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Zygomycosis originating from an odontogenic infection in a pediatric oncology patient

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Abstract

The Zygomycetes are an increasingly frequent cause of invasive mould infection in immunocompromised patients. Here we describe the first well-documented case of Rhizopus infection of odontogenic origin, which presented as a rapidly progressive soft tissue infection in a neutropenic child. The infection resolved with limited surgical debridement and antifungal therapy.

Keywords

Zygomycoses; dental infection; immunocompromised

1. Introduction

Zygomycosis, commonly but less accurately described as mucormycosis, is caused by members of the class *Zygomycetes* (Ribes et al., 2000). This class contains two orders, *Mucorales* and *Entomophthorales*. Most human infections are caused by members of the *Mucorales*, including *Absidia corymbifera*, *Mucor spp.*, *Rhizomucor spp.*, and *Rhizopus spp.* The most common sites of primary infection include the sinuses (rhinocerebral zygomycosis), lung, skin or soft tissues and the gastrointestinal tract. Primary infections of other anatomic sites are rare. We review the case of a child with neuroblastoma who developed typical rhinocerebral Rhizopus infection arising from a dental abscess.

2. Case Report

A 4-year-old male with relapsed Stage 4 neuroblastoma (International Neuroblastoma Staging System) who was receiving alternating cycles of cyclophosphamide/topotecan and ifosfamide/carboplatin/etoposide presented to his local hospital with a 2-day history of fever, neutropenia and 12-hour history of rapidly progressive left maxillary soft tissue swelling (Figure). He had not received corticosteroids prior to this hospitalization, had no history of antecedent dental pathology and had been neutropenic for approximately 14 days

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prior to the onset of facial swelling. He was urgently transferred for evaluation. On admission to our center he appeared ill and he had, in addition to facial swelling, distinctive purple discoloration of the left maxillary gingival, alveolar process and adjacent palate and a mild left peripheral facial nerve palsy. His peripheral blood leukocyte count was $400/\text{mm}^3$ and the absolute neutrophil count was $200/\text{mm}^3$. He had mild hyponatremia and hypochloremia with a serum glucose concentration of 94 mg/dL (normal 70–125 mg/dL). Computerized tomography of the brain and face demonstrated air within the left maxillary molar, which was surrounded by a 1×1.9 cm radiolucency consistent with a periapical abscess. Preseptal and facial cellulitis with edema extending to the submandibular region was noted; however, there was minimal mucoperiosteal thickening of the left maxillary sinus and no intracranial involvement.

Extraction of the affected tooth and debridement of necrotic alveolar soft tissue and bone was immediately undertaken. Notably, no purulence was noted and the involved tissue did not bleed. Histopathological examination demonstrated necrotic soft tissue and alveolar bone containing numerous broad, pauciseptate fungal hyphae. Culture of the abscess cavity and alveolar bone grew *Rhizopus* sp. Empirical therapy with liposomal Amphotericin B (5 mg/kg daily) and broad-spectrum antibacterials was followed, after identification of the organism, by the addition of oral posaconazole (6 mg/kg po twice daily). G-CSF was given until resolution of the leukopenia 3 days later. Amphotericin B was discontinued after 21 days. Delayed debridement of the affected alveolar ridge, extraction of 2 teeth, and placement of a palatal splint were undertaken 4 months after initial surgery. Extensive and disfiguring surgery was not required and no evidence of disease was evident on CT scans obtained 7 months after diagnosis. Posaconazole was well tolerated and no recurrence or dissemination of fungal infection occurred during subsequent courses of myelosuppressive chemotherapy beginning 4½ months after the patient's acute illness. Suppressive therapy with posaconazole was administered for 18 months until the time of the patient's death due to progressive neuroblastoma.

3. Discussion

Risk factors for invasive *Mucorales* infection include diabetes mellitus, immunosuppression (especially due to cytotoxic chemotherapy or transplantation), and the use of corticosteroids, deferoxamine or desferrioxamine (Ribes et al., 2000). Rhinocerebral zygomycosis accounts for up to 50% of infections, most commonly in patients with diabetes mellitus and ketoacidosis. *Rhizopus* spp. are responsible for 50–90% of these infections (Ribes et al., 2000; Roden et al., 2005; Zaoutis et al., 2007). Fungal spores are inhaled into the sinuses and grow rapidly at normal or elevated body temperatures. Fungi produce a variety of lipases and proteases and directly invade blood vessels, producing extensive tissue necrosis. Clinically, patients typically present with sinus pain and rapidly progressive facial or periorbital soft tissue swelling or frank tissue necrosis extending to the periorbital soft tissues, orbits, central nervous system or palate. Proptosis, loss of vision, cranial nerve palsies and coma are common in later stages of infection.

