Original Article

Mucormycosis: An Increasing Concern; Experience from a Tertiary Care Centre

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Abstract

Background: Mucormycosis is an angioinvasive life threatening infection caused by the fungus belonging to the order Mucorales and family Mucoraceae. The prevalence of mucormycosis is on a rising trend. The known risk factors for mucormycosis includes uncontrolled diabetes mellitus, malignancies such as lymphomas, leukemia, organ transplant, long term corticosteroid or immunosuppressive therapy, renal failure, burns, protein-energy-malnutrition etc.

Material and methods: This is a prospective study conducted over a period of six months. Samples showing broad aseptate ribbon like fungal hyphae were included in the study. Clinical, demographic details, risk factors, results of radiological and pathological investigations were collected and analysed.

Results: In the study period, 76 samples were received for KOH examination in the laboratory, out of which 15 samples were found to be positive for broad aseptate ribbon like fungal hyphae. The mean age of the study group was 43.4 years. Out of 15 patients, 66.6% were males and 33.3% were females. All the cases were of Rhinocerebral

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mucormycosis and uncontrolled diabetes mellitus was the risk factor present in all the cases. Five patients were diagnosed with diabetes at the time of admission. Three cases presented with diabetic ketoacidosis, two cases had chronic kidney disease and one was a known case of pulmonary tuberculosis.

Conclusion: In the past few years, there has been a steady increase in the cases of mucormycosis, both worldwide and in India. As the disease progresses rapidly, prompt diagnosis and early management plays a crucial role in survival of the patient.

Key words: mucormycosis, Uncontrolled diabetes mellitus, Rhinocerebral.

Introduction

Mucormycosis, an angio-invasive potentially life-threatening infection is known to be caused by a fungus belonging to the order Mucorales and family Mucoraceae. The deadly disease has been known to the mankind since 1876, when in Germany the first case was described by a scientist named Furbinger. Fungal hyphae and sporangia were detected in the haemorrhagic infarct of the right lung of the patient who died of cancer. Following this, the first case was published in the year 1885, when Arnold Paltauf's drawings demonstrated rhizoid like structures and sporangiophores. The disease has evolved over the years and currently, it is the second most common mould pathogen after *Aspergillus*, known to cause invasive fungal disease in immunocompromised patients.[1-4]

Currently, the incidence of mucormycosis is considered to be highest in Indian subcontinent with a rate of 140 cases per 1,000,000 population per year in India and Pakistan. The incidence is the lowest in United states estimated to be 1.7 cases per 1,000,000 population per year.[1]

The known risk factors for mucormycosis includes uncontrolled diabetes mellitus, malignancies such as lymphomas, leukemia, organ transplant, long term corticosteroid or immunosuppressive therapy, renal failure, burns, protein-energy-malnutrition etc.[1,3,5-7]

Based on the anatomic site involved and the clinical manifestations, mucormycosis is classified into at least six clinical categories: (i) rhinocerebral, (ii) pulmonary, (iii) cutaneous, (iv) gastrointestinal, (v) disseminated, and (iv) miscellaneous. Miscellaneous includes forms like osteomyelitis, peritonitis, endocarditis, renal etc.[2,4] Amongst these forms, Rhinocerebral mucormycosis is the most common clinical form. It alone accounts for almost one third to half of all the cases of mucormycosis.[4,8]

This study was conducted to find out the incidence of mucormycosis, to study the various types and risk factors present in a tertiary care centre in north Rajasthan. To the best of our knowledge such data is not present form this part of India.

Aims and objectives:

The study was conducted to study the demography, epidemiology, risk factors, correlation of microbiological, histopathological and radiological picture of patients with mucormycosis.

Inclusion criteria

All consecutive individuals diagnosed with mucormycosis were included in this study. Patients with mucormycosis were defined as those individuals with clinical symptoms and the demonstration of fungi in the tissue either by direct microscopy (broad ribbon like aseptate hyphae), or culture methods.

