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Mucormycosis in chronic granulomatous disease: Association with iatrogenic immunosuppression

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To the Editor

Chronic granulomatous disease (CGD) results from mutations in either X-linked (gp91^{phox}) or autosomal (p47^{phox}, p67^{phox}, and p22^{phox}) genes encoding the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Impaired generation of reactive oxygen species predisposes to recurrent life-threatening bacterial and fungal infections. Septated hyaline molds (particularly *Aspergillus* species) are the primary fungal pathogens in CGD. Fungi of the order Mucorales (pauciseptated molds) are environmentally ubiquitous and cause mucormycosis in select immunocompromised patient populations, such as those with diabetic ketoacidosis and hematologic malignancy and recipients of transplants or deferoxamine. We investigated the prevalence of mucormycosis in patients with CGD.

Medical and microbiology records of all patients with CGD evaluated at the National Institutes of Health were reviewed (n = 278). Of these, 12 patients had specimens with pathologic/microbiological evidence of Mucorales. By using international consensus criteria,¹ only 4 had proved invasive disease, 4 had colonization, and 4 had contaminants. A fifth invasive case was referred (Table I).^{2–4}

Patient 1 was a 14-year-old boy with fulminant miliary pneumonitis who had *Aspergillus fumigatus* on lung biopsy.² Adjunctive high-dose steroids were administered for hypoxia, but he died after approximately 1 month. Autopsy found aspergillosis and disseminated *Absidia corymbifera*.

Patient 2 was a 19-year old man who was receiving prednisone, methotrexate, and hydroxychloroquine for autoinflammatory manifestations. Biopsy of an enlarging pulmonary mass revealed *Rhizopus oryzae*, which was successfully treated with liposomal amphotericin B and posaconazole.

Patient 3 was a 20-year-old man with recurrent gastrointestinal obstructions in whom pulmonary nodules developed during high-dose prednisone therapy. Biopsy yielded *Rhizopus* species. Amphotericin B and tapering of steroids resolved the infection.

Patient 4 was a 24-year-old man who presented with *Staphylococcus aureus* cervical and hepatic abscesses. Radiofrequency ablation of the liver abscesses led to septic shock with multiorgan failure. After 3 weeks of stress-dose steroids, the *Rhizopus microsporus* group was isolated from lung biopsy. New lesions in the liver, spleen, and brain caused death. Autopsy showed disseminated mucormycosis.

Patient 5 was a 12-year-old boy in whom refractory CGD colitis developed, requiring high-dose steroids, azathioprine, and steroid enemas. After 1 month, nodules in the lungs, spleen, and brain grew *Rhizopus* species. Despite liposomal amphotericin B and posaconazole, he died.

Of 279 patients, 5 (1.8%) had definite invasive mucormycosis. All cases were immediately preceded by a steroid-based immunosuppressive regimen for 3 or more weeks. None of the patients had neutropenia, metabolic acidosis, or iron overload. Review of the literature identified 2 other cases of mucormycosis in patients with CGD (Table I). Furthermore, spontaneous mucormycosis was reported only once out of 16 fungal pneumonias in 72 mice with CGD.⁵

Molds infect a broad range of immunocompromised hosts. Although invasive aspergillosis is most common in patients with hematologic malignancy or transplants, mucormycosis has the same demographic niche but also affects those with diabetic ketoacidosis and those receiving iron chelation. Despite the environmental ubiquity of both these molds, the host factors relating to differential susceptibility are ill defined. CGD provides an opportunity to examine susceptibility to these 2 mycoses within the framework of a defined immune defect. Although patients with CGD are uniquely susceptible to spontaneous invasive aspergillosis, spontaneous mucormycosis in patients with CGD is rare. In our cohort mucormycosis only occurred in patients receiving significant immunosuppression for several weeks. Differences in environmental exposure do not seem to account for this discrepancy because both *Aspergillus* species and Mucorales were identified from 4 patients with CGD with mulch pneumonitis.² None of these latter 4 patients had been receiving immunosuppression at the time of exposure; none had mucormycosis. Although those 4 patients were initiated on steroids for their pneumonitis, duration was typically less than 2 weeks.

In addition to susceptibility to infections, patients with CGD have dysregulated hyperinflammatory responses with granuloma formation and visceral obstruction. Although intense immunosuppression (eg, 1 mg/kg/d prednisone) typically relieves these complications, prolonged high-dose treatment might be permissive for infections not typical

of CGD, such as mucormycosis. However, lower-dose steroid therapy (<0.5 mg/kg/d) is well tolerated without any apparent increased risk for invasive mold infection.