Our patient presented with classic features of rhinocerebral zygomycosis, but his infection appeared to arise from a highly unusual anatomic focus. Our case provides the best evidence to date that the *Zygomycetes* may cause primary odontogenic infections. Several additional reports describe rhinocerebral zygomycosis temporally associated with dental procedures, but an antecedent odontogenic focus of fungal infection was not obvious or investigated. Fogarty and coauthors described a 74 year-old with corticosteroid-dependent pulmonary disease who developed progressive soft tissue and left maxillary alveolar bone infection following dental extractions (Fogarty et al., 2006). Histological examination of debrided bone demonstrated fungal hyphae and *Mucor* sp. and several bacterial co-pathogens were

isolated from debrided tissue. Salisbury and coworkers reported a 60-year-old with acute myelogenous leukemia who similarly developed progressive gingival necrosis following the extraction of four second molars (Salisbury et al., 1997). Stains of debrided soft tissue demonstrated hyphal elements and an unspecified member of the *Mucorales* family was isolated from tissue. Although the ability of yeast, particularly *Candida* spp., to colonize the oral mucosa and gingiva is well described, the types of molds and frequencies with which they are found at these sites has not been thoroughly evaluated. *Aspergillus fumigatus* is found more frequently and higher numbers in the periodontal pockets of adult smokers, however, than nonsmokers (Kamma et al., 1999). Similar colonization or persistence in immunocompromised patients might increase their risk of invasive fungal infection.

The overall mortality of zygomycosis in oncology patients is reported to be 66%. Mortality rates are lower, however, in recent decades and in patients with localized infection (Roden et al., 2005). In a review of published experience with *Zygomycetes* infections in pediatric patients, infection was fatal in 44% of children with malignancy and 67% of those undergoing bone marrow transplantation (Zaoutis et al., 2007). The highest survival rates are obtained with a combination of antifungal therapy and surgery (Roden et al., 2005; Zaoutis et al., 2007). Since these fungi are angioinvasive and infections are characterized by thrombosis and extensive tissue necrosis, aggressive and disfiguring surgical therapy is sometimes necessary. In our case, radical debridement was not pursued because of the overall poor prognosis of the patient's primary malignancy. His excellent outcome may be attributable to several factors, including the presence of relatively localized disease, prompt recognition and treatment of the infection, the availability of highly effective antifungal agents and the rapid resolution of his neutropenia. Although dental abscesses are typically polymicrobial bacterial infections, our patient's presentation was suspicious for invasive fungal disease and empirical antifungal therapy was begun before culture results were obtained. The traditional drug of choice for zygomycosis is amphotericin B. Posaconazole, a triazole recently licensed for prophylaxis of invasive *Aspergillus* and *Candida* infection in immunocompromised adolescents and adults has significant in vitro activity against many unusual fungal pathogens, including the *Zygomycetes* (Almyroudis et al., 2007). The overall success rate in 91 adult and pediatric patients with zygomycosis who received posaconazole as salvage therapy because of treatment failure or intolerance of other antifungal agents was 60% (van Burik et al., 2006). Success rates were similar in patients who did and did not undergo surgical debridement. Posaconazole is currently only available in an oral formulation and is therefore difficult to administer to critically ill patients or persons with gastrointestinal disorders. Like other azoles, it may have interactions with chemotherapeutic and other medications because of its inhibition of cytochrome CYP3A4 and is metabolized by the liver. In view of these promising reports, however, randomized clinical trials of posaconazole, alone and in combination with traditional therapies, are needed to identify the best strategies for treating serious fungal infections. Our case illustrates that good outcomes may depend on maintaining a high index of suspicion for unusual pathogens, aggressively pursuing the specific etiology of serious infections and promptly treating these infections with effective antifungal therapy.

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