RESEARCH PAPER | Medical science | Volume : 5 | Issue : 8 | August 2015 | ISSN - 2249-555X

Mucormycosis an Emerging Fungal Infection

KEYWORDS

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ABSTRACT *Background*

Mucormycosis is an emerging infection associated with high mortality. These fungi are very common molds to which exposure is probably quite frequent, still, clinical disease is rare and affects severely immunocompromised patients or patients with diabetes mellitus. Mucormycosis is manifested by a wide variety of syndromes, devastating rhino-orbital-cerebral and pulmonary infections are the major presentation. The diagnosis of mucormycosis relies upon the identification of organisms in tissue, however culture often yields no growth. The identification of risk factors, clinical features and radiological findings increase the possibility of an early diagnosis, which may prevent progressive tissue invasion, reduce the need and/or extent of surgical resection, and improve survival.

Aims and Objective

To describe theclinical presentation, risk factors and the mortality rate of mucormycosis in a resource limited setting.

Material and Methods

We studied 28 patients of mucormycosis admitted to our institution over a period of one year. Demographic features, predisposing conditions, clinical features, radiological features and in hospital mortality were obtained from the medical records.Tissue sections were reviewed with Gomori'smethenamine silver (GMS) and periodic acid Schiff (PAS) stains .

Results

The study material included 18 males and 10 females with age ranging from 34 – 76 years. The clinical syndrome included rhino-orbital-cerebral in 20, followed by pulmonary in 6 patients and disseminated and gastrointestinal mucormycosis in 1 patient each. Diabetes mellitus being the commonest underlying risk factors identified in 24 patients out of which 4 patients also had history of steroid usage. Other underlying conditions noted were HIV and Acute myeloid leukemia in 1 patient each. Out of 20 patients with rhino-orbital-cerebral mucormycosis, 15 patients presented with fever, headache, acute sinusitis and periorbital swelling. 3 patients presented with nasal necrosis in addition and 2 patients presented in addition with decreased vision. Pulmonary mucormycosis patients presented with dyspnea and cough. Gastrointestinal mucormycosis patients presented with abdominal pain, voimiting and hemetemesis.Out of 15 tissue samples submitted for histopathological examination only 8 samples showed fungal hyphae resembling mucormycosis. Cultures were positive only in 4 samples. Out of 20 patients with rhino-orbital-cerebral mucormycosis, 4 patients underwent surgical debridement. All the patients were treated with amphotericin B in a dose of 1.0 – 1.5 mg/kg. Total number of patients who died in this current study was 16, out of which 11 pts had rhino-orbital-cerebral mucormycosis, 4 patients had pulmonary mucormycosis and 1 patient had disseminatedmucormycosis. Out of 11 patients with rhino-orbital-cerebral mucormycosis, 2 patients had undergone surgical debridement and 4 patients had renal failure.

Conclusion

Mucormycosis as an infection is uncommon and is largely confined to severly immunocompromised patients such as diabetes. There are several clinical presentation of mucormycosis, the most common being the rhino-orbital-cerebral and pulmonary forms. The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. However, culture often yields no growth. A high index of clinical suspicion, leading to early diagnosis and prompt treatment initiation may result in a more favourable outcome.

Introduction

Mucormycosis (formerly known as zygomycosis) is a rare infection caused by molds belonging to the subphylum Mucoromycotina in the order Mucorales. These fungi are ubiquitous in nature, particularly in soil, decaying wood, and other organic matter.(1) In contrast to the wide spread distribution of these fungi, the infrequency of disease caused by these organisms attests to their low virulence potential in the human host.(2) Mucormycosis is manifested by a variety of different syndromes in humans, particularly in the immunocompromised patients and those with diabetes mellitus.(2,3) Almost all patients with invasive mucormycosis have some underlying disease that predisposes to the infection as well as influence the clinical presentation. Devastating rhino –orbital-cerebral & pulmonary infections are the most common and dreaded syndromes caused by these fungi.(4,5,6,7,8,9,10) Treatment of mucormycosis involves a combination of surgical debridement of the involved tissues & antifungal therapy.

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Material and Methods

The current study is a retrospective observational study between may 2014 and april 2015. Twenty eight patients diagnosed with mucormycosis in our institution were included in the study. The demographic features, predisposing conditions, clinical features, radiological manifestations and patient's outcome were obtained from the medical records. The clinical syndromes were classified as rhino-orbital-cerebral, pulmonary, gastrointestinal, cutaneous, disseminated and miscellaneous.

