second largest in the world [6]. Diabetes Mellitus (DM) is the most prevalent cause of mucormycosis in India [7], while overuse of corticosteroids has also been linked to opportunistic fungal infections like Mucormycosis. If an immunocompromised patient has had a cumulative dosage of prednisolone higher than 600 mg or total methylprednisone dose of 2-7 g in the previous quarter, they are at risk for mucormycosis [8-15].

Although antifungal medicine can help with mucormycosis, surgery is ultimately required. Traditionally, mucormycosis was treated with an I.V. infusion of saline followed by amphotericin infusion. Because of the infection's high fatality rate, primordial recognition and recovery from predisposing circumstances are critical for effective treatment. Debridement procedures and medicinal delivery can also assist to ameliorate the situation [16-20].

LITERATURE REVIEW

Methodology

Databases of PubMed and Google Scholar were screened for studies on Mucormycosis in COVID-19. After going through abstracts of the studies the articles for review were selected. The selected articles focused on etiology, features, diagnosis and treatment of mucormycosis. Articles that had been recently published were given priority.

Diagnosis

A significant amount of anticipation, recognition of host issues, and early examination of clinical symptoms are all necessary for mucormycosis diagnosis. Double vision in a diabetic individual and pleuritic discomfort in a neutropenia host could be indicators of infection, necessitating the imaging modalities use and subsequent sample collection for histological, microbiological, and complex molecular testing. Mucorales infection usually shows up as rhino cerebral, pulmonary, soft tissues, and disseminated disease, but it can affect any organ [21].

Corzo Leon, et al. postulated a method for detecting rhino cerebral mucormycosis in diabetic patients. Clinical manifestations that should be regarded as "red flags" includes cranial nerve palsy, double vision, pain in sinuses, proptosis, periorbital edoema, along palate ulcers [22]. Radiologically Mucormycosis is said to be associated with numerous (>10) nodules and pleural effusion [23]. The reverse halo sign, which appears to indicate the presence of mucormycosis on a Computerized Tomography (CT) scan, is another finding that suggests the existence of mucormycosis [24]. In neutropenic leukaemic patient along with lung infection, the appearance of reverse halo sign on CT is a robust predictor of pulmonary mucormycosis. MRI brain can be done for the better demarcation of CNS involvement. PET/CT with (18 Fdg) is another new imaging technology that may aid in the diagnosis and treatment of mucormycosis [25]. Endo bronchial ultrasound-guided fine needle aspiration is also an efficacious diagnostic technique whenever it is available [26].

Direct microscopy is convenient in detection of hyphae in clinical specimens since it is quick and implies pathology. After staining with potassium hydroxide, optical brightener (calcofluor white), or with Gomorimethamine-silver specimens can be analysed [27]. With a diameter 5-25 um that are non-or pauciseptate hyphae are hyaline, ribbon like structures. With branching angles of 90°, the width is uneven. When hyphae are shattered, direct examination is difficult, hence culture is required for the confirmation of diagnosis. Tissue staining could be done with Gomorimethamine silver and PAS. Hyphae could be visualised in necrosed tissue with indications of angioinvasion or infarction; in non granulocytopenic or those who have more latent infection, neutrophil infiltrates or granuloma development can be seen. Immunohistochemistry done with commercially accessibleantizygomycete antibodies can occasionally aid in the diagnosis [28]. With varying degrees of effectiveness, ELISA [29], immunoblots [30], and immune diffusion tests [31] were also assessed. An Enzyme Linked Imuno Spot (ELISPOT) assay was used to detect Mucorales specific T lymphocytes in haematological patients who developed invasive mucormycosis [32]. Mucorales-specific T lymphocytes were not seen in any of the controls.

In order to make a diagnosis, biological specimens from clinically affected locations must be analysed. When possible, tissue samples for histopathology and culture should be collected. Unfortunately, in those with hematologic malignancies, this is usually an issue due to severe thrombocytopenia. If a biopsy isn't an option, all obtainable specimen, such as sputum, ought to be analysed and cultured immediately. In the case of sinusitis, biopsies are required. To measure therapeutic response, endoscopy of ear, nose, and throat to be performed and done on a frequent basis.

