

## NOTES

### Gastric Mucormycosis due to *Rhizopus oryzae* in a Renal Transplant Recipient

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Received 26 April 1996/Returned for modification 21 May 1996/Accepted 13 June 1996

**Gastric mucormycosis is a rare disease with a reported fatal outcome of 98%. Manifestations range from colonization of peptic ulcers to infiltrative disease with vascular invasion and dissemination. In our renal transplant patient a deep gastric ulceration infected with *Rhizopus oryzae* (class *Zygomycetes*), which is known to be an agent of mucormycosis, was diagnosed in the early posttransplant period after antirejection therapy. The infection was successfully managed with amphotericin B and omeprazole.**

Mucormycosis, an infection caused by fungi of the class *Zygomycetes*, order *Mucorales*, is usually found in immunocompromised patients, with disease manifestations differing for each of the underlying conditions. The rhinocerebral form can be found most often in diabetic patients (8), the pulmonary and disseminated manifestations are found in association with hematological malignancies (5, 10), and the gastrointestinal form of the disease is primarily found in patients suffering from extreme malnutrition (8). Mucormycosis has also been recognized in patients requiring hemodialysis, predominantly after desferrioxamine therapy (17), and in immunosuppressed patients following organ transplantation (11).

We describe a renal graft recipient with gastric ulcer invasively infected with *Zygomycetes*. This is the first report of a transplant recipient with gastrointestinal mucormycosis from whom *Rhizopus oryzae* was isolated.

**Case report.** A 37-year-old woman underwent cadaveric kidney transplantation in August 1995. She had developed end-stage renal disease as a result of chronic pyelonephritis and had commenced maintenance hemodialysis 30 months earlier. No previous intake of the iron-chelating agent desferrioxamine was reported. Initial immunosuppressive therapy consisted of cyclosporine A and steroids. Because of insufficient postoperative function of the transplanted kidney, hemodialysis was required until day 25. Biopsy of the transplanted kidney on day 9 revealed modest interstitial rejection, and a steroid pulse was given; this was followed by a course of antithymocyte globulin (ATG; thymoglobulin; Merieux). For prophylaxis of cytomegalovirus (CMV) infection ganciclovir was coadministered, and to prevent endogenous fungal infection, oral amphotericin B was added. After ATG therapy, the serum creatinine level decreased only slowly to a minimum of 2.4 mg/dl. Intravenous iron was started on day 23 because of low transferrin saturation levels. On day 25 melena and an acute drop in the hematocrit value to 17% necessitated the transfusion of 6 volumes of

packed erythrocytes. Upper gastrointestinal endoscopy showed a large ulcer measuring 3 cm in diameter and covered by a greyish exudate.

Histological examination of the first biopsy specimen revealed deep ulceration with extensive necrosis of the gastric mucosa mixed with polymorphonuclear leukocytes and with its base reaching the subserous fatty tissue. Numerous nonseptate right angular branched fungal hyphae indicative of *Zygomycetes*, detectable with hematoxylin and silver stains, were deposited not only within the exudation but also on the neighboring intact mucosa (Fig. 1), in the granulomatous tissue in the lamina muscularis, and at the base of the ulceration. Blood vessel invasion was not detectable. *Helicobacter pylori* and other microorganisms were absent. In situ hybridization with probes for the detection of the CMV genome (Loxo, Dossenheim, Germany) was negative. Microbiologically, a fungal etiology was confirmed.

Since a fungal etiology of the gastric ulcer was established, daily intravenous treatment with amphotericin B at 1 mg/kg of body weight was initiated. The serum creatinine level increased to a maximum of 4.4 mg/dl after 15 days of antifungal therapy; nevertheless, daily administration of the full dose was continued for an additional 3 weeks until a total dose of 1,850 mg of amphotericin B was given. After the withdrawal of amphotericin B therapy, the serum creatinine level decreased rapidly to a stable value of 1.8 mg/dl. Repeated gastroscopic follow-up examinations confirmed complete healing of the ulcer. During antifungal treatment a concomitant CMV infection was diagnosed (appearance of immediate-early antigen [pp65]-positive cells and virus-specific immunoglobulin M antibodies) and was treated by intravenous ganciclovir administration.

**Mycologic results.** Microbiologically, a preliminary diagnosis of mucormycosis was made by staining the specimen (fluid obtained from a gastric ulcer) with fluorescent Uvitex 2B (Fungigal A; R&R, Kander, Germany), and fungal elements were demonstrated as broad nonseptate hyphae with right-angled branching. Furthermore, the material was inoculated onto Sabouraud dextrose agar, which was incubated at 37 and 22°C for 1 week. After 7 days of incubation only the Sabouraud

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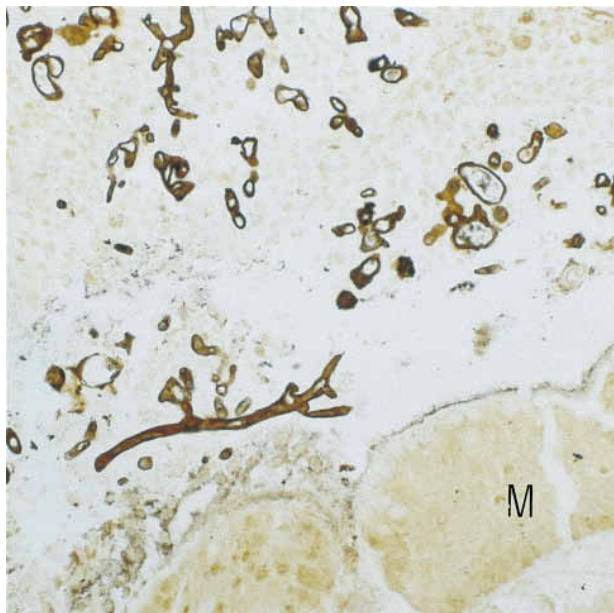


