Mucormycosis is an uncommon acute and often fatal opportunistic fungal infection that usually occurs in patients with poorly controlled diabetes mellitus, acute leukemias, or other immunosuppressive conditions [1,2]. A new association, that of mucormycosis occurring in patients receiving deferoxamine therapy for iron or aluminum excess, has been reported with increasing frequency since 1986 [3-16]. Although this association has been strongly linked with chronic renal failure requiring hemodialysis, it is now clear that other conditions in which deferoxamine may be required (thalassemia, sideroblastic anemia, myelodysplasia) are also associated with mucormycosis [5,7,8,16]. We report a case of mucormycosis in a patient who had received deferoxamine for iron overload secondary to myelodysplastic syndrome, and review previous cases of deferoxamine-associated mucormycosis.

CASE REPORT

A 56-year-old woman with myelodysplastic syndrome for six years and transfusion-related iron overload had received treatment with deferoxamine, 1 to 1.5 g per week, for seven months. She did well until June 1988, when she developed fever and a nonproductive cough. She was admitted to another hospital where she was treated with tobramycin, ticarcillin-clavulanic acid, and erythromycin for presumed pneumonia. Of the cases described in detail, 19 men and seven women were affected. The mean age was 49.6 years, whereas the remaining six patients had hematologic disorders associated with states of iron or aluminum excess [6-13,15]. In addition to patients with renal failure, patients with hematologic disorders, all of whom were treated with deferoxamine, have been reported with mucormycosis [3-5,14,16]. Including the current one, we have found 26 cases of mucormycosis occurring in patients undergoing dialysis have been in those receiving deferoxamine for aluminum or iron excess [6-13,15]. Although the first dialysis patient with mucormycosis, reported by Gluskin et al [17], was not noted to be receiving deferoxamine, subsequent cases of mucormycosis in patients undergoing dialysis have been in those receiving deferoxamine for aluminum or iron excess [6-13,15]. In addition to patients with renal failure, patients with hematologic disorders, all of whom were treated with deferoxamine, have been reported with mucormycosis [3-5,14,16]. Including the current one, we have found 26 cases of mucormycosis associated with states of iron or aluminum excess treated with deferoxamine (Table 1).

Of the cases described in detail, 19 men and seven women were affected. The mean age was 49.6 years, with a range from 23 to 70 years. Of those cases in which the organism was identified, Rhizopus species occurred in 13 [6,10,11,15,16] and Cunninghamella bertholletiae in three [4,5,14]. Chronic renal disease requiring maintenance hemodialysis was present in 20 of the 26 patients (77%) [6-13,15], whereas the remaining six patients had hematologic disorders associated with states of iron or aluminum excess treated with deferoxamine (Table 1).