Treatment

Mucormycosis is best treated with a multimodal approach that includes correcting or eliminating core predisposing factors, as well as the use of potent antifungal drugs early on at the appropriate dose, total eradication of all infected tissues, and adjuvant treatment. Patients with uncontrolled diabetes who have been diagnosed with mucormycosis should have their metabolic abnormalities rectified as soon as possible. Corticosteroids and immune suppressants to be lowered to the smallest dose practicable as soon as possible. Early detection is essential in order to begin therapeutic measures as soon as possible in order to avoid continuous tissue invasion and its deadly consequences, mitigate the probability of Corrective surgery can be disfiguring, but it can also improve the outcome and survival rate [33].

Mucormycosis treatment guidelines were published by European Conference on Infection in Leukamia (ECIL) in

2017 [34], and the European Confederation of Medical Mycology (ECMM) updated them in 2019 [35]. Liposomal Amphotericin-B (L72 AMB) is strongly recomended for first line treatment in adults by both societies. According to the ECIL, alternative lipid formulations, Amphotericin-B Lipid Complex (ABLC), might be utilised in mucormycosis without involving the CNS. L-AMB and ABLC are invincibly suggested as first-line treatments for neonates and children.

Mucormycosis is treated with liposomal Am-B, which has been shown to be efficacious. Amphotericin-B attaches to ergostrol in the fungi cell membrane, causing holes and subsequent ion leakage, which causes the fungus to die. In hospitalised adults and children, liposomal Am-B injections at a beginning dosage of 5-7.5 mg/kg/day, diluted in 500 mL of 5% dextrose over 4-5 hours for 14-21 days, are widely utilised. Alternative therapies, such as an oral suspension of posaconazole, 400 mg twice day or 200 mg four times day, may be administered to patients who are intolerants or nonresponsive to Am-B.

Posaconazole along with isavuconazole are examples of triazoles. Posaconazole is recommended as a salvaged or maintenance treatment by ECIL-6, while it is recommended as a first-line treatment by ESCMID/ ECMM at a dose of 200 mg q6 h of the oral solution by ESCMID/ECMM. The introduction of intravenous and tablet forms of posaconazole have resulted in increased availability and drug exposure [36]. This could boost the triazole's position in the antifungal arsenal, particularly against the difficulty to treat mucormycosis.

CotH-3, a Mucorales peptide that binds the endothelial cell receptor GRP78, has recently been related to mucormycosis endothelial invasion. Antibodies in opposition CotH-3 were created for the inhibition of endothelial invasion. Anti Coth-3 antibodies prevented mucormycosis in neutropenia and diabetic mice and worked in conjunction with antifungal therapies [37].

VT-1161 new inhibitor of the fungus CYP-51 enzymes along Mucorales action *in vitro*. In *R. arrhizus* models, VT-1161 given as a curative or preventative medication increased the lifespan of neutropenic mice [38].

The angio-invasive nature of mucormycosis agent's causes widespread thrombosis, tissue infarction, and necrosis, all of which might make it difficult for antifungal drugs to reach the infection site. Debridement of all devitalized tissue as soon as feasible, appears to be reasonable in order to attenuate the mass of infectious moulds and avoid the spread of mucormycosis to surrounding structures. Surgery is useful in rhino orbital cerebral mucormycosis. Preoperative MRI or CT scans should be utilised to evaluate the extent of the tissues and its margins before undergoing extensive surgery. Surgical excision of necrotic lesions on a regular basis has demonstrated to improve outcomes. After a successful operative procedure; the patient may undergo plastic surgery. Surgical recommendations vary depending on the location and severity of the problem.

Preventive measure

For the prevention of mucormycosis in COVID-19 patients The Indian Council of Medical Research (ICMR) has released basic guidelines which are as follow [39].