FIG. 1. Histological section of the gastric ulcer showing the gastric mucosa (M) covered with necrotic material containing numerous nonseptate, rectangular, branching hyphae, indicative of the class *Zygomycetes*. Warthin Starry silver stain was used. Magnification,  $\times 400$ .

dextrose slant yielded growth of two different kinds of *Mucorales* and *Candida* (*Torulopsis*) *glabrata*. All other cultures remained sterile. The two different molds were isolated on Sabouraud dextrose agar, and slide cultures on potato dextrose agar were performed. The first species which grew abundantly was a whitish, expanding mold. Microscopically, brownish sporangiophores and well-developed rhizoids were detected. The maximum growth temperature was 30°C. The colony of the second species was fast growing and was white at first, showing brown to black dots later in the incubation period. Spherical

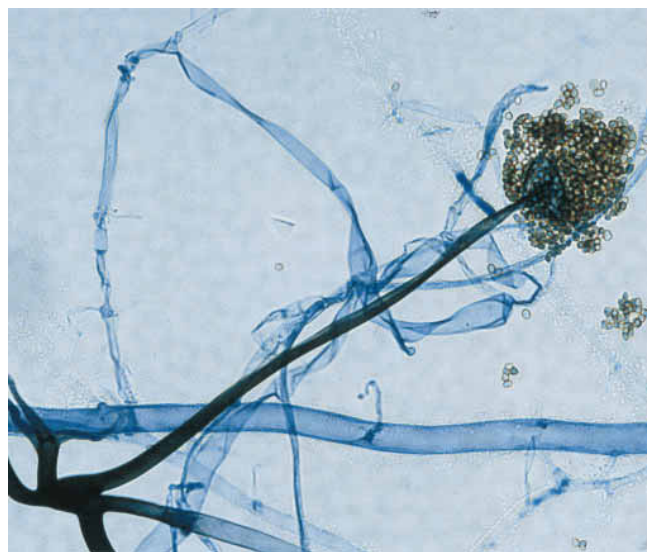


FIG. 2. Microscopic morphology of *R. oryzae*. Rhizoids, a single sporangiophore, and oval sporangiospores are seen. The evagination of the sporangiophore called collumella extends into the sporangium. Lactophenol cotton blue stain was used. Magnification,  $\times 36$ .

unbranched brownish grey sporangia and simple rhizoids were seen microscopically (Fig. 2). The maximum growth temperature was 40°C. The final identification was carried out by the Centraalbureau voor Schimmelcultures in Baarn, The Netherlands. The first species was reported as *Rhizopus stolonifer*, the second one was reported as *R. oryzae*.

**Discussion.** *Zygomycetes* are ubiquitous fungi, often present in soil and decaying organic material. Despite their widespread distribution, disease manifestations are generally restricted to severely immunocompromised patients, attesting to the low intrinsic virulence potential of these organisms (8). The most common infections caused by *Zygomycetes* include those caused by members of the four genera *Rhizopus*, *Rhizomucor*, *Absidia*, and *Mucor*, with *R. oryzae* being the species most frequently isolated from patients (16), while *R. stolonifer* has never been implicated in a human infection. Gastrointestinal infection is thought to arise from the ingestion of spores and has been traditionally linked to extreme malnutrition (2, 8).

In nontransplant recipients the stomach was the most frequently involved site, with 67% of all manifestations being gastrointestinal and with a reported mortality rate of 98% (9). Histologically, invasion of vessel walls producing thrombosis, hemorrhage, necrosis, and ulceration of the tissue with an almost uniformly fatal outcome has been separated from colonization of ulcer disease, with a more favorable prognosis (7). More recently, an additional category of invasive disease with infiltration of viable tissue but without vascular involvement has been proposed, but it still represents severe disease (15).

After a review of the literature, we found that species identification of the fungi by culture has been completed only for a minority of patients. Isolation of *R. oryzae* has been reported only once, from a perforated stomach wall of an infant (32 weeks of gestation) with respiratory distress syndrome, sepsis, and a nasogastric tube (12).

Several risk factors might have favored this rare infection in our patient. Uremia implies alterations in the immune system, with granulocyte dysfunction and depressed cell-mediated immunity (4). Normal human serum inhibits the growth of *Rhizopus* spp. (3), while the sera of uremic patients decrease the inhibitory effects of macrophages on spore germination (6). Also, metabolic acidosis, another feature of uremia, increases the availability of iron, which is a known growth factor for *Rhizopus* spp. Antirejection therapy with high doses of corticosteroids and ATG could have exerted an additional important risk factor. The immunosuppressive effect of concomitant CMV infection with an increased risk of superinfection with opportunistic pathogens is also well established in transplant patients (13).

Therapy of mucormycosis with amphotericin B remains standard. Currently applied azole derivatives do not appear to be effective (14), despite a single report of a cure of invasive gastrointestinal mucormycosis in a patient with AIDS achieved with ketoconazole (1). Surgical intervention was also considered for our patient. However, the stable clinical condition, an early causative diagnosis and treatment, as well as frequent gastroscopic follow-up examinations justified an attempt for conservative management.

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