Rhino-orbital-cerebral mucormycosis was suspected based on the presenting features such as unilateral periorbital facial pain, numbness, visual impairment/loss, eyelid edema, chemosis, proptosis, opthalmoplegia, multiple cranial nerve palsies, and focal neurological deficits. Pulmonary mucormycosis was suspected in patients who presented with dyspnea, cough, chest pain and chest radiograph showing lobar pneumonia, cavities or wedge shaped infarcts. Gastrointestinal mucormycosis was suspected in patients with nonspecific abdominal pain and distension associated with nausea, vomiting and hematemesis.

Suspicion of diagnosis was based on clinical presentation, radiological finding and unresponsiveness of infections to conventional antibiotic therapy. For suspected cases of pulmonary involvement, fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) were performed. In rhino-orbital-cerebral mucormycosis, bone destruction and invasion into soft tissues of the orbit or intracranial spread were confirmed on computed tomography (CT)/magnetic resonance imaging (MRI). In gastrointestinal mucormycosis, endoscopy with biopsy was performed.

Tissue sections were reviewed with Gomori's methenamine silver (GMS) and periodic acid Schiff (PAS) stains. Diagnosis of mucormycosis was made when biopsy revealed characteristic wide (≥6 to 30µm), thick – walled, ribbon – like, aseptate hyphal elements that branch at right angles. Bronchoalveolar lavage fluid (BAL), cerebrospinal fluid (CSF) and Sputum were sent for bacterial, fungal, viral and mycobacterial cultures.

Treatment of mucormycosis consisted of antifungal therapy in combination with surgical debridement of affected tissues. All the patients were treated with amphotericin B in a dose of 1.0 – 1.5 mg/kg and dose adjustment was made in patients with renal failure. 4 patients with rhino-orbital-cerebral mucormycosis underwent surgical debridement.

Results

The study included 18 males and 10 females with age ranging from 34 to 76 years. Predisposing factors were identified in all 28 patients, with DM identified in 24 patients, followed by usage of glucocorticoids in 6 patients of which 4 patients also had DM and 2 patients had only the history of steroid usage. HIV and acute myeloid leukemia was noted in 1 patient each. Out of 24 patients with DM, 9 patients had diabetic ketoacidosis.

The clinical syndromes included rhino-orbital-cerebral mucormycosis in 20 patients, pulmonary mucormycosis in 6 patients, gastrointestinal mucormycosis and disseminated mucormycosis were observed 1 patient each.

Out of 24 patients with diabetes, 20 patients (83.3%) had rhino-orbital-cerebral mucormycosis out of which 9 patients had Diabetic ketoacidosis. Out of 4 patients with DM and steroid usage 3 patients had pulmonary mucormycosis and 1 patient had gastrointestinal mucormycosis. Pulmonary mucormycosis was also observed in 2 patients with steroid usage and 1 patient with acute myeloid leukemia. Disseminated mucormycosis was observed in a patient with HIV. Out of the 20 patients who had rhino-orbital-cerebral mucormycosis, 4 patients had chronic kidney disease at the time of presentation.

Of 20 Patients with rhino-orbital-cerebral mucormycosis, 15 patients presented with fever, headache, acute sinusitis and periorbital swelling. 3 patients presented with nasal necrosis in addition and 2 patients presented in addition with decreased vision. Pulmonary mucormycosis patients presented with dyspnea and cough. Gastrointestinal mucormycosis patients presented with abdominal pain, voimiting and hemetemesis.

Tissue submitted for histopathological examination included biopsy and debridement and for culture CSF, sputum and BAL fluid samples were analyzed. Out of 15 tissue samples submitted for histopathological examination only 8 samples showed fungal hyphae resembling mucor with surrounding dense neutophilic inflammatory reaction. Cultures were positive only in 4 samples. All the 4 samples yielded Rhizopus oryzae and these patients had rhino-orbital-cerebral mucormycosis.

In pulmonary mucormycosis out of 6 patients, 2 patients had focal consolidation, 2 patients had pleural effusion, 1 patient had consolidation with cavitary lesions and 1 patient had multiple nodules.

All our patients with rhino-orbital-cerebral form of mucormycosis had CT and MRI available. Imaging showed anatomical involvement of maxillary sinus, orbit, ethmoid cells and nasal cavity in 11 patients. 9 patients in addition had cavernous sinus and sphenoid sinus. 1 patient had carotid artery involvement and 1 patient had evidence of infarction in the centrum semiovale.

