneys and isolated if only renal involvement was confirmed either after a thorough review of organs at autopsy or following a detailed clinical and radiological evaluation in those diagnosed during life.

Results

Clinico-pathological features are summarized in Table 1. The age of the 18 patients ranged from 9 months to 70 years with a mean of $31.7 \pm 16.8$ years. There were 15 males and three females. Nine patients had isolated renal involvement whereas the other nine had disseminated zygomycosis. The disease was limited to one kidney in five patients (cases 4, 6, 13, 14 and 15) whereas the remaining 13 had bilateral involvement. Other organs affected in disseminated disease were the lung (seven), intestines and liver (four each), heart (three) pancreas and adrenals (two each), and mediastinum and spleen (one each).

Underlying predisposing conditions were found in only five patients (one with isolated renal and four with disseminated disease). Among these, two had viral hepatitis (cases 4 and 15) and one each with post-appendectomy sepsicaemia (case 11), overlap syndrome, on steroids (case 13) and acute myeloid leukaemia (case 14). The 10 patients (cases 6–12 and 16–18) who were tested for HIV-1 infection, were all found to be negative by ELISA. None of the patients had a history of intravenous drug abuse.

Presenting clinico-laboratory features have been enlisted in Table 2. Fever was the commonest symptom (88%) followed by flank pain and tenderness (70%) and the patients had been ill for a mean of 15 days (range 7–24 days) before confirmation of the diagnosis. Among 13 patients with bilateral renal involvement, all but one (92.3%) had renal failure (mean serum creatinine $884 \pm 146 \text{mol/l}$) with anuria requiring dialysis while one patient (case 5) had a normal serum

### Table 1. Renal mucormycosis: clinicopathological features ($n=18$)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Year</th>
<th>Age/ Sex</th>
<th>Clinical features</th>
<th>Underlying disease</th>
<th>Diagnostic mode</th>
<th>Organs involved</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1986</td>
<td>57M</td>
<td>Fever, pain abdomen, oliguria, UTI</td>
<td>None</td>
<td>Biopsy</td>
<td>Both kidneys</td>
<td>Amphotericin</td>
<td>Died</td>
</tr>
<tr>
<td>2.</td>
<td>1986</td>
<td>55M</td>
<td>Melena, haematuria, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys lungs, intestines, pancreas</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>3.</td>
<td>1987</td>
<td>70M</td>
<td>Fever, pain abdomen</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys mediastinum, liver</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>4.</td>
<td>1988</td>
<td>28M</td>
<td>Fever, pain abdomen, jaundice, UTI</td>
<td>Viral hepatitis</td>
<td>Biopsy</td>
<td>Right kidney</td>
<td>Nephrectomy Amphotericin</td>
<td>Alive</td>
</tr>
<tr>
<td>5.</td>
<td>1988</td>
<td>25M</td>
<td>Fever, haemoptysis</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys mediastinum, liver</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>6.</td>
<td>1991</td>
<td>26M</td>
<td>Fever, flank pain, pyuria, UTI</td>
<td>None</td>
<td>Biopsy</td>
<td>Left kidney</td>
<td>Nephrectomy Amphotericin</td>
<td>Alive</td>
</tr>
<tr>
<td>7.</td>
<td>1991</td>
<td>17M</td>
<td>Fever, flank pain, haematuria, anuria</td>
<td>None</td>
<td>Biopsy</td>
<td>Both kidneys</td>
<td>Amphotericin Amphotericin</td>
<td>Died</td>
</tr>
<tr>
<td>8.</td>
<td>1992</td>
<td>35M</td>
<td>Fever, pyuria, UTI, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys</td>
<td>Amphotericin Amphotericin</td>
<td>Died</td>
</tr>
<tr>
<td>9.</td>
<td>1992</td>
<td>25M</td>
<td>Fever, pain abdomen, haematuria, anuria</td>
<td>None</td>
<td>Biopsy (PM)</td>
<td>Both kidneys</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>10.</td>
<td>1992</td>
<td>26M</td>
<td>Fever, pain abdomen, haematuria, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>11.</td>
<td>1992</td>
<td>28M</td>
<td>Fever, pain abdomen, pyuria, anuria</td>
<td>Septicaemia</td>
<td>Autopsy</td>
<td>Both kidneys, liver, spleen</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>12.</td>
<td>1992</td>
<td>26M</td>
<td>Fever, flank pain, haematuria, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys, liver</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>13.</td>
<td>1992</td>
<td>32F</td>
<td>Fever, pain abdomen, joint pains, haematuria</td>
<td>Overlap syndrome</td>
<td>Autopsy</td>
<td>Right kidney, heart, intestines</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>14.</td>
<td>1993</td>
<td>28F</td>
<td>Fever, pallor, cough, hepatosplenomegaly, jaundice, haematuria, shrunken liver</td>
<td>Myeloid leukaemia</td>
<td>Autopsy</td>
<td>Right kidney, lung, liver, pancreas</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>15.</td>
<td>1993</td>
<td>28M</td>
<td>Jaundice, haematuria, anuria</td>
<td>Viral hepatitis</td>
<td>Autopsy</td>
<td>Left kidney, lung</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>16.</td>
<td>1995</td>
<td>9/12M</td>
<td>Fever, haematuria, anuria</td>
<td>None</td>
<td>Biopsy</td>
<td>Both kidneys</td>
<td>Amphotericin</td>
<td>Died</td>
</tr>
<tr>
<td>17.</td>
<td>1996</td>
<td>25M</td>
<td>Fever, pain abdomen, haematuria, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys, bladder intestines, lungs</td>
<td>—</td>
<td>Died</td>
</tr>
<tr>
<td>18.</td>
<td>1997</td>
<td>20M</td>
<td>Fever, pain abdomen, haematuria, anuria</td>
<td>None</td>
<td>Autopsy</td>
<td>Both kidneys, bladder adrenals</td>
<td>—</td>
<td>Died</td>
</tr>
</tbody>
</table>