Exclusion criteria

Individuals with any other fungal infection or no fungal infection were excluded from the study.

Material and Methods

This is a prospective study done over a period of six months from October 2023 to March 2024 at Dr S S Tantia Medical college, hospital and research centre at Sriganganagar, Rajasthan. We receive various samples from different clinical departments such as otorhinolarungology, medicine, Dental for KOH (potassium hydroxide) examination. We collected information of patients whose samples showed broad ribbon like aseptate fungal hyphae on KOH examination. All the clinical details of these patients were collected such as demographic detail, chief complaints, site involved, comorbidities present, risk factors (such as diabetes, malignancy etc) radiological investigation, microbiological, histopathological findings etc. Tissue samples, such as nasal/sinus

tissue biopsies were subjected to conventional microscopy, culture and histopathological examination. Microscopy was performed using the KOH mount method. Samples were also inoculated onto two sets of Sabouraud dextrose agar with and without chloramphenicol. The positive cultures were identified by their macroscopic and microscopic characteristics. The tissue samples submitted for histopathological examination were examined using haematoxylin & eosin and periodic acid Schiff stain. Informed consent was obtained from all the patients included in the study.

Results

In the study period, 76 samples were received for KOH examination in the laboratory, out of which 15 samples were found to be positive for broad aseptate fungal hyphae. The mean age of the study group was 43.4 years .Out of 15 patients, 66.6% were males and 33.3% were females.

Clinical presentation

Most common clinical presentation was periorbital swelling (46.6%) followed by pain in one side of jaw (33.3%) , difficulty in breathing (13.3%) and foul smelling nasal discharge (6.6%). (Fig. 1) All of the fifteen patients were diagnosed to have rhino-cerebro-orbital-mucormycosis.

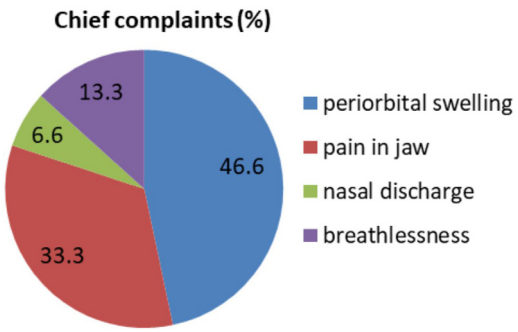

Fig. 1 Chief complaints of patients diagnosed with mucormycosis

Microbiological investigation

A nasal tissue was collected from all these patients and sent to microbiology department for KOH examination. Immediately on receiving the sample, KOH examination was performed which revealed presence of broad ribbon shaped aseptate hyaline fungal hyphae. (Fig. 2) Eleven of the samples demonstrated growth on culture media which was confirmed to be *Rhizopus* spp.

Fig. 2 KOH mount showing broad aseptate ribbon like fungal hyphae

Pathology investigation

Biopsy was performed for all the patients. A nasal tissue collected in formalin was sent to the pathology department Histopathological examination revealed broad aseptate ribbon like fungal hyphae in 14 patients. PAS (periodic acid schiff) stain was also performed in all these samples which were also positive for mucormycosis. (Fig.3)

