Successful Medical Management of Isolated Renal Zygomycosis: Case Report and Review

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We describe the medical management of isolated renal zygomycosis in an adult patient with AIDS during chemotherapy for AIDS-related lymphoma. After initial presentation during the first cycle of chemotherapy, the infection was contained within the kidney following recovery of the neutrophil count without medical or surgical intervention. Since he was not considered to be a candidate for nephrectomy, his infection was treated with amphotericin B lipid complex during subsequent chemotherapy. Neutropenia was minimized by the addition of cytokine support therapy with granulocyte colony-stimulating factor and reduced doses of chemotherapy. Following this strategy, his lymphoma completely resolved, and renal zygomycosis was controlled. At the time of this writing, he had been in complete remission for 18 months without evidence of progressive fungal infection. This report and our literature review indicate that isolated renal zygomycosis can be associated with a favorable prognosis, occurs with greatest frequency in patients with AIDS, is associated with parenteral access, and may be managed by medical therapy alone.

Although zygomycosis most commonly presents as rhinocerebral, pulmonary, or disseminated disease [1, 2], an increasing number of cases of isolated renal zygomycosis have been reported over the last decade. This rise may reflect the increased prevalence of parenteral inoculation, mainly through intravenous drug use (IVDU). Although combined medical and surgical therapy remains the cornerstone of management, recent data indicate that, in some patients, renal zygomycosis may be managed without nephrectomy. In this report, we describe the successful medical management of unilateral renal zygomycosis in a patient with AIDS-related lymphoma who was receiving multiple cycles of modified EPOCH (etoposide, prednisone, vincristine, doxorubicin, cyclophosphamide) chemotherapy [3] and we review the literature on isolated renal zygomycosis. The present case highlights the importance of recovery of the neutrophil count in host defense against zygomycosis and presents a strategy for medical management of nonsurgical patients. Furthermore, in contrast to the poor prognosis associated with other sites of zygomycosis, our review indicates that isolated renal zygomycosis is associated with a relatively favorable prognosis.

Case Report

A 42-year-old homosexual man with AIDS and a CD4 cell count of 51/mm³ presented with stage IVB AIDS-related lymphoma. Evaluations of bone marrow, sputum, CSF, blood, and urine specimens were negative for fungal organisms. To minimize neutropenia, modified EPOCH chemotherapy (25% of the usual cyclophosphamide dose) and cytokine support therapy with granulocyte colony-stimulating factor (G-CSF) were started. The patient’s lymphadenopathy responded to chemotherapy. Neutropenia (absolute neutrophil count [ANC], 480/mm³) developed on day 10. Fever developed on day 11 and was treated empirically with intravenous ceftazidime. Fluconazole and acyclovir were subsequently added to the therapeutic regimen for treatment of persistent fever. On day 16, his ANC increased to 3,680/mm³.

Because of persistent fevers and mild left flank discomfort, repeated body CT was performed. The scan showed new left hydronephrosis and a perinephric infarct with extension to the psoas muscle (figure 1A). CT scans of the cerebrum, sinuses, and chest did not demonstrate any abnormal findings. Examination of a fine needle aspirate of the left perinephric mass revealed abundant, broad, sparsely septated hyphal invading infarcted renal tissue; culture of this tissue specimen yielded Rhizopus microsporus. Determination of the arterial blood gas level demonstrated a normal pH. Because of the patient’s poor prognosis, surgical debridement and antifungal management were not pursued. He was discharged to home hospice care on day 21; at the time of discharge, he was febrile, but his ANC had recovered to 7,905/mm³.

Over the next 2 weeks, the patient’s condition improved with resolution of fevers, dyspnea, and flank pain. A repeated CT scan 3 weeks after discharge showed an evolving left kidney infarct (figure 1B). Repeated urine culture yielded Rhizopus.

