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MUCORMYCOSIS: A REVIEW

General Medicine

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ABSTRACT

Mucormycosis is a fungal disease that primarily affects orbits, paranasal sinuses, lungs and causes tissues to necrose. Important risk factors include uncontrolled Diabetes mellitus, Corticosteroid therapy, Iron overload and recent COVID-19 infection. The various routes through which sporangiospores enter the body include- Inhalation, ingestion, inoculation via wounds, contaminated medical equipment etc. It is infarction of tissues caused by the angio-invasive agents of mucormycosis that distinguishes this illness from others. It is important to have a high index of suspicion and to do intrusive tests as soon as feasible. Intravenous antifungals are used, and if surgical debridement is required, that is done as well. Overall, the prognosis is not good.

KEYWORDS

INTRODUCTION

As its name suggests, mucormycosis is a fungal illness. Mucormycosis was initially documented in 1855 by Fredrich Kuchenmeister, who noted pulmonary involvement in his patient. Plautaf coined the term Mycosis mucorina in the first well documented systemic case.[1] At that time, most of the Mucormycetes were initially classified as members of the genus Mucor. These organisms were later re-assigned different genera and families under the same sub-phylum Mucoromycotina. In 1884, Lichtheim established pathogenicity of sub-phylum Mucoromycotina in rabbits and described 2 species: Mucor Corymbifera (which later became Absidia and now is Lichtheimia) and Mucor Rhizopidiformis (now Rhizopus).

Etiology:-

The taxonomy of fungi causing Mucormycosis include the following:-

FAMILY	GENUS (Species listed for some)
Mucoraceae	Rhizopus oryzae Rhizopus delemar Rhizopus microsporus Rhizomucor Mucor Actinomucor
Lichtheimiaceae	Lichtheimia (previously Absidia)
Cunninghamallaceae	Cunninghamella
Thamnidiaceae	Cokeromyces
Mortierellaceae	Mortierella
Saksenaceae	Saksenaceae Apophysomyces
Syncephalastraceae	Syncephalastrum

Epidimiology:-

Since the risk of mucormycosis varies greatly between populations, it is challenging to provide an accurate estimate of the disease's prevalence. Auditing 929 occasions of mucormycosis distributed somewhere in the range of 1940 and 2003, analysts found that diabetes mellitus was the most predominant gamble factor, present in 36% of revealed cases. Hematologic malignancies and strong organ or hematopoietic cell transplantation followed, each accounting for 17% and 12% of reported cases, respectively.[2] We'll get into the specifics of the Mucormycosis outbreak that broke out in India during the COVID-19 pandemic later on in this piece.

Risk Factors:-

The various risk factors for Mucormycosis include:-[3]

- Diabetes Mellitus (especially with Ketoacidosis)
- Glucocorticoid therapy
- Hematological malignancies
- Hematopoetic stem cell transplantation
- Iron Overload
- Deferoxamine therapy
- HIV AIDS
- Organ transplantation
- Recent COVID-19 Infection
- Injection drug use
- Malnutrition
- Trauma/Burns

Pathogenesis:-

The various routes through which sporangiospores enter the body include- Inhalation, ingestion, inoculation via wounds, contaminated medical equipment etc. Mononuclear and polymorphonuclear phagocytes have no trouble dealing with the spores in immunocompetent people. As a result, mucormycosis is more common among people whose phagocytes are dysfunctional.[4]

In order to survive in high-glucose, acidic environments, Rhizopus species develop an enzyme called ketone reductase. Rhizopus growth is inhibited by serum from healthy people but stimulated by serum from those with diabetic ketoacidosis. Mucormycosis may survive by stealing iron from its host and using it for its own enzymatic processes, hence iron metabolism plays a crucial part in the development of the disease. Mucormycosis was reported to develop fast in iron-rich medium and very slowly in iron-poor media. The use of deferoxamine, which promotes the development and pathogenicity of mucormycosis because it chelates both iron and aluminum, is not recommended. Rhizopus species benefit from the siderophore feroxamine, a deferoxamine-iron chelate that promotes fungal growth and tissue penetration by boosting iron intake by the fungus.[5]Deferasirox and deferiprone, two other iron chelating agents, do not act as siderophores and do not increase the risk of mucormycosis, so this is something to keep in mind. The hallmark of mucormycosis is tissue infarction since the causative agents are angio-invasive.