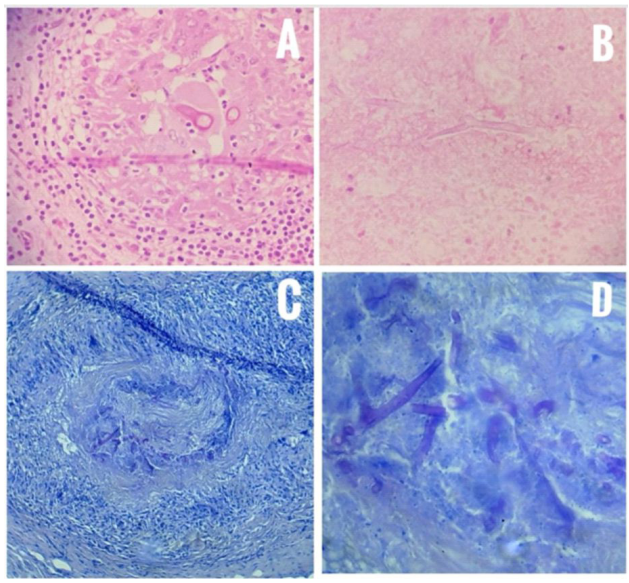

Fig. 3A, 3B- H and E stained section shows areas of necrosis and broad aseptate hyphae. 3C, 3D- PAS stained section shows positive staining for fungal hyphae. PAS stained image show vascular wall invaded with fungal hyphae suggestive of angioinvasion.

Radiology investigation

Various radiological examination performed were NCCT PNS (non contrast computed tomography paranasal sinuses), CECT (contrast enhanced computed tomography) maxilla and MRI(magnetic resonance imaging) orbit depending on the clinical symptoms. Imaging studies were done in 12 patients which showed findings suggestive of fungal sinusitis. (Fig. 4)

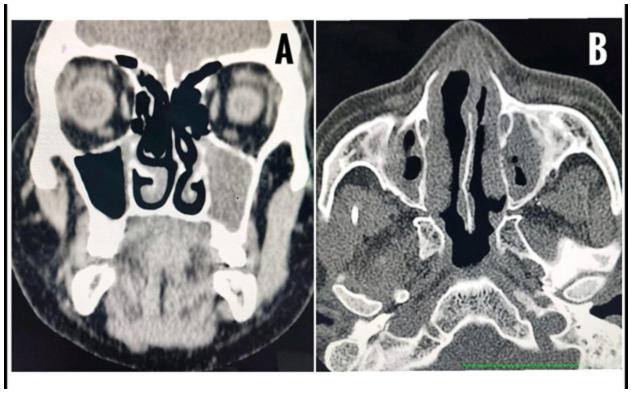

Fig. 4 A- Coronal CT showing bilateral maxillary sinusitis (left >right) with obliteration of left osteomeatal complex containing hyperdense foci likely representing fungal sinusitis. 4B-Axial CT PNS showing mucosal thickening in bilateral maxillary sinusitis with hyperdense contents and rarefaction/remodeling of walls of maxillary sinuses likely representing fungal sinusitis.

Risk factors

All the patients were diabetic, five of them were diagnosed for the first time at the time of admission. Average HbA1c (glycosylated hemoglobin) was found out to be 9.9. Three patients presented with ketoacidosis at the time of admission. Two patients were known case of chronic kidney disease. One patient was a known case of pulmonary tuberculosis.(Fig.5)

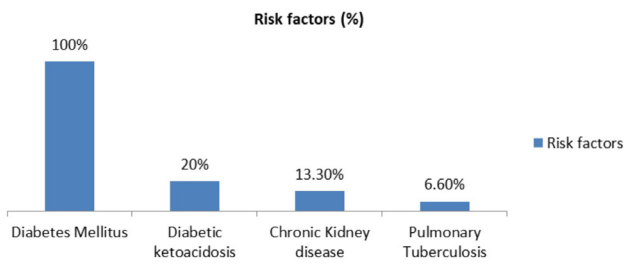

Fig. 5 Risk factors present in patients diagnosed with mucormycosis

Management

Two of the patients underwent surgical debridement at our institute. Amphotericin B is not available at our institute, so all the patients were referred to a higher centre for further medical treatment of mucormycosis. Therefore, follow up of patients for final outcome could not be performed.