Out of 20 patients with rhino-orbital-cerebral mucormycosis, 4 patients underwent surgical debridement. All the patients were treated with amphotericin B in a dose of 1.0 – 1.5 mg/kg. Total number of patients who died in this current study was 16, out of which 11 patients had rhino-orbital-cerebral mucormycosis, 4 patients had pulmonary mucormycosis and 1 patient had dissociated mucormycosis. Out of 11 patients with rhino-orbital-cerebral mucormycosis who died, 2 patients had undergone surgical debridement and 4 patients had CKD.

Table1. Patient characteristics

Age	Patient (yrs)	Gender	Primary disorder	Infection site	Outcome
1	34	Male	Diabetes mellitus	Rhino-orbital-cerebral	Survived
2	66	Male	Diabetes mellitus DKA/CKD	Rhino-orbital-cerebral	Died
3	42	male	Steroid usage	Pulmonary	Died
4	76	Male	Diabetes mellitus	Rhino-orbital-cerebral	Died
5	66	Female	Diabetes mellitus DKA	Rhino-orbital-cerebral	Died
6	65	Male	Diabetes mellitus CKD	Rhino-orbital-cerebral	Died

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7	44	Male	Diabetes mellitus	Rhino-orbital-cerebral	Survived
8	35	Male	Diabetes mellitus Steroid usage	Pulmonary	Died
9	67	Female	Diabetes mellitus DKA	Rhino-orbital-cerebral	Died
10	53	Male	Diabetes mellitus DKA	Rhino-orbital-cerebral	Survived
11	56	Female	Steroid usage	Pulmonary	Survived
12	71	Male	Diabetes mellitus	Rhino-orbital-cerebral	Survived
13	36	Male	Diabetes mellitus DKA	Rhino-orbital-cerebral	Died
14	42	Female	Diabetes mellitus Steroid usage	Pulmonary	Survived
15	57	Female	Diabetes mellitus	Rhino-orbital-cerebral	Survived
16	48	Female	AML	Pulmonary	Died
17	61	Male	Diabetes mellitus DKA	Rhino-orbital-cerebral	Survived
18	39	Male	Diabetes mellitus Steroid usage	Pulmonary	Died
19	70	Male	Diabetes mellitus	Rhino-orbital-cerebral	Survived
20	61	Female	Diabetes mellitus	Rhino-orbital-cerebral	Survived
21	60	Male	Diabetes mellitus DKA	Rhino-orbital-cerebral	Died
22	35	Male	Diabetes mellitus Steroid usage	Gastrointestinal	Survived
23	69	Male	Diabetes mellitus CKD	Rhino-orbital-cerebral	Died
24	51	Male	Diabetes mellitus CKD	Rhino-orbital-cerebral	Died
25	56	Male	HIV	Disseminated	Died
26	44	Female	Diabetes mellitus DKA	Rhino-orbital-cerebral	Survived
27	68	Male	Diabetes mellitus	Rhino-orbital-cerebral	Died
28	63	Female	Diabetes mellitus DKA	Rhino-orbital-cerebral	Died

Discussion

Mucormycosis is an emerging infection associated with high mortality (11) and is largely confined to severly immunocompromised patients. The most common underlying diseases are Diabetes mellitus, particularly with ketoacidosis,(7) treatment with glucocorticoids, hematologic malignancies, hematopoietic stem cell transplantation, solid organ transplantation, treatment with deferoxamine, iron overload, AIDS, trauma/burns, malnutrition. DM was identified as the most common risk factor followed by hematologic malignancies and solid organ or hematopoietic cell transplantation.(7) In this study DM was observed as the commonest risk factor in 24 patients followed by glucocorticoid usage in 6 patients out of which 4 had associated DM, Acute myeloid leukemia and HIV were noted in 1 each patient.

There are six different manifestations of mucormycosis based on clinical presentation and involvement of a particular body site: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated and miscellaneous.(12,13). Studies have shown Rhinocerebral mucormycosis and pulmonary infections are the most common syndromes observed (4,5,6,7,8,9,10), while cutaneous, renal, gastrointestinal and disseminated disease are less commonly seen. Our study showed similar findings, rhinocerebral was most common presentation accounting for 20 patients (71.4%), followed by pulmonary mucormycosis observed in 6 patients (21.4%). Gastrointestinal and disseminated mucormycosis was observed in one patient each (3.6% each).