Clinical Presentation:-

1. The most prevalent kind of mucormycosis is rhino-orbital-cerebral mucormycosis. Spores enter the paranasal sinuses and cause the condition to develop. Diabetic ketoacidosis is often accompanied by this symptom picture. Fever, nasal ulceration or necrosis, periorbital or facial edema, impaired vision, ophthalmoplegia, sinusitis, headache, etc. are common presenting symptoms. Periorbital edema, proptosis, and vision loss are all symptoms of orbital involvement.Infarction of the sensory branches of the Trigeminal nerve (Cranial Nerve V) is a frequent cause of facial numbness [6].
2. Pulmonary Mucormycosis- This rapidly progressive form of mucormycosis occurs when spores are breathed into alveoli and bronchioles. This is a dangerous form of the disease as it causes

pneumonia, infarction and necrosis of lung tissue which can further disseminate into the mediastinum and heart, and also disseminate into the blood stream to affect other organs as well. [7] Patients usually present with fever and massive hemoptysis.

3. Gastrointestinal Mycormycosis- This is a rare form of mucormycosis that can occur after ingestion of spores. Patients usually present with severe abdominal pain and hematemesis. The GI lesions can be ulcerations that result in perforation and peritonitis. Complications of this form include bowel infarction and hemorrhagic shock.[8] Prognosis is especially poor for this form.
4. Cutaneous Mucormycosis- Inoculation of the spores into the dermis causes this kind of mucormycosis. Spores may enter the body via many different routes, including the place where an intravenous catheter was inserted, from a spider bite, from an insulin injection, and through infected traumatic wounds, contaminated dressings, burns, splints, etc. [9]
5. Renal Mucormycosis- Isolated renal form of mucromycosis has been said to occur due to fungemia (dissemination of spores in the bloodstream). Fever and soreness in the flank are common symptoms. Participation might be one-sided or two-way.[10]
6. CNS Involvement- This form of mucormycosis can manifest via 2 ways- an adjacent paranasal sinus infection or due to fungemia (similar to renal mucormycosis). Patients can present with focal neurological deficits, involvement of basal ganglia and also in some cases, frontal lobe. [11]

Diagnosis:-

The initial approach to diagnosis of mucormycosis primarily requires the following-

- Thorough history taking- history of uncontrolled Diabetes Mellitus requiring admission, history of immunosuppressive disease, any past treatment with glucocorticoids and/or immunosuppressants, history of organ transplantation, history of hematological malignancies, any history of IV drug use, history of Deferoxamine therapy and any recent COVID-19 infection
- Strong grounds for suspicion based on the clinical evaluation

The diagnosis of mucormycosis requires histology and culture confirmation to identify the organisms in the tissue. Therefore, invasive testing must be done if needed, as soon as possible. However, it is also important to note that agents causing mucormycosis can colonise the airways or can be culture contaminants, hence culture results must be correlated with clinical findings before confirming infection.

Polymerase Chain Reaction(PCR) based tests on the specimens can be used for diagnosis of Mucormycosis. PCR would be ideal for the patient as it would negate the need for invasive testing, but however, it's commercial availability is limited. A Positive result on PCR can be used to start anti-fungal therapy but a Negative result does not rule out mucormycosis.[12]

Evaluation of the paranasal sinuses endoscopically is recommended in instances with Rhino-orbito-cerebral infection in order to detect tissue necrosis and collect samples. Use calcofluor white and methenamine silver stains to search for the mark wide, non-septate hyphae with right-point spreading in the examples. Imaging must be done to look for bony erosions in the paranasal sinuses (CT scan is more sensitive in detecting bony erosions)[13]

In cases of Pulmonary mucormycosis, it is difficult to make a definitive diagnosis as the Similar to pneumonia, illness caused by other angioinvasive fungus has no distinguishing features. In order to confirm a diagnosis, tissue microscopy must be performed. Imaging tests performed on the chest, such as X-rays and CT scans, may reveal the following:-

- Multiple nodules; pleural effusions; or focal consolidation
- Angioinvasive sinusitis (including mucormycosis) may be indicated by the presence of a halo sign (ground-glass attenuation around a ring of consolidation).
- Ground-glass attenuation encircled by a ring of consolidation (the inverse of the classic halo sign)
- Cavitary lesions can be present (mostly associated with Covid-19 associated mucormycosis)[14]

Bronchoalveolar Lavage(BAL) can also be used to demonstrate specimen that show recognizable broad, septate hyphae. Additionally, hyphae can be observed in lung biopsy samples.