Discussion

In the past few years, there has been a steady increase in the cases of mucormycosis, both worldwide and in India.[5,9-11]

The most common type of clinical presentation in our study was rhino-cerebral mucormycosis, which is the most common type worldwide.[1,4,8]

The patients usually present with facial swelling, pain around the eye, pain in and around jaw, headache and in some cases black colored lesions can be seen in and around nasal and oral cavity. The disease begins with involvement of sinuses followed by orbits and if not treated promptly may involve brain. Blindness is the most common and morbid complication of the disease.[12]

Majority of our patients were males (66.6) with a mean age of 43.4 years. Similar data have been published by Yadav *et al*[1] in 2021 from Jodhpur, Rajasthan who showed mean age of 47.5 years with 60% patients being males. Studies published by Tamer Roushdy[13] in 2021 and Hoenigl *et al*[14] in 2022 also demonstrated similar results (75% and 78% males respectively).

Diabetes mellitus is the commonest risk factor for mucormycosis in Asian subcontinent and almost 70% of rhinocerebral cases have been detected in diabetic patients.[4,5,9]

Uncontrolled Diabetes is associated with a higher risk of acquiring mucormycosis infection because of the following changes that occur in a diabetic patient (i) there is availability of glucose to the pathogen, (ii) the T cell response as well as the humoral response is deranged,(iii) in the presence of lower pH there is reduced inhibitory activity of the serum towards Rhizopus pathogen, (iv) there is increased expression of certain host cell receptor that helps in invasion of the epithelial cells by the pathogen and (v) there is excessive production of reactive oxygen species.[8,12,15]

All the cases in our study were either known diabetic or were diagnosed with diabetes at the time of admission. Two of our patients were diagnosed with diabetic ketoacidosis. It is known that the enzyme ketoreductase produced by *Rhizopus* allows the organism to utilize patient's ketone bodies and hence increases the risk of acquiring mucormycosis infection. Also, the ketone bodies transiently damages the ability of transferring to bind to iron and thus allows the microorganism to evade the host defense mechanism and thus the growth of pathogen flourishes.[7]

As the disease progresses rapidly, prompt diagnosis and early management plays a crucial role in survival of the patient. Depending on the clinical manifestations, various modalities available are antifungal therapy, surgical debridement, use of hyperbaric oxygen.[12]

With the growing number of diabetic patients in the country, India has been labeled as the world capital of diabetes. The main reason for this is the change in the lifestyle pattern of people which is leading to increase in obesity , hypertension, physical inactivity.[16,17]

Globally, it has also been observed that the incidence of patients with undiagnosed diabetes is steadily increasing.[17] As per World Health Organisation data for 2015, 69.2 million (8.7%) of world population remain undetected for diabetes mellitus type 2.[16] The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019.[18] It is also estimated that nearly 57% of adults with diabetes are undiagnosed in India[17].

As Diabetes mellitus alters the normal immunological response, therefore a diabetic patient becomes susceptible not only to the classical complications of diabetes but also to the otherwise rare and fatal infections like mucormycosis.[6,7]

Our study highlights the following important facts. (i) There is a constant increase in incidence of mucormycosis in India. (ii) uncontrolled diabetes mellitus is the most common risk factor (iii) Rhino-cerebro-orbital mucormycosis is the most common presentation in our setting. (iv) awareness of fungal diseases is increasing among the clinicians at our centre.

Limitations

Our study was conducted for a small duration of time. A larger study should be planned at our setting in collaboration with all the clinical departments to study in detail the disease of mucormycosis.

Conclusion

With the increasing prevalence of diabetes, undiagnosed diabetes and rare infections like mucormycosis in diabetics, it has become a matter of public health concern to improve measures to diagnose and treat diabetes effectively. The prevalence of mucormycosis is increasing in diabetic patients. For effective management of mucormycosis, it has become imperative for the clinicians to work in collaboration with the laboratory. Prompt diagnosis and aggressive surgical as well as medical management are the corner stone for effective control of the disease.

Ethical statement: The article does not involve any intervention on human subjects hence ethical clearance was not taken.

Conflict of interest: NIL

Financial support: NIL

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