RESULTS

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Underlying Conditions</th>
<th>Dose (g/week)</th>
<th>Duration (months)</th>
<th>Reason</th>
<th>Organism Involved</th>
<th>Treatment/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>65/M</td>
<td>Sideroblastic anemia</td>
<td>NS</td>
<td>4</td>
<td>Fe</td>
<td>NS</td>
<td>Heart, lung, brain, kidney, spleen, liver, adrenal</td>
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<td>[4]</td>
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<td>Thalassemia, sideroblastic anemia, diabetes</td>
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<td>Fe</td>
<td>Cunninghamella</td>
<td>Rhinocerebral</td>
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<tr>
<td>[5]</td>
<td>42/M</td>
<td>Thalassemia, splenectomy, chemotherapy</td>
<td>NS</td>
<td>NS</td>
<td>Fe</td>
<td>Cunninghamella</td>
<td>Skin, muscle, nodes</td>
</tr>
<tr>
<td>[6]</td>
<td>32/M</td>
<td>Dialysis</td>
<td>7</td>
<td>0.6</td>
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<td>Rhizopus</td>
<td>Heart, lung, brain</td>
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<tr>
<td>[7]</td>
<td>32/M</td>
<td>Dialysis, splenectomy</td>
<td>2.5-6</td>
<td>18</td>
<td>Al/Fe</td>
<td>NS</td>
<td>Heart, lung, brain</td>
</tr>
<tr>
<td>[8]</td>
<td>45/M</td>
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<td>2-6</td>
<td>4</td>
<td>Al</td>
<td>NS</td>
<td>Lung, bowel</td>
</tr>
<tr>
<td>[9]</td>
<td>57/M</td>
<td>Dialysis</td>
<td>4-6</td>
<td>10</td>
<td>Fe</td>
<td>NS</td>
<td>Bowl</td>
</tr>
<tr>
<td>[10]</td>
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<td>Dialysis, splenectomy</td>
<td>2-4</td>
<td>12</td>
<td>Al</td>
<td>NS</td>
<td>Rhinocerebral</td>
</tr>
<tr>
<td>[11]</td>
<td>36/F</td>
<td>Dialysis</td>
<td>4</td>
<td>6</td>
<td>Al</td>
<td>Rhizopus</td>
<td>Brain, thyroid, adrenal, heart</td>
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<tr>
<td>[12]</td>
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<td>3</td>
<td>12</td>
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<td>Rhizopus</td>
<td>Skin</td>
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<tr>
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<td>1</td>
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<td>Rhizopus</td>
<td>Lung</td>
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<tr>
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<td>12</td>
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<td>Brain</td>
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<tr>
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<td>3</td>
<td>Al</td>
<td>Rhizopus</td>
<td>Heart, brain, lung, stomach, bowel, liver</td>
</tr>
<tr>
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<td>Al</td>
<td>Rhizopus</td>
<td>Rhinocerebral</td>
</tr>
<tr>
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<td>6</td>
<td>9</td>
<td>Fe</td>
<td>Rhizopus</td>
<td>Rhinocerebral</td>
</tr>
<tr>
<td>[19]</td>
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<td>Dialysis, glucocorticoids</td>
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<td>17</td>
<td>Al</td>
<td>Rhizopus</td>
<td>Lung, brain, skin</td>
</tr>
<tr>
<td>[20]</td>
<td>49/F</td>
<td>Dialysis</td>
<td>2-4</td>
<td>16</td>
<td>Al</td>
<td>NS</td>
<td>Lung, liver, spleen, heart</td>
</tr>
<tr>
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<td>10.5</td>
<td>20</td>
<td>Fe</td>
<td>Rhizopus</td>
<td>Lung, skin, brain</td>
</tr>
<tr>
<td>Current case</td>
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<td>Myelodysplasia</td>
<td>1-1.5</td>
<td>7</td>
<td>Fe</td>
<td>Rhizopus</td>
<td>Brain, lung</td>
</tr>
</tbody>
</table>

NS = not stated; Fe = iron overload; Al = aluminum overload; AmB = amphotericin B.

Mucormycosis is a fungal infection caused by Mucorales species, often seen in patients with pre-existing medical conditions. The table above lists patients who received deferoxamine therapy due to iron or aluminum excess. The table includes details such as the patient's age, gender, underlying conditions, dose and duration of deferoxamine therapy, reason for administration, organism involved, organs involved, and treatment/outcome.

In this series of patients, the indications for deferoxamine therapy were either iron overload (nine patients) [3-5,11,13,14, current case], aluminum overload (14 patients) [6,8-11,15], or both iron and aluminum excess (three patients) [7,10,12]. The mean duration of deferoxamine therapy was 9.3 months, with a range from 19 days to 20 months. The dose of deferoxamine ranged from 1 to 14 g per week.

The clinical course noted in the patients in this series did not differ from that noted in patients with other risk factors for mucormycosis. Fourteen patients (54%) had disseminated infection [3,5-8,10-12,15,16, current case]; pulmonary and brain involvement was most prominent in these patients. Seven patients (27%) had rhinocerebral disease [4,9,10,11,13], two had pulmonary infection [10,14], and one each had only cerebral, small bowel, or skin involvement, although it is likely that the latter patient had disseminated infection [8,10,11]. Presentation was acute in all but one patient, who presented with subacute infection of lymph nodes and subcutaneous tissue [5].