Treatment:-

Anti-fungal therapy and debridement of necrosed tisuues are essential components of mucormycosis treatment, but there are other issues, such as hyperglycemia, metabolic acidosis, deferoxamine use, etc., that must be addressed as well.

Treatment of mucormycosis often begins with intravenous amphotericin B. Three different formulations of amphotericin B-

1. Amphotericin B deoxycholate

Mucormycosis therapy - FDA-approved

Extremely hazardous CNS Penetration Weakness

2. Amphotericin B liposomal

Amphotericin B deoxycholate has lower nephrotoxicity.

It penetrates the central nervous system more effectively than Amphotericin B deoxycholate and Amphotericin B Liposomal Complex.

- Expensive

3.Compound Liposomal Amphotericin B for Fungi

Amphotericin B deoxycholate has lower nephrotoxicity.

- Expensive

Step-down Therapy:-

Posaconazole and Isavuconazole are antifungal medications that can be taken orally as step-down therapy following Amphotericin B treatment. Isavuconazole treatment necessitates loading doses within the first 48 hours. Stacking portions of 200 mg (i.e., two containers) of oral isavuconazole ought to be allowed at regular intervals for six dosages, with support dosing of 200 mg orally once day starting 12 to 24 hours following the last stacking portion. When a positive clinical reaction has been accomplished, as a rule following half a month of treatment with a lipid detailing of amphotericin B, the patient might be changed to oral step-down treatment with deferred discharge posaconazole or isavuconazole tablets. [15]

Salvage Therapy:-

Salvage therapy with isavuconazole or posaconazole may be beneficial for patients who do not respond to or are unable to tolerate Amphotericin B. A loading dose of 300 mg every 12 hours is given on day one; A maintenance dose of 300 mg every 24 hours is given on days two through seven. Isavuconazole is given in loading doses of 200 mg every 8 hours orally or intravenously for the first six doses. Maintenance doses of 200 mg are given every 24 hours or intravenously.

Surgical Debridement:-

Aggressive surgical debridement must be considered as soon as possible to remove necrotic tissues. Rhino-orbito-cerebral and pulmonary mucormycosis patients, in particular, have had a better prognosis after surgical debridement. Surgical debridement can in some cases be very disfiguring, especially in cases of rhino-orbito-cerebral form due to removal of palate, nasal cartilage, orbit etc but however in recent times, endoscopically guided limited removal of tissues has also been achieved.[16]

COVID-19 Associated Mucormycosis:-

During the 2nd wave of the COVID-19 pandemic, there was an enormous rise of cases on mucormycosis with around 14,872 cases as of May 28th,2021.[17] This was attributed to many factors including use of steroids in the management of COVID-19, use of unsterile oxygen, use of unsterile cannulas and oxygen masks etc. Patients admitted with COVID-19 and with uncontrolled sugars were also found to be at higher risk of development of mucormycosis.[18] There were several patients who had had to undergo eye removal surgeries in order to remove necrosed tissues and to save their lives.

In COVID infection, the immune system's ability to fight infections is compromised due to an increase in pro-infammatory cytokines like interleukin-1 (IL-1), IL-2, IL-6, and Tumor Necrosis Factor-, an increase in anti-infammatory cytokines like IL-4 and IL-10, decreased CD4 interferon- expression, and a decrease in CD4 and CD8 cells.[19] Doctors can limit the spread of and reduce the severity of COVID-19 by taking precautions, encouraging patients to practice good hygiene, and identifying and treating the virus quickly.

Prognosis and/or Outcomes

Even with prompt antifungal treatment and surgical debridement after an early diagnosis, the prognosis is usually not good. In Rhino-orbito-cerebral infection, the factors related to poor outcome include delayed

diagnosis, cavernous sinus and/or carotid involvement, presence of hemiplegia/hemiparesis, bilateral sinus involvement, leukemia and renal disease etc.[20] In cases of of Pulmonary mucormycosis, prognosis is worse due to the inability to widely debride and/or excise tissues with mortality rates as high as 87%. Among COVID-19-associated cases, severe COVID-19 with need for mechanical ventilation appears to predict increased mortality.