Six weeks after his discharge, recurrent lymphadenopathy developed. Understanding the risk of progressive fungal infection, he elected to receive further chemotherapy. As before, he received EPOCH chemotherapy and cytokine support therapy...
Figure 1. Serial CT images revealing isolated left renal zygomycosis in a patient with AIDS-related non-Hodgkin’s lymphoma. A, contrast-enhanced abdominal CT image obtained at the time of diagnosis that shows abscess formation with development of hydroureteral changes and extension into the left perinephric space and psoas muscle. B, contrast-enhanced abdominal CT image obtained 3 weeks after diagnosis and hospital discharge that shows an evolving infarction of the left kidney with resolution of ascites and edematous changes. C, contrast-enhanced abdominal CT image obtained after four cycles of chemotherapy for recurrent lymphoma that shows no significant change in the left kidney infarction. D, non-contrast-enhanced abdominal CT image obtained 11 months after the last cycle of chemotherapy that shows continued hydronephrosis and a complex mass in the lower pole of the left kidney.

with G-CSF, completing six additional cycles withANC nadirs of 477, 760, 608, 1,152, 672, and 546/mm³, respectively. However, prednisone was omitted from chemotherapy because of its adverse effects on neutrophil and phagocyte function [4, 5]. Antiretroviral therapy and prophylaxis for Pneumocystis carinii pneumonia were discontinued during chemotherapy because of concerns about myelosuppression.

During each chemotherapy cycle, amphotericin B lipid complex (ABLC) therapy was started when the ANC nadir approached <1,000/mm³ and was stopped after recovery of the neutrophil count (ANC, >1,000/mm³). ABLC therapy, compared with standard amphotericin B, was administered to minimize nephrotoxicity. The initial ABLC dose of 5 mg/(kg · d) was associated with an increase in the serum creatinine level from 1.1 to 1.9 mg/dL; the serum creatinine level improved when the dose was reduced to 2.5 mg/(kg · d). CT evaluation after the fourth cycle showed no significant changes in the left perinephric area (figure 1C). Several urinalyses and urine cultures revealed persistent microscopic hematuria and R. microsporus, respectively. At the time of this writing, his lymphoma had been in complete remission for 18 months after chemotherapy with no clinical evidence of progressive rhizopus infection (figure 1D).

Literature Review

Using MEDLINE and literature citations, we identified 16 cases of isolated renal zygomycosis. Although the earliest case was reported in 1960 [6], most cases have been reported over the last decade, a finding that may reflect the increased inci-
dence of IVDU-associated infections [6–20]. Even though most of the reported cases occurred in patients with AIDS, zygomycosis nevertheless rarely occurs in this patient population [18, 21]. Indeed, a recent review of cases of zygomycosis in patients with AIDS indicated that IVDU is a significant risk factor [18]. Our patient had no history of IVDU but did have a central venous catheter, which may have served as a portal of entry for *R. microsporus*. In addition to parenteral intravenous access, other significant risk factors for patients identified by our review were diabetes mellitus and corticosteroid administration.

Of the 17 patients with isolated renal zygomycosis (table 1), including the present patient, 13 (76%) survived their infection. Four patients with bilateral renal infection did not. Of the 13 surviving patients, 9 were treated with combined nephrectomy and intravenous amphotericin B, 1 underwent nephrectomy only, 1 received amphotericin B therapy only, 1 (our patient) received ABLC therapy alone, and 1 received no specific therapy. Our case is the first to be successfully managed with ABLC therapy alone.

Our review identified one patient who survived without medical or surgical intervention. He had AIDS and was initially hospitalized because of *P. carinii* pneumonia; he was treated with corticosteroids and intravenous antibiotics. During hospitalization, he developed isolated renal zygomycosis and refused therapy with nephrectomy and amphotericin B; after cessation of corticosteroid and antibiotic treatment, his focal infection was successfully contained. A CT scan 6 months later demonstrated decreased renal lesions. Although difficult to prove, corticosteroid-induced phagocyte dysfunction may have significantly contributed to the development of zygomycosis in this patient. Subsequent control may have been related to recovery of phagocyte function following discontinuation of corticosteroid treatment. He died 7 months later of CNS lymphoma, and postmortem examination showed multiple left kidney abscesses containing Mucoraceae.