The underlying medical condition and associated risk factors determine the type of mucormycosis that develops in a patient. Hyperglycemia, usually with an associated metabolic acidosis, is the most common underlying condition for rhino-orbital-cerebral mucormycosis.(7) Pulmonary mucormycosis is seen in patients with hematologic malignancies,(14) treatment with glucocorticoids and solid organ transplant. Treatment with glucocorticoids, DM, solid organ transplantation and malnutrition are the common underlying conditions for gastrointestinal mucormycosis. (22,23,24,25,26) Disseminated mucormycosis is rare and occurs most commonly in severly immunocompromised patients, burn patients and individuals who have received deferoxamine. (3,7)

DM was the most common underlying condition observed in patients with rhinocerebral mucormycosis. Out of 20 diabetics with rhino-orbital-cerebral mucormycosis , 9 patients had diabetic ketoacidosis. It was observed that out of 6 patients with pulmonary mucormycosis, 5 patients had use of glucocorticoids as a risk factor and out of these 5 patients, 3 had DM as an associated risk factor along with steroid usage and 1 patient with pulmonary mucormycosis had acute myeloid leukemia. Pulmonary mucormycosis is less common than rhinocerebral infection in diabetics.(15,16,17,18,19,20,21) and it was observed that in this study, patients with diabetes who developed pulmonary mucormycosis also had the additional risk factor of steroid usage. 1 Patient with gastrointestinal mucormycosis had DM and steroid usage as the underlying predisposing factor. Disseminated mucormycosis had occurred in a patient who was HIV positive.

Rhino-orbital-cerebral mucormycosis which is presumed to start with inhalation of spores into the paranasal sinuses of a susceptible host and should be suspected in patients presenting as fever, periorbital or facial swelling, acute sinusitis, headache and nasal ulceration or necrosis. (27) Rhinocerebral mucormycosis is rapidly progressive with marked increase in mortality and if not diagnosed early and treated promptly, results in death.(7,28) In this study out of 20 patients with rhinocerebral mucormycosis 11 patients had died.

Pulmonary mucormycosis is a rapidly progressive infection that occurs after inhalation of spores into the bronchioles and alveoli.(6) The outcome in patients with pulmonary mucormycosis is worse than for patients with rhinocerebral involvement, with mortality rates as high as 87%. (7,16,28,29,30)This may be in part due to underlying conditions and to the inability to widely excise the involved tissues. In this study out of 6 patients with pulmonary mu-

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cormycosis 4 died, 2 patients recovered.

Out of 15 tissue samples submitted for histopathological examination only 8 samples were positive and cultures were positive only in 4 samples. Unfortunately cultures are positive in fewer than half of the cases of mucormycosis. The likely explanation for the low sensitivity of culture is that Mucorales form long filamentous structures that are killed by tissue homogenization. In one case series, only 25 percent of sputum or BAL specimens were positive premortem.(14) However, the absence of hyphae should not dissuade clinicians from the diagnosis of mucormycosis when the clinical picture is highly sensitive.

Treatment of mucormycosis involves a combination of surgical debridement of involved tissues and antifungal therapy. (31) Intravenous amphotericin B (lipid formulation) is the drug of choice for initial therapy (32) in view of lesser systemic toxicity. It can be followed by oral Posaconazole or at times adjuvant therapy with drugs like caspofungin are tried. (35,36) Rhizopus oryzae, the most common cause of mucormycosis, expresses the target enzyme for echinocandins, suggesting that these agents may have clinical utility. (33,34) At this time larger studies are needed to establish whether combination therapy is beneficial. In this study all the patients received amphotericin B considering the affordability issues of the patients.

Despite early diagnosis and aggressive combined surgical and medical therapy, the prognosis for recovery from mucormycosis is poor. An exception is cutaneous involvement, which rarely disseminates. Independent risk factors for mortality include disseminated infection, renal failure, while the use of surgery and administration of any antifungal agents were associated with a better outcome. (7) In this study patients with disseminated mucormycosis , all the patients with mucormycosis with renal failure and 2 patients who had undergone surgical debridement did not survive. Overall mortality rate in this study was 57% of which the mortality rates of patients with rhino-orbital-cerebral mucormycosis was the highest – 68.75% (11 out of 16).

Conclusion

Mucormycosis is an emerging infection associated with high mortality. The identification of risk factors, clinical features and radiological findings increase the possibility of an early diagnosis, which may prevent progressive tissue invasion, reduce extent of surgical resection and improve survival. The diagnosis of mucormycosis relies upon the identification of organisms in tissue by histopathology with culture confirmation. However, culture often yields no growth and histopathological identification of an organism with structural typical of mucorales may provide the only evidence of infection. A clinician must think of this entity in the appropriate clinical setting and pursue invasive testing in order to establish a diagnosis as early as possible.

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