The clinical course was commented upon in 19 cases (four with rhinocerebral infection, 12 with disseminated infection, and three with localized disease). In patients with rhinocerebral infection, the mean duration of illness until death was only five days, and in those with disseminated infection, only six days. Rhinocerebral infection presented as facial pain or rhinorrhea;
blindness occurred in three of four patients, and all four had increasing confusion and coma prior to death. Disseminated infection presented as necrotic cutaneous lesions in two patients [12,16] and as pneumonitis (cough, fever, and pulmonary infiltrates) in seven patients [8,9,17,18, current case].

Only nine patients received any treatment that might have been helpful against mucormycosis. Three patients received amphotericin B alone: our patient, Sanes' [16] patient, who received only one day of amphotericin B therapy prior to death, and Sand's [5] patient, who had subacute infection and was cured with 2 g of amphotericin B. Two patients had surgery alone—one had debridement of infected sinuses, which did not establish a diagnosis prior to death [13], and one had localized intestinal mucormycosis that was cured by surgical extirpation of the involved small bowel [8]. Four patients underwent surgical debridement of infected tissue and received treatment with amphotericin B [4,10,14]. In three instances, less than a week of therapy with amphotericin B was given prior to death.

In 19 of 26 cases (73%), the diagnosis was not made until necropsy. Twenty-three of the 26 patients (88%) died of mucormycosis. Three patients survived with the following: localized disease of the bowel cured by surgical extirpation [8], a subacute course involving skin, subcutaneous tissue, and nodes, which responded to amphotericin B therapy [5], and rhinocerebral infection treated with both surgical debridement and 1.5 g of amphotericin B [10].

Necropsy reports uniformly described tissue invasion with broad non-septate hyphae. Invasion through blood vessel walls with multiple infarcts and multiple abscesses was a common finding.

**COMMENTS**

Mucormycosis is an opportunistic mycotic infection caused by organisms belonging to the order Mucorales and the class Zygomycetes. The organisms most commonly implicated in clinical disease belong to the genera Mucor, Rhizopus, Absidia, and Cunninghamella [18]. Although wound infections with these organisms may occur in healthy individuals [19], invasive infection almost always occurs in patients with underlying diseases, especially acute leukemias and poorly controlled diabetes mellitus [1,2]. Rhinocerebral and pulmonary forms of the disease are the most common presentations of invasive infection, but widespread dissemination may also occur [1,2].

Neutrophils and monocytes/macrophages are essential host defenses against the zygomycetes [20-23]. Patients with acute leukemia are at risk for developing mucormycosis primarily because of neutropenia [24]. However, patients with diabetes have normal numbers of neutrophils and generally normal phagocytic function [25]. Thus, another factor predisposing the diabetic patient to mucormycosis must be sought, and that factor may be ketoacidosis. Clinically, mucormycosis rarely occurs in diabetic patients unless they are experiencing ketoacidosis [20]. It has been shown in humans that ketoacidosis decreases neutrophil chemotaxis [26] and that in experimental alloxan-induced diabetes, ketoacidosis, and not hyperglycemia, is associated with invasive mucormycosis [27]. Not only is chemotaxis sluggish in ketoacidosis, but recent data show that serum inhibitory activity, which is normally present against the zygomycetes, is abolished in the course of ketoacidosis [28]. Thus, ketoacidotic serum will allow the growth of Rhizopus, but normal serum will not, unless the pH is lowered [28].

It is possible that acidosis is the essential factor leading to mucormycosis in patients undergoing dialysis. However, this seems unlikely since most patients have well-compensated acid-base balance, acidosis has not been noted specifically in those dialysis patients reported with mucormycosis, and furthermore, this factor would not explain the recent dramatic increase in mucormycosis seen in patients undergoing dialysis.

The increasing incidence of mucormycosis among patients undergoing dialysis and patients with chronic hematologic diseases can best be explained by the fact that all of these patients have been receiving the chelating agent, deferoxamine, which may alter the balance between iron metabolism of the host and iron requirements of the fungus. Many microorganisms require iron to grow, and conditions of iron excess have been known to predispose to infection with certain bacteria [29,30]. In fact, recent reports have emphasized that transfusion-related iron overload in patients undergoing dialysis predisposes these patients to bacteremia with Yersinia and Listeria [31,32].

