

ZYGOMYCOSIS IN QATAR: A RETROSPECTIVE REVIEW OF SIX CASES

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SUMMARY: Six cases of zygomycosis that were diagnosed at Hamad Medical Corporation over an eleven-year period are retrospectively reviewed. All patients had at least one predisposing condition. Renal transplant and diabetes mellitus were the most common predisposing conditions. Sites of involvement were pulmonary in two patients, rhinocerebral two, rhino-orbital, and cutaneous in one each. The clinical features in patients with rhinocerebral and rhino-orbital involvement were very suggestive of the diagnosis, while patients with pulmonary and cutaneous involvement, the disease was not suspected and was only made after the histopathology or culture results were available. Diagnosis was made premortum in all patients. Diagnosis was confirmed by histopathology in three patients and by culture in the other three. Five of the six patients died. Poor outcome correlated with rhinocerebral and pulmonary involvement, while cutaneous disease was associated with favorable outcome. Therapy with amphotericin B, surgical debridement, and correction of the underlying predisposing condition offers the best chance for survival.

Key-words: Mucormycosis - Zygomycosis - Phycomycosis.

INTRODUCTION

Zygomycosis is a relatively uncommon opportunistic fungal infection caused by species of the class Zygomycetes; order Mucorales and Entomophthorales (1). Zygomycosis is a relatively new term. Other widely used terms to refer to zygomycosis are mucormycosis, and phycomycosis (1). These fungi are ubiquitous saprophytic organisms and are common inhabitants of decaying materials (2). They show minimal intrinsic pathogenicity in normal persons, but can cause fulminant infection in immunocompromised patients such as those with diabetes mellitus, hematologic or oncologic diseases, transplant recipient, renal failure, burns, and those receiving corticosteroids and deferoxamine therapy (3-6). Infection is acquired by inhalation of spores or direct inoculation of skin. In the susceptible host the spores can germinate and give rise to the hyphal form which is angioinvasive, leading to thrombosis of arteries and veins, infarction of sur-

rounding tissue, production of black necrotic debris and systemic dissemination (7). The major clinical presentations are rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated zygomycosis (8). Zygomycosis is associated with high mortality especially in the disseminated form (9). Late diagnosis of zygomycosis contributes to this poor outcome (3). In the past, zygomycosis was almost uniformly fatal and was usually recognized only at autopsy. The past decade has witnessed some improvement in outcome; this was attributed to timely diagnosis, aggressive surgery in conjunction with promising antifungal therapies including lipid formulations of amphotericin B and immunotherapy-based approaches such as the use of colony-stimulating factors (10). We herein report our experience at Hamad Medical Corporation with six patients with zygomycosis seen over the last 11 years and review pertinent literature.

PATIENTS AND METHODS

Cases of zygomycosis were identified from the medical records, and the infectious diseases log book. Between 1993 and 2003, seven cases of zygomycosis were diagnosed at Hamad Medical Corporation. The records for one patient were missing, so six patients were available for review. Diagnosis was based on consistent clinical and radiologic features and characteristic histopathologic findings or culture positive for zygomycosis.

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cetes. The following data were collected: age, sex, nationality, underlying conditions, associated infections, antibiotic, immunosuppressive agents, or corticosteroids use symptoms, physical findings at presentation, total white blood cell count, erythrocyte sedimentation rate, radiologic findings, culture of infected tissue, treatment, complications, and outcome.