- With or without the use of steroids, good sugar control to be achieved during COVID-19.
- Use of steroids in a rational way, at right dose, at right time, and for right length of time
- Antibiotic/antifungal use that is prudent.
- During oxygen therapy, use sterile or clean water as a humidifier.

DISCUSSION

Commonly seen mucormycosis in clinical practice is Rhino orbital cerebral mucormycosis, but it can affect any region of the body, including the nose, orbit, sinuses, CNS, lungs, liver, skin, jaw bone, and cardiovascular system.

Smith and Krichner's clinical diagnosis criteria for mucormycosis, published in 1950, are still regarded the gold standard they include [9].

- Facial discomfort and Blood from nasal discharge on same side
- Black, necrosed turbinates
- Peri-nasal and soft periorbital edoema with discolouration and induration
- Proptosis and ptosis of the eye ball and eyelids respectively, and total paralysis of eye muscles, as well
- Cranial nerve palsy that are not related to lesions that have been recorded.

In COVID-19 infected patients mucormycosis can be triggered by number of factors like: The SARS-CoV-2 virus may infiltrate and flourish in islet cells [10], impairing pancreatic beta cell function and leading to acute DKA. Mucormycosis is more likely to occur in Diabetic Ketoacidosis [DKA] than in people who do not have DKA [11]. Hyperglycaemia causes transferrin and ferritin to be glycosylated, reducing iron binding and resulting in free iron. Fungal growth is aided by acidosis and increased availability of free iron. Ferrioxamine (iron-rich form of deferoxamine) ferrioxamine utilised by mucorales as a xenosiderophore to gather iron. Iron chelation therapy with deferiprone ordeferasirox in diabetic ketoacidotic mice has been proven in several investigations to prevent mucormycosis and increase longevity. While adjunctive deferasirox was efficacious and well tolerated. Iron's inhibitory effect on neutrophil chemotaxis was likewise reduced by deferasirox.

At normal value of ketone bodies there is an elevated expression of fungal protein CotH-3 and GRP78 (Glucose Regulator Protein 78) in endothelium [12].

The uncontrolled utilisation of glucocorticoid in COVID-19 patient has resulted in increase in COVID associated mucormycosis [13]. Corticosteroid and immunosuppressive drug at high doses for a long time (>3 weeks) use can lead to infection of angioinvaisve

fungi [14]. Glucocorticoid leads to immunosuppression, hyperglycaemia, and lymphopenia which lead to impaired immunity.

Platelets serve a critical function in enhancing host immunity after being exposed to an invading pathogen, and they also have antifungal and antibacterial properties: membrane bound molecules CD154 and platelet TLR that let the platelet attachment and activation of many cell; association with spores and hyphae induces platelet triggering, platelet accumulation and clotting, and fungi elimination by preventing hyphae development. The existence of necrotic areas in tissues that did not show any signs of fungal development suggests that thrombotic ischemia was induced by systematic platelet activation. Severely affected COVID-19 patients more likely develop the clot in vital organs, which further complicates the condition. As a result of this, mucormycosis spreads swiftly.

Natural killer cells (NK cells) can directly and indirectly kill fungi. They also synthesize chemokines and cytokines that modulate other immune cells activity. Natural killer cells can harm Mucorales hyphae. In COVID-19 Natural killer cell counts above a certain threshold can seriously compromise IgG immunity. CD16 present on NK cells interacts with the infected cell coated with antibody, results in antibody dependent cellular toxicity. As a first line of defence, the inate immune system modifies immunological responses and defends against COVID-19.

Mucormycosis is distinguished by its ability to enter the vasculature and induce tissue necrosis and thrombosis [15]. Mucor interacts with the GRP78 which helps in fungal endocytosis. Fungal ligand which binds to GRP78 comes under the spore coating family protein (CotH-3) [16].

Stress causes GRP78 to be released from endoplasmic reticulum of endothelial cells [17]. SARS-CoV-2 infection leads to endoplasmic reticulum stress which leads to the release of GRP78, it has been seen that SARS-CoV-2 virus use GRP78 for internalization in host tissue [18]. GRP78 also leads to the internalization and increases virulence and pathogenicity of mucorales [16].