*PM, Post-mortem.*
Table 2. Renal mucormycosis: main clinical features (n = 18)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>16</td>
<td>88</td>
</tr>
<tr>
<td>Flank pain</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Haematuria</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>(Gross)</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Anuria*</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>Pyuria</td>
<td>13</td>
<td>70</td>
</tr>
<tr>
<td>Bacterial UTI</td>
<td>10</td>
<td>53</td>
</tr>
</tbody>
</table>

*ARF in 12 out of 13 pts (92%) with bilateral involvement.

creatinine. The differential diagnoses considered at presentation in patients with renal failure included rapidly progressive glomerulonephritis (seven), acute cortical necrosis (two) and acute tubular necrosis (three). Other laboratory features included pyuria and haematuria in 70% (gross in 35%) and concomitant bacterial UTI in 53% of the patients.

Radiological findings were available in 17 patients. Ultrasonography revealed enlarged kidneys in 15 patients with a perinephric collection in eight (53%) of them. Contrast enhanced computerised tomography (CECT) was carried out in seven patients and it confirmed enlargement of the kidneys with reduced or absent contrast excretion with the majority (86%) having, in addition, multiple low attenuation areas in the parenchyma and perinephric collections (Figure 1). The radiological differential diagnosis in these patients included acute severe pyelonephritis and focal bacterial nephritis.

The kidneys were examined grossly in 13 cases, 10 of which were diagnosed at autopsy and three after therapeutic nephrectomy. In 12 instances the kidneys showed large areas of infarction with vascular thrombosis. Thrombi occluding the lumina of main renal artery and vein were identified grossly in seven cases. In one case (patient 5), there was no gross necrosis and the renal surface was studded with multiple tiny tubers. Microscopic examination revealed multiple areas of infarction and necrosis in the cortex and medulla, along with arterial thrombosis and arteritis. There were multiple microabscesses as well as granulomas with Langerhans and foreign body giant cells. Fungal hyphae conforming to the morphology of mucor were seen in the vascular thrombi, invading the vessel wall, in areas of necrosis, within granulomas, and also within necrotic glomeruli and tubules. Culture identification was possible in two of our patients. *Rhizopus arrhizus* and *Apophysomyces elegans* were identified in patients 6 and 7, respectively, with help of the Centre for Disease Control, Atlanta (USA).

Anti-fungal treatment could be given to only six patients with isolated renal zygomycosis on the basis of biopsy reports in five and strong suspicion after CECT in one patient (case 8). Amphotericin B was administered intravenously in dose of 1 mg/kg/day for 3–60 days (average 24 days) with an average total dose of 1.1 g. Therapeutic nephrectomy was carried out in three patients including two with unilateral involvement and one with bilateral disease. Only the two patients with unilateral disease (cases 4 and 6) who also had a nephrectomy survived. They received a total dose of 2 and 2.5 g amphotericin B, respectively.