Predisposition of patients with CGD to invasive aspergillosis, particularly with the weakly virulent *Aspergillus nidulans*, suggests that NADPH oxidase-related pathways are central to the control of *Aspergillus* species. It is therefore notable that Mucorales, agents that occupy a similar environmental niche and are clearly capable of causing fatal invasive infection in the proper setting, do not cause disease in patients with CGD without superimposed immune impairment. These observations suggest that NADPH oxidase-independent pathways are chiefly responsible for resistance to Mucorales and that these pathways must be precisely those that are being lesioned among the patients with CGD with mucormycosis. However, CGD appears to be a prerequisite for this permissiveness, likely interacting with iatrogenic macrophage/T-cell immunosuppression to decrease some critical threshold of resistance because these modest immunosuppressive maneuvers do not by themselves lead to mucormycosis in otherwise immunocompetent individuals.

Based on these observations and review of the literature, a model of immunity to these mycoses is proposed. To cause disease, spores must germinate to produce hyphae, activating neutrophils, macrophages, and T cells. When both the NADPH oxidase (in neutrophils and macrophages) and oxidase-independent pathways (in neutrophils, macrophages, and T cells) are intact, no mycosis develops. In patients with CGD, the anti-*Aspergillus* species activity is fragile but apparently sufficient to permit clearance of the low levels of spores typically encountered (approximately 200–2000/d). High-level exposure (eg, mulching and composting) overwhelms this fragile defense, and spores germinate to hyphae. On the other hand, NADPH oxidase-independent mechanisms effectively clear the sporangiospores of Mucorales, preventing disease. In patients with CGD receiving high-dose immunosuppression that affects macrophages and T cells, susceptibility to mucormycosis is apparently enhanced.

In patients with diabetes mellitus, NADPH oxidase activity is not impaired or is actually enhanced. In diabetic ketoacidosis acidosis might favor iron acquisition by Mucorales,⁶ and there is alteration of monocyte and T-cell functions.^{7,8} Patients undergoing dialysis frequently have enhanced NADPH oxidase activity,⁹ and mucormycosis typically occurs only when deferoxamine is used to chelate iron. The iron-deferoxamine complex might actually favor iron uptake by *Rhizopus* species, thereby enhancing growth.⁶ In these latter patient groups, enhanced NADPH oxidase activity might explain the relative paucity of aspergillosis, indicating that it is the impairment of oxidase-independent pathways leading to mucormycosis.

Fungal infections in patients with CGD, both with and without additional immunosuppression, provide insight into human immunity to *Aspergillus* species and Mucorales. NADPH oxidase-dependent pathways are critical for immunity to *Aspergillus* species, whereas oxidase-independent pathways, including those involving T lymphocytes, appear to be key for defense against Mucorales.

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TABLE I

Summary of cases of mucormycosis in patients with CGD

Patient features	Type of CGD	Immunosuppression	Clinical disease	Causative agent	Outcome
14-year-old boy ^{#2}	p47 ^{phox}	Methylprednisolone, 10 mg/kg/d, for 3 d; then prednisone, 1 mg/kg for 7 d; then prednisone, 0.5 mg/kg	"Muc pneumonia" with multiorgan failure	<i>Aspergillus fumigatus</i> (lungs, brain); <i>Absidia corymbifera</i> (lungs, liver, spleen, kidneys)	Deceased
19-year-old man [*]	p47 ^{phox}	Prednisone, 10 mg daily; methotrexate, 25 mg daily (with leucovorin); hydroxychloroquine, 400 mg daily	Pulmonary mass	<i>Rhizopus oryzae</i>	Survived
20-year-old man [*]	X-linked	Prednisone, 30 mg daily	Pulmonary nodules	<i>Rhizopus</i> species	Survived
24-year-old man [*]	X-linked	Steroids equivalent to prednisone, 50–80 mg daily, for 3 wk	<i>S aureus</i> -induced septic shock with multiorgan failure and diffuse bilateral pulmonary infiltrates	<i>Rhizopus microsporus</i> group	Deceased
12-year-old boy [*]	X-linked	Methylprednisolone, 1.33–2 mg/kg daily, and azathioprine, 50 mg daily	Pulmonary and splenic nodules, brain abscess, renal infiltrates	<i>Rhizopus</i> species	Deceased
13-year-old girl ⁸	NS	High-dose corticosteroids; cyclophosphamide	Thoracic wall mass; bronchopleural fistula; quadriceps myonecrosis; subarachnoid hemorrhage	Mucoraceous fungi on histopathology; culture not reported	Deceased
10-month-old boy ⁹	NS	Preceding RSV, unclear if corticosteroids administered	Mass of small intestine	<i>R microsporus</i> var. <i>rhizopodiformis</i>	Survived

NS, Not specified; RSV, respiratory syncytial virus.

^{*} Current report.