It is ironic that treatment with an agent that binds iron, such as deferoxamine, should be associated with an increased risk of infection with an iron-requiring organism such as Rhizopus. One would think that a chelator should decrease the risk of infection, and, in fact, that suggestion has been made [28]. The paradox of increased infection during chelation therapy can be explained by elucidation of how pathogenic microorganisms acquire iron from their host.

In human plasma or on mucosal surfaces, the amount of free iron available for microbial growth is very low; almost all of the iron is bound to proteins, such as transferrin and lactoferrin, or is locked in tissue stores. Microorganisms have evolved complex mechanisms to compete for iron in the host, usually by secreting siderophores, which trap iron and deliver it to the microorganism for enhancing growth. One of these siderophores is desferrioxamine B mesylate (deferoxamine) produced by Streptomyces pilosus. Thus, deferoxamine therapy provides benefit not only to humans receiving it for iron excess, but also to certain microorganisms, which do not produce their own siderophores but have the ability to utilize siderophores from other organisms [33]. The use of deferoxamine by bacteria to capture iron and increase virulence has been noted for both Yersinia enterocolitica and Vibrio vulnificus [34,35]. Clinically, yersinia bacteremia has been noted in patients undergoing dialysis who have received deferoxamine, but it is unclear whether the excess iron, use of the chelator, or both factors increased the risk for this infection [32,36,37].

It is likely that the zygomycetes Rhizopus and Cunninghamella were able to utilize iron mobilized by deferoxamine to proliferate and cause invasive infection. These zygomycetes have been shown to produce only minimal amounts of siderophores and then only at room temperature after weeks in culture [38,39]. The fact that many of these patients were treated for aluminum excess and did not have iron overload implicates deferoxamine even more strongly.

The dismal rate of premortem diagnosis in the pa-
patients reviewed contrasts sharply with the improved rate of diagnosis noted in recent years by Parfrey [2] and by Marchevsky et al [1]. This lack of early diagnosis in the patients presented in this review probably reflects the fact that the association of mucormycosis with either aluminum or iron overload treated with deferoxamine has only very recently been noted. Certainly, it is common knowledge that sinusitis, proptosis, or palatal lesions in a patient with poorly controlled diabetes mellitus or a hematologic malignancy should immediately suggest rhinocerebral mucormycosis. Similarly, a new infantile pulmonary infiltrate or necrotic skin lesions in such a patient also suggest mucormycosis. It is clear from the 26 patients reported in the last seven years that the aforementioned constellation of symptoms and signs in a patient receiving deferoxamine for iron or aluminum excess should also immediately raise the possibility of mucormycosis.

The diagnosis of mucormycosis is best made by biopsy and histopathologic examination of involved tissues. Microscopy will reveal broad, irregularly shaped, non-septate hyphae with right-angle branching; the fungi are often seen invading through tissue planes and blood vessels. Cultures are necessary to identify the fungal species and to perform antifungal susceptibility studies.

Since the mid-1970s, the prognosis of mucormycosis has improved markedly [1,2]. Treatment is based on early surgical debridement, amphotericin B administration, and stabilization of any underlying disease process [2,20]. If surgical debridement or correction of the underlying disease process cannot be accomplished, the response to amphotericin B alone is poor. The Mucorales are modestly susceptible to amphotericin B, although in many instances it appears that in vitro susceptibility testing has not correlated well with the response of the patient to treatment with amphotericin B [20]. Newer antifungal agents, such as imidazoles and triazoles, appear to have no role in the treatment of mucormycosis [40]. A patient with mucormycosis related to deferoxamine therapy should be able to be effectively treated, since the underlying risk factor can be corrected. However, the diagnosis must be made quickly for therapy to be effective.

The implications of the association between deferoxamine therapy and mucormycosis are evident. The indications for deferoxamine therapy should be carefully weighed against the potential risk of mucormycosis. If deferoxamine is chosen, high clinical suspicion should be maintained for mucormycosis, especially if the patient presents with the aforementioned signs and symptoms. Immediate biopsy examination of involved tissue is essential for diagnosis, and cessation of deferoxamine, as well as aggressive surgical and antifungal therapy, is mandatory for survival.

REFERENCES