RESULTS

Six cases of confirmed zygomycosis were diagnosed over an eleven year period. Half of the cases were seen in the last two years of the study, suggesting an increase in incidence over time. All cases were diagnosed premortum, since postmortem examination is rarely performed in our hospital. Age of patients ranged between 20 and 53 years (mean 45 years). The male to female ratio was 1:1. Four patients were Qatari and two were Pakistani. Underlying predisposing conditions were present in all patients. Renal transplant and diabetes mellitus were the most common and were present in three patients each. Other predisposing conditions were trauma and neutropenia secondary to chemotherapy for acute lymphoblastic leukemia (ALL) in one patient each. Five of the six patients were on antibiotics at the time of diagnosis of zygomycosis. One patient with ALL with chemotherapy induced neutropenia developed rhino-orbital zygomycosis while receiving fluconazole for candidemia. Concomitant infection was present in four patients. These were gastroenteritis, acute pyelonephritis, wound infection, and candidemia. Sites of involvement were pulmonary in two patients, rhinocerebral two, rhino-orbital, and cutaneous in one each. The clinical features were related to the site of involvement. Fever was present in all patients. Patients with rhino-orbital and rhinocerebral mucormycosis presented with blood-tinged nasal discharge, palatal ulcer, eye swelling, blurred vision, diplopia, and ptosis. In addition the patients with rhinocerebral mucormycosis had altered sensorium, cranial nerve palsies and hemiplegia. Patients with pulmonary involvement presented with cough, sputum and shortness of breath. The patient with trauma presented with necrosis and blackish discoloration of his wound. All patients had leukocytosis except the one who developed zygomycosis in association with neutropenia. The mean white blood cell count in these five patients was 19,760/mm³ (range 12,700/mm³ to 34,400/mm³). Radiologic studies were helpful in suspecting the diagnosis and were abnormal in all patients with rhino-orbital, rhinocerebral, and pulmonary mucormycosis. Magnetic resonance imaging and computed tomographic scans revealed opacification of the involved sinuses in patients with rhino-

orbital and rhinocerebral mucormycosis, in addition to narrowing of the internal carotid artery in the patient with rhinocerebral mucormycosis. In patients with pulmonary involvement chest radiographs and CT scans showed lung consolidation in one patient and cavity in the other. Diagnosis was made based on suggestive radiologic finding with histologic confirmation showing broad branching in perpendicular non-septate fungal hyphae in three patients. In the other three patients, diagnosis was made on the basis of suggestive clinical and radiologic picture, and positive culture growing zygomycetes. *Rhizopus* was the genus isolated in these three patients. Amphotericin B treatment was administered to five patients. The duration of treatment ranged from one day to 40 days. The outcome in our patients was poor. Five of the six patients expired. All patients with pulmonary, rhino-orbital, and rhinocerebral mucormycosis died. Survival was achieved only in the patient with post traumatic cutaneous mucormycosis. This patient was treated with repeated wound debridement and a total of 2.5 gm of amphotericin B. One patient with rhino-orbital mucormycosis improved after receiving amphotericin B but expired later on due to ALL refractory to treatment.

DISCUSSION

Zygomycosis is a rare, and frequently fatal opportunistic fungal infection that complicates the clinical course of susceptible patients, including patients with diabetes mellitus, hematologic or oncologic diseases, transplant recipients, trauma and burns patients, and those undergoing deferoxamine therapies (1, 3-6). In this study we report our experience at Hamad Medical Corporation with six patients with zygomycosis seen over 11 years. Six cases of zygomycosis were diagnosed between 1993 and 2003. No case of zygomycosis has been diagnosed at our institution since it was opened in 1982 till 1992. All our cases were diagnosed premortum. Because the literature indicates that most cases of zygomycosis are diagnosed after death (7), and since postmortem examination is not done routinely at our institution, it is likely that many cases of zygomycosis are missed, and this may account for the very small number of cases that were diagnosed at our institution. All our patients had predisposing conditions for zygomycosis. Immunosuppression related to renal transplantation and diabetes mellitus were the most common predisposing conditions. Other predisposing conditions were trauma, ALL and neutropenia. Steroids were used in four patients. Five patients were on antibiotics, and four were having concurrent infection at the time they developed zygomycosis. All these factors may have contributed to