**Discussion**

The present series confirms the devastating outcome of systemic zygomycosis as described earlier [1,3,5]. The Zygomycetes are opportunistic organisms with

![Fig. 1. A CECT scan of abdomen in a patient with bilateral renal mucormycosis showing enlarged kidneys with non-enhancing areas and perinephric collection (arrow).](image-url)
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/aluminium 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 frequently found to be associated with diabetic ketoacidosis, the gastrointestinal with malnutrition and the pulmonary and disseminated forms with leukaemia or lymphoma [3,4].

Renal involvement occurs as part of disseminated zygomycosis in 22% of cases [10] but isolated renal disease has also been documented as single case reports [12–17]. Though a number of apparently healthy individuals with zygomycosis have been described [7–9], the majority of them have underlying predisposing conditions mainly HIV infection and intravenous drug abuse [17,18]. The latter condition has also been experimentally linked to the development of isolated zygomycosis in the brain as well as in the kidney [12,19]. In contrast the majority of our patients had been previously healthy.

Among the 15 cases with renal zygomycosis analysed recently, 11 were unilateral and four bilateral [12]. However the majority of our patients (13 out of 18) had bilateral renal involvement and all except one developed irreversible renal failure. Similar clinical experience has been described in earlier reports with bilateral disease [1,13]. These cases have often been mistakenly treated as rapidly progressive glomerulonephritis or acute pyelonephritis.

Renal failure is usually the result of near total occlusion of the renal arteries and/or their branches as documented in our patients also. Both small and large arteries exhibit hyphal invasion and consequent thrombosis leading to massive cortical and medullary infarction [1,13–15]. An analysis of the changing pattern of acute renal failure at our centre between 1965 and 1986 [20] has shown that we did not encounter zygomycosis as a cause of renal failure prior to 1986. However, we have seen it with increasing frequency in the last decade. While there has been only isolated cases of zygomycosis reported from other parts of India [1,21–23], it is likely that the seemingly higher incidence in our area is mainly because autopsies are done very infrequently at other centres in the country and diagnosis is seldom made during life. Whereas the infection has been reported to occur mostly in immunocompromised patients in the West, the majority of our patients were healthy individuals. None of our patients had a history of drug abuse. We are looking into the possibility of an increased environmental load in our area contributing to this.

Other important clinical clues to the diagnosis of renal zygomycosis in our patients have been fever, flank pain and tenderness, gross haematuria and pyuria. These symptoms would be consistent with a diagnosis of acute pyelonephritis (unless renal failure supervenes in bilateral disease). But these patients paradoxically may show unusual radiographic findings on ultrasonography and computerized tomography.

![Photomicrograph of the renal artery (V) showing a sub-total occlusion by a thrombus (H&E × 48). Inset shows vessel wall (W) with non-septate mucor hyphae (arrow) (PAS × 475).](image)
We have previously reported the characteristic CT findings in renal zygomycosis [24] which include enlarged non-enhancing kidneys with absent contrast excretion and low-attenuation areas suggesting intra-renal abscesses and perinephric collections. The diagnostic value of CT has been stressed by others who also described areas of low attenuation with diminished enhancement referred as a ‘diffuse patchy nephrop-ram’ [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 μm in diameter), non-septate and right angled-branching hyphae amidst a neutrophilic infiltrate is important for diagnosis of zygo-
mycosis [3]. These fungi are easily seen on routine H&E and PAS stains but silver methenamine is the most useful. Culture identification of Zygomycetes has been difficult because >90% of the patients with disseminated zygomycosis, have been diagnosed at autopsy [10], as was also evident in our study. 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 suspi-
cion 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 suggesting acute pyelonephritis and abdominal ultrasonography shows renal enlargement with or without a perinephric collection, an immediate CECT should be carried out [12,24]. In 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 the 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].

In conclusion, renal zygomycosis has been observed as an important cause of acute renal failure in our centre in the last decade. This infection can occur as part of the disseminated zygomycosis or as isolated renal disease even in apparently healthy individuals. Early recognition of this condition is very important in view of the serious consequences this infection has for the affected individual. If suspected on clinical examination and/or radiology, an aggressive approach including a kidney biopsy is mandatory so that definite medical and surgical therapy can be carried out in time to improve the outcome of an otherwise fatal disease.

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