CONCLUSION

Mucormycosis is an uncommon but potentially fatal fungal illness that may manifest in a variety of organs, including the lungs, orbit, paranasal sinuses, etc. Patients with uncontrolled diabetes mellitus precipitating metabolic acidosis are among those at high risk of developing the disease. Mucormycosis is has also been documented as an important complication of COVID-19. The diagnosis of the disease is still a challenge for clinicians and it is hoped that better techniques arise to aid for early diagnosis of the disease.

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Conflict of Interest:-
The authors say they have no competing interests.

REFERENCES:-

1. Chander J (2018). "26. Mucormycosis". *Textbook of Medical Mycology* (4th ed.). New Delhi: Jaypee Brothers Medical Publishers Ltd. pp. 534–596. ISBN 978-93-86261-830.
2. Epidemiology and outcome of zygomycosis: a review of 929 reported cases" Maureen M.Roden PMID: **16080086** DOI: 10.1086/432579
3. Rhinocerebral mucormycosis: predisposing factors J S McNulty PMID: 7132514
4. A COMPREHENSIVE REVIEW ON MUCORMYCOSIS (BLACK FUNGUS) AND ITS ASSOCIATION WITH COVID-19 Shahnaz Alom Current Trends in Pharmaceutical Research, 2021 Vol 8 Issue 1 ISSN: 2582-4783 (Online)
5. Zygomycosis (mucormycosis): emerging clinical importance and new treatments Richard N Greenberg PMID: **15640705** DOI: 10.1097/00001432-200412000-00003
6. Survival factors in rhino-orbital-cerebral mucormycosis R A Yohai PMID: 7974189 DOI: 10.1016/s0039-6257(05)80041-4
7. Mucor mediastinitis B A Connor PMID: 446151 DOI: 10.1378/chest.75.4.525
8. Gastric mucormycosis M H Ismail PMID: 2219440
9. Mucormycosis: emerging prominence of cutaneous infections R D Adam PMID: 7948560 DOI: 10.1093/clinids/19.1.67
10. Isolated renal mucormycosis: case report and review E Levy PMID: 7579048 DOI: 10.1681/ASN.V5122014
11. Isolated central nervous system mucormycosis S U Siddiqi PMID: 7939928 DOI: 10.1097/00007611-199410000-00006
12. Genetic identification of the main opportunistic Mucorales by PCR-restriction fragment length polymorphism M Machouart PMID: 16517858 PMCID: PMC1393117 DOI: 10.1128/JCM.44.3.805-810.2006
13. Computed tomographic findings in patients with invasive fungal sinusitis John M DelGaudio PMID: 12578456 DOI: 10.1001/archotol.129.2.236
14. Pulmonary mucormycosis R A Murphy PMID: 8838948 DOI: 10.1016/s0037-198x(96)80043-5
15. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole George R Thompson 3rd PMID: 20524153 DOI: 10.1007/s11046-010-9324-3
16. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients Hsin-Yun Sun PMID: 20626095 DOI: 10.1097/tp.0b013e3181dde8fc
17. Rising incidence of mucormycosis in patients with COVID-19: another challenge for India amidst the second wave? Akshay Raut Nguyen Tien Huy DOI:https://doi. org/10.1016/S2213-2600(21)00265-4
18. Alom S, Ali F, and Zaman K Md. A comprehensive review on mucormycosis (black fungus) and its association with covid-19, Curr Trends Pharm Res, 2021; 8 (1): 11-40
19. RHINO-ORBITO-CEREBRAL MUCORMYCOSIS WITH COVID-19 INFECTION IN NORTH INDIA, DR.PRIYANKA SINGH, DR,ANAVI MUNJAL, DR.MONIKA SAIN INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH | VOLUME-10 | ISSUE-11 | November-2021
20. Survival factors in rhino-orbital-cerebral mucormycosis R A Yohai PMID: 7974189 DOI: 10.1016/s0039-6257(05)80041-4
21. Pulmonary mucormycosis: results of medical and surgical therapy M Tedder PMID: 8166512 DOI: 10.1016/0003-4975(94)90243-7
22. Cumulative Mortality and Factors Associated With Outcomes of Mucormycosis After COVID-19 at a Multispecialty Tertiary Care Center in India Twinkle Choksi PMID: 34882192 PMCID: PMC8662533 DOI: 10.1001/jamaophthalmol.2021.5201