predisposition for zygomycosis. The finding that no case of zygomycosis has been diagnosed before 1993 and that half of the cases were diagnosed in the last two years of the study suggests a recent increase in disease incidence. A similar increase in incidence of zygomycosis has been observed by others (11, 12). Possible contributing factors for the increase in the number of cases observed at our institution include increased awareness, and increase in the number of patients at risk particularly transplant recipients especially renal transplant patients which increased from 110 patients in 1990 to 260 patients in 2003, and more aggressive chemotherapy in patients with malignant disease. Rhinocerebral and pulmonary zygomycosis were the most common forms of the disease. Predisposing factors in patients with rhinocerebral zygomycosis were renal transplant contrary to that reported by others where poorly controlled diabetes mellitus was the predisposing factor in two thirds in patients (2, 9). For the patients with pulmonary disease the predisposing factors were diabetic ketoacidosis and renal transplant. Although pulmonary zygomycosis was reported in patients with diabetes mellitus and renal transplant recipients, most cases have been reported in association with neutropenia in patients with hematologic malignancies or bone marrow transplantation (3, 9, 13). The clinical features of rhinocerebral and rhino-orbital zygomycosis were nasal congestion, dark blood-tinged rhinorrhea, facial or periorbital swelling, blurred vision, diplopia, and ptosis. Spread to central nervous system lead to mental deterioration and contralateral hemiplegia. Although these features are not pathognomonic for zygomycosis, and can be mimicked by aspergillosis, however their presence should suggest the diagnosis and stimulate further tests to confirm or exclude the diagnosis. Disease progression in patients with rhinocerebral zygomycosis was rapid resulting into death within few days. The clinical features of pulmonary zygomycosis in our patients were non-specific and did not point to the diagnosis. They could be seen in other pulmonary infections. The diagnosis was only made after biopsy results were available. Disease progression in patients with pulmonary zygomycosis was slow, with time from first symptoms to death up to three months. The sixth patient with cutaneous zygomycosis had wound in his thigh which was contaminated with soil at the time of trauma. Possible contributing factors to the occurrence of zygomycosis in this patient include presence of traumatized and devitalized tissue, bacterial infection and use broad spectrum antibiotics.

Zygomycosis is diagnosed histologically when broad, irregularly shaped, non-septate hyphae with right angle branching are demonstrated in tissues or by

recovery of zygomycosis in culture of specimens obtained from the site of presumed involvement (11). The diagnosis was confirmed in our patients by histologic demonstration of the typical fungal hyphae in three patients, and by culture in the other three. Human infection with Zygomycosis is most commonly caused by species of *Rhizopus*, *Absidia*, and *Rhizomucor* (14). It is interesting that all our patients in whom culture was done yielded growth of *Rhizopus*. Whether this indicates that the most prevalent species of zygomycetes in our community is *Rhizopus* or not need further studies.

Therapy of zygomycosis includes correction of the underlying predisposing condition whenever possible, antifungal agents and surgical debridement (9). Amphotericin B is the drug of choice for the treatment of zygomycosis (15). Duration of treatment is not well defined but prolonged treatment until resolution of manifestations seems prudent (9). Lipid formulations of amphotericin B seems appropriate alternative to conventional amphotericin B in patients who are intolerant to or develop renal toxicity related to amphotericin B (16, 17). Tobon *et al.* (18) recently reported the successful treatment of invasive Zygomycosis with posaconazole in a heart-kidney transplant recipient who failed to respond to amphotericin B (deoxycholate). In this series amphotericin B treatment was administered to five patients with a duration ranging from one day to 40 days. Debridement was done only in the patient with cutaneous mucormycosis. In the four patients with rhinocerebral and pulmonary zygomycosis debridement was not attempted because the diagnosis was made when the patients were in very advanced stage and shortly before death. The patient with rhino-orbital zygomycosis improved with the use of amphotericin B and granulocyte colony-stimulating factor to reverse his neutropenia without the need for debridement.

The outcome in patients with zygomycosis has been traditionally considered to be poor with more than 50% mortality, however more recent literature suggests improved prognosis with 80% survival (9). The improved survival can be attributed to early diagnosis leading to prompt institution of medical therapy and aggressive surgical debridement of devitalized tissues (9, 11, 19). Factors that may affect outcome include host factors such the degree of immunosuppression, the ability to reverse the immunosuppression, and the site of involvement (20). Several studies have demonstrated that patients with cancer associated zygomycosis, disseminated disease are associated with poor outcome, while patients with non-cancer related zygomycosis and patients with localized disease have better prognosis (3, 11, 14). In this series

