Invasive Zygomycosis With a Fatal Outcome

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Critical Situations: Dermatology in the Acute Care Setting

REPORT OF CASES

CASE 1

A previously healthy 24-year-old male Egyptian farmer had nasal obstruction, mucopurulent nasal discharge, recurrent attacks of headache, hyposmia, and a painless non-pruritic erythematous plaque on his nose and adjacent parts of the face and nasal mucosa (Figure 1). The condition had started 12 months earlier as a small erythematous indurated plaque that gradually increased in size to approximately 12 cm in diameter. The lesion was firm, with a well-defined, slightly raised border. A similar plaque about 4 cm in diameter was seen on the lateral aspect of his right thigh. There was no adenopathy. The patient denied any other symptoms, specifically fever, night sweats, or weight loss. Laboratory findings were all within normal range, including those for serum immunoglobulin levels and CD4 and CD8 T-cell counts. The results of a tuberculin test were negative for organisms. Plain x-ray films of the patient's sinuses (Water’s projection) showed pansinus opacification. Computed tomography of his paranasal sinuses also revealed pansinus opacification with focal areas of hyperdensity. Magnetic resonance imaging of his brain showed multiple space-occupying lesions in the parietal, frontal, and temporal brain lobes (Figure 2).

Skin biopsy specimens from the patient's thigh and face both showed identical findings of well-defined granulomas with multiple giant cells and eosinophils. Periodic acid–Schiff and hematoxylin-eosin staining showed thin-walled aseptate hyphae with an eosinophilic sheath (a classic finding termed the Splendore-Hoeppli phenomenon) phagocytized within giant cells (Figure 3).

Fungal cultures from skin and sinus specimens were grown on Sabouraud agar without cycloheximide. The thigh specimen cultures yielded yellowish flat furrowed waxy colonies that showed microscopically short sporan-giophores, consistent with a finding of Conidiobolus coronatus, whereas the cultures grown from the nasal sinus specimens yielded white flat powdery colonies with short aerial mycelia that microscopically showed short conidiophores, consistent with Basidiobolus ranarum.

The patient developed seizures that were initially controlled by phenytoin sodium. He was treated with amphotericin B (1 mg/kg per day). After 7 days he developed fever, abdominal pain, and vomiting and was treated with oral itraconazole (400 mg/d). Despite therapy, the lesions enlarged in size and the patient's general condition rapidly deteriorated, resulting in the development of hemiparesis, loss of consciousness, and sudden death.

CASE 2

A 9-year-old Egyptian boy with facial and nasal clinical features of 6 months' duration that were almost identical to those seen in the patient in case 1 was admitted to the hospital for evaluation (Figure 4). Laboratory findings were all within normal range. Computed tomography revealed bilateral ethmoidal opacification with focal areas of hyperdensity, suggesting fungal sinusitis. Magnetic resonance imaging of the patient's brain showed no evidence of involvement. Endoscopic bilateral ethmoidectomy was performed, and histopathologic and mycologic examination revealed findings similar to those of the facial lesion in case 1. The patient was treated with oral itraconazole (2.5 mg/kg per day) and showed marked resolution of his sinus condition (as evidenced by a postoperative computed tomographic scan) and improvement of his skin condition after 5 weeks of therapy.

DIAGNOSTIC CHALLENGE

The differential diagnosis of an enlarging facial plaque in an immunocompetent individual includes a malignancy, such as B-cell lymphoma; a primary inflammatory process, such as sarcoidosis; or an infection, particularly by fungi or mycobacteria. Skin biopsy and culture are essential to making a correct diagnosis and initiating potentially life-saving treatment, as these 2 cases illustrate.

Zygomycosis is the name given to infections caused by the fungi in the class Zygomycetes. This class is divided into 2 orders, Mucorales and Entomophthorales, which...
classically produce very different clinical patterns of disease in humans. Mucorales, which includes the genera *Mucor*, *Rhizopus*, and *Absidia*, is the cause of mucormycosis, an acute angioinvasive and frequently fatal infection seen almost exclusively in significantly immunocompromised individuals, particularly those with hematologic malignancies. In contrast, Entomophthorales (genera *C. coronatus* and *B. ranarum*) infects primarily immunocompetent individuals and produces chronic, generally indolent, cutaneous, nasal, or sinus disease. Although these infections are often slowly progressive, the cases presented herein illustrate the potentially devastating effects of unrecognized and untreated infections.

Rhinocerebral zygomycosis is a serious condition with an overall mortality rate of 48%. Infection generally is caused by inhaled spores and begins in the sinuses, spreading by direct extension outward to the paranasal skin and inward to the central nervous system. Most cases of invasive fatal rhinocerebral zygomycosis are caused by the order Mucorales and are seen almost exclusively in immunocompromised individuals. After *Aspergillus* and *Candida* infections, mucorales infections are the third most common fungal infections seen in patients with hematologic malignancies. In contrast, rhinocerebral zygomycosis caused by the order Entomophthorales is rarely
seen in immunocompromised individuals, although a few cases have been reported.\(^3\) Entomophthorales (genera \(C\) coronatus and \(B\) ranarum) infections are more classically seen as chronic infections in immunocompetent individuals from tropical and subtropical climates. \(C\) coronatus is most commonly acquired by the inhalation of spores from decaying organic material and begins as chronic sinusitis that may extend to nearly all adjacent facial and subcutaneous tissues and structures. \(B\) ranarum typically causes a chronic infection of the peripheral or subcutaneous tissue, generally on the arms, trunk, and buttocks, and is usually acquired by traumatic implantation.\(^3,5\)

Entomophthorales organisms are aerobic and grow in most culture media after 2 to 5 days of inoculation at temperatures of 25°C to 37°C, whereas mucorales organisms typically show growth at 55°C.\(^1,6\) Because Entomophthorales organisms are ubiquitous and may be laboratory contaminants, diagnosis should be verified by histologic demonstration of organisms in affected tissue. Perineural invasion, angioinvasion, and infarction are common histologic findings in Mucorales infection. In contrast, Entomophthorales infections are characterized by a mixed granulomatous inflammatory infiltrate with eosinophils, histiocytes, neutrophils, plasma cells, and giant cells. In addition, hyphal elements may be surrounded by a dense eosinophilic sleeve-like material, as mentioned in the subsection describing case 1.\(^5,7\) A polymerase chain reaction assay has recently been developed and may be useful in cases in which the diagnosis is suspected but histology and culture findings are negative.\(^8\)

Potassium iodide has been the traditional drug employed in the treatment, although several other drugs, such as amphotericin B, co-trimoxazole, ketoconazole, itraconazole, and fluconazole have been successfully tried.\(^1,4\) Recently, an amphotericin lipid complex was introduced for treatment of invasive fungal infection with improved efficacy and reduced risk of nephrotoxicity and infusion toxicity.\(^9\) Treatment also includes aggressive surgical debridement and control of underlying risk factors. Treatment failures with amphotericin B have been reported, and itraconazole may be preferred as a first-line agent.\(^1\)

In conclusion, we present 2 cases of zygomycosis in immunocompetent individuals. In both cases, fungi consistent with \(C\) coronatus were isolated from sinus and facial lesions. As a somewhat incidental finding, the patient in case 1 also had a concurrent cutaneous infection with \(B\) ranarum. These cases dramatically illustrate the importance of prompt recognition and treatment of this disease. Delay in seeking medical care in case 1 resulted in extensive central nervous system involvement and death. The favorable outcome in case 2 is correlated with an earlier diagnosis and prompt medical and surgical treatment.

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REFERENCES


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