Our literature review also emphasizes the prognosis associated with different sites of presentation of zygomycosis. Of 361 cases with diverse presentations, 12% occurred in patients with hematologic malignancies and/or chemotherapy [22]. Although the overall survival rate was 39%, this rate primarily reflected the relatively good prognosis associated with rhino-cerebral involvement (56% survival rate among 117 patients). In contrast, the survival rate among patients with disease at other sites, such as gastrointestinal, pulmonary, cardiac, or CNS, was 3%. In a series of 26 cases of zygomycosis associated with hematologic malignancies, there were no survivors [2]. Twenty-one of these 26 patients presented with pulmonary involvement. Isolated CNS zygomycosis was associated with a survival rate of <15% [23].

Our own review demonstrates a relatively good prognosis for isolated renal zygomycosis, which is associated with a survival rate of 76% (13 of 17 patients). In part, this improved prognosis may be due to surgical resectability of isolated renal

### Table 1. Clinical characteristics of 17 patients with isolated renal zygomycosis.

<table>
<thead>
<tr>
<th>Patient no. [reference]</th>
<th>Age (y)/sex</th>
<th>Underlying condition(s)</th>
<th>Other predisposing factors</th>
<th>Fungus*</th>
<th>Diagnostic procedure</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 [7]</td>
<td>67/M</td>
<td>Trauma</td>
<td>Corticosteroids, iv access</td>
<td>Phycomycetes</td>
<td>Renal biopsy</td>
<td>AmB</td>
</tr>
<tr>
<td>4 [9]</td>
<td>69/M</td>
<td>DM</td>
<td>Mucoraceae</td>
<td></td>
<td>Nephrectomy</td>
<td>Nephrectomy</td>
</tr>
<tr>
<td>5 [10]</td>
<td>68/M</td>
<td>DM</td>
<td>Mucoraceae</td>
<td></td>
<td>Surgical biopsy</td>
<td>Nephrectomy</td>
</tr>
<tr>
<td>7 [12]</td>
<td>18/M</td>
<td>?</td>
<td>Mucoraceae</td>
<td>Surgical biopsy</td>
<td>Nephrectomy, AmB</td>
<td></td>
</tr>
<tr>
<td>8 [13]</td>
<td>40/M</td>
<td>DM</td>
<td>Mucoraceae</td>
<td></td>
<td>Autopsy</td>
<td>NA</td>
</tr>
<tr>
<td>9 [14]</td>
<td>64/M</td>
<td>CHF and COPD</td>
<td>Corticosteroids</td>
<td>Mucoraceae</td>
<td>Surgical biopsy</td>
<td>Nephrectomy, AmB</td>
</tr>
<tr>
<td>11 [16]</td>
<td>24/M</td>
<td>AIDS</td>
<td>IVDU</td>
<td><em>A. corymbifera</em></td>
<td>Surgical biopsy</td>
<td>Nephrectomy, AmB</td>
</tr>
<tr>
<td>12 [17]</td>
<td>26/M</td>
<td>AIDS</td>
<td>Mucoraceae</td>
<td></td>
<td>Surgical biopsy</td>
<td>Nephrectomy, AmB</td>
</tr>
<tr>
<td>13 [18]</td>
<td>36/M</td>
<td>AIDS</td>
<td>IVDU</td>
<td><em>Absidia</em> species</td>
<td>CT-guided renal biopsy</td>
<td>AmB</td>
</tr>
<tr>
<td>14 [19]</td>
<td>54/M</td>
<td>AIDS</td>
<td>Corticosteroids, iv access</td>
<td>Mucoraceae</td>
<td>Autopsy</td>
<td>None</td>
</tr>
<tr>
<td>16 [20]</td>
<td>40/M</td>
<td>AIDS</td>
<td>IVDU</td>
<td>Mucoraceae</td>
<td>Surgical biopsy</td>
<td>Nephrectomy, AmB</td>
</tr>
<tr>
<td>17 [PR]</td>
<td>42/M</td>
<td>AIDS</td>
<td>Lymphoma, neutropenia, corticosteroids, iv access</td>
<td><em>Rhizopus microsporus</em></td>
<td>CT-guided renal biopsy</td>
<td>ABLC, G-CSF</td>
</tr>
</tbody>
</table>

NOTE. ABLC = amphotericin B lipid complex; AmB = amphotericin B deoxycholate; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; G-CSF = granulocyte colony-stimulating factor; IVDU = intravenous drug use; NA = not available; PR = present report; ? = unknown.