Case no	Year of diagnosis	Age (yr)/sex	Nationality	Underlying condition	Steroid use	Site of involvement	Method of diagnosis	Genus of zygomycetes	Therapy	Outcome
1	1993	49/F	Q	D.M, diabetic ketoacidosis	No	Pulmonary	Histopathology	Unknown	Amphotericin B	Died
2	1998	44/F	P	Renal transplant	Yes	Rhinocerebral	Histopathology	Unknown	Amphotericin B	Died
3	1999	53/M	Q	Renal transplant, D.M	Yes	Pulmonary	Histopathology	Unknown	None	Died
4	2002	20.M	P	Trauma		Cutaneous	Culture	Rhizopus	Amphotericin B and debridement	Survived
5	2002	51/M	Q	ALL, neutropenia	Yes	Rhino-orbital	Culture	Rhizopus	Amphotericin B	Died
6	2003	53/F	Q	Renal transplant, D.M	Yes	Rhinocerebral	Culture	Rhizopus	Amphotericin	Died

five of the six patients died. All the patients with rhinocerebral and pulmonary zygomycosis died, while the patient with cutaneous disease survived. Possible contributing factors to survival in the patient with cutaneous zygomycosis include lack of immunosuppression, early diagnosis, repeated debridement and prolonged antifungal therapy. The patient with rhino-orbital zygomycosis responded to antifungal therapy with resolution of the manifestations of zygomycosis; however he later on died due refractory cancer.

In conclusion, zygomycosis remains a very rare disease in Qatar; however incidence may be increasing. The actual number of cases may be more, because postmortem examination is rarely done at our institution. Rhinocerebral and pulmonary involvement are the most common forms of the disease. Because all patients had a predisposing condition for zygomycosis, the disease should be suspected in any patient with compatible clinical picture in the presence of a predisposing condition. Therapy requires correction of the underlying predisposing condition, antifungal agents and surgical debridement. The outcome remains dismal with rhinocerebral and pulmonary disease having bad prognosis.

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BREASTFEEDING REDUCES RISK OF ASTHMA IN FIRST FOUR YEARS OF LIFE, FROM JOURNAL OF ALLERGY & CLINICAL IMMUNOLOGY

Exclusive breastfeeding from birth to four months reduces the risk of asthma during the first four years of life, according to a study in the October 2004 *Journal of Allergy & Clinical Immunology* (JACI). The JACI is the peer-reviewed scientific journal of the American Academy of Allergy, Asthma & Immunology (AAAAI).

Inger Kull, RN, and colleagues from the Department of Occupational and Environmental Health in Stockholm, Sweden, evaluated the relationship between breastfeeding and asthma in 4,089 newborns. Data was collected from the parents on symptoms related to wheezing and other allergic diseases in their child at one, two and four months of age. Data on breastfeeding was collected after 1 year of age. Exclusive breastfeeding was defined as the period when the infants were given only breast milk, and no cow's milk or solid foods had been introduced.

Researchers found:

Four year olds who had been exclusively breast-fed for the first four months showed a lower risk of asthma.

9.1% of children exclusively breast-fed for less than 4 months had asthma, compared to 6.4% among children breast-fed 4 months or more.

Continued partial breastfeeding after exclusive breastfeeding also had a protective effect.

The protective effects of breastfeeding were greatest among children whose parent(s) did not have asthma or allergies.

The researchers had previously showed the same results in children at 2 years of age. This study expands on those findings, showing that a more prolonged period of breastfeeding not only reduces the risk of asthma during the first four years of life, but it also appears to reduce the severity of the disease as well.

The AAAAI is the largest professional medical specialty organization in the United States representing allergists, asthma specialists, clinical immunologists, allied health professionals and others with a special interest in the research and treatment of allergic disease. Established in 1943, the AAAAI has nearly 6,000 members in the United States, Canada and 60 other countries. The AAAAI serves as an advocate to the public by providing educational information through its Web site at www.aaaai.org or the toll-free physician referral and information line at 1 (800) 822-2762.

EDITOR'S NOTE: This study was published in the peer-reviewed, scientific journal of the American Academy of Allergy, Asthma & Immunology, but does not necessarily reflect the policies or the opinions of the Academy. The study will appear in the October 2004 JACI, but is currently available on the JACI Web site. To receive a copy of the study, please contact John Gardner (jgardner@aaaai.org) at (414) 272-6071. For more information and access to the archive of past JACI news releases, visit the Media Center of the AAAAI Web site, www.aaaai.org.