* The term “Phycomycetes” used in these reports has since been replaced with the term “zygomycetes.”
lesions. Although small in number, two of three patients receiving only medical therapy did well in conjunction with resolution of their underlying metabolic or immunologic disorders. Even though case reports are not a definitive way to study prognosis, our review nevertheless suggests that isolated renal zygomycosis has a substantially better prognosis than other sites of presentation of zygomycosis.

Discussion

This case illustrates several important features of the pathogenesis, predisposing risk factors, and management of renal zygomycosis. Our patient’s infection was successfully contained without medical intervention after recovery from neutropenia. Although the pathogenesis of zygomycosis is only partially understood, neutrophil and/or macrophage function appears to play a critical role in host defenses [4, 5]. Our patient’s lymphoma was successfully treated with no evidence of progressive fungal infection despite immunosuppression related to repeated cycles of chemotherapy. Containment of his renal zygomycosis may have been a consequence of the suppressive effects of ABLC and the discontinuation of prednisone therapy.

Although this patient had AIDS, there is little evidence that T cell–mediated defects per se are critical for host susceptibility to zygomycosis [4, 24]. Therefore, HIV-infected patients would not be considered more susceptible to zygomycosis, as reflected by the infrequent case reports. It is likely that parenteral access plays a more important pathogenic role. Our case has several features in common with the 18 cases in the AIDS literature [15–17]. First, most cases were associated with a parenteral risk factor or with corticosteroid-induced immunosuppression. Second, isolated renal disease was the predominant infection, present in 44% of cases. Last, all eight patients with renal zygomycosis survived their initial infection.

Unlike the more common presentations of rhinocerebral and pulmonary zygomycosis, where respiratory inoculation is the primary portal of infection, renal zygomycosis is primarily associated with parenteral inoculation. Most cases of renal zygomycosis are seen in the setting of IVDU. In our case, we believe that the most likely portal of entry was parenteral via a central venous access. Following intravenous inoculation in mice, the kidney and brain are the predominant sites of focal infection [25].

This case report and our literature review suggest that renal zygomycosis may be medically managed, particularly if conventional management with surgery and amphotericin B administration is not practical. Use of ABLC may have been effective during our patient’s subsequent cycles of chemotherapy to minimize the risk of progression of fungal infection. Since our patient’s infection was successfully contained without medical intervention following recovery of the neutrophil count at the time of initial presentation, we modified chemotherapy to minimize his immunodeficiency during subsequent cycles. This approach allowed us to successfully treat his lymphoma without exacerbation of his zygomycosis, despite repeated neutropenic episodes. Moreover, although the patient had only one functioning kidney, he tolerated ABLC therapy without dose-limiting nephrotoxicity.

Indeed, in patients with underlying renal impairment, the use of ABLC over standard amphotericin B may allow the administration of effective antifungal therapy without encountering dose-limiting renal toxicity [26]. Even though lipid-formulated amphotericin B has been used to successfully treat zygomycosis at other sites, to our knowledge, this is the first documented case of its use in the treatment of isolated renal zygomycosis [27–29]. Although complete eradication of infection may not have been achieved in our patient, ABLC may have suppressed progression of fungal infection during risk periods. On the basis of the observation that zygomycosis can be contained in patients who recover adequate neutrophil function, we administered ABLC only during the intermittent periods of neutropenia.

Although surgery and amphotericin B therapy should still be considered the standard of care for the management of isolated renal zygomycosis, this approach may not be appropriate for patients with malignancy, advanced AIDS, or significant renal impairment. In such settings, the clinician should be aware that the recovery of the neutrophil count alone, discontinuation of corticosteroid therapy, and/or treatment with ABLC may provide an effective alternative approach. At the time of this writing, 18 months after chemotherapy while receiving combination antiretroviral therapy, our patient was doing well with an improved CD4 cell count, undetectable serum titers of HIV, no evidence of recurrent lymphoma, and no evidence of progressive fungal infection.

References