An indirect association between COVID-19 infection and mucormycosis is dissemination of fungal spores through water use in oxygen humidifier [19].

COVID-19 infection leads to impairment of immunity due to decrease in CD4+ and CD8+ count, lymphopenia which leads to secondary fungal infection [20].

Mucormycosis affects the sinuses, brain, and lungs; however, it can also have an impact on the GIT, mouth cavity, cutaneous tissue, and other organs. It can induce a variety of symptoms in various organs:

- When sinusitis gets worse, it clogs the nostrils and causes a black release
- Cheekbone pain, as well as inconsistency in facial pain
- Fever, headache
- Decrease in sensation over one half of face
- Poor vision or double vision (diplopia)
- Jaw and teeth loosening
- Breathlessness, chest discomfort, bloody sputum
- Abdominal pain, bleeding from GIT

CONCLUSION

In conclusion, COVID-19 has been linked to variety of fungal and bacterial infections due to impairment of immunity. Also the rampant use of corticosteroid and diabetes mellitus has increased the risk of opportunistic fungal infection. An effort should be made at the health care level to judiciously use the corticosteroid in COVID-19 infection and optimal management of hyperglycaemia in patients. Avoidance of unnecessary anti-bacterial and immunosuppressant Rhino cerebral mucormycosis causes inflammation on one side of the face, a bluish lesion within and outside the stoma, headaches, and sinus blockage. These symptoms increases the suspicion in post COVID patient for mucormycosis and one should seek of medical advice one should strictly monitor the blood glucose level. Early detection and treatment of mucormycosis can improve survival rates and minimizes fatality.

REFERENCES

1. Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J Clin Med 2020; 9:575.
2. Jebril N. World Health Organization declared a pandemic public health menace: a systematic review of the coronavirus disease 2019 “COVID-19”. 2020.
3. Eucker J, Sezer O, Graf B, et al. Mucormycoses. Mycoses 2001; 44:253-260.
4. Shoham S, Levitz SM. The immune response to fungal infections. British J Haematol 2005; 129:569-582.
5. Skiada A, Pavleas I, Drogari-Apiranthitou M. Epidemiology and diagnosis of mucormycosis: an update. J Fungi 2020; 6:265.
6. Unnikrishnan R, Mohan V. Whither diabetes research in India today?. Diabetes Metab Syndr 2020; 14:195-198.
7. Prakash H, Chakrabarti A. Global epidemiology of mucormycosis. J Fungi 2019; 5:26.
8. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet 2003; 362:1828-1838.
9. Singh AK, Singh R, Joshi SR, et al. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. Diabetes Metab Syndr 2021; 15:102146.
10. Muller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab 2021; 3:149-165.
11. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012; 54:23-34.

12. Gebremariam T, Lin L, Liu M, et al. Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. J Clin Invest 2016; 126:2280-2294.
13. John TM, Jacob CN, Kontoyiannis DP. When uncontrolled diabetes mellitus and severe COVID-19 converge: the perfect storm for mucormycosis. J Fungi 2021; 7:298.
14. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood 2011; 118:1216-1224.
15. Baldin C, Ibrahim AS. Molecular mechanisms of mucormycosis the bitter and the sweet. PLoS Pathog 2017; 13:1006408.
16. Gebremariam T, Liu M, Luo G, et al. CotH3 mediates fungal invasion of host cells during mucormycosis. J Clin Invest 2014; 124:237-250.
17. Ibrahim IM, Abdelmalek DH, Elfiky AA. GRP78: A cell's response to stress. Life Sci 2019; 226:156-163.
18. Ibrahim IM, Abdelmalek DH, Elshahat ME, et al. COVID-19 spike-host cell receptor GRP78 binding site prediction. J Infect 2020; 80:554-562.
19. Rammaert B, Lanternier F, Zahar JR, et al. Healthcare-associated mucormycosis. Clin Infect Dis 2012; 54:44-54.
20. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. Mycopathologia 2020; 185:595-606.
21. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis 2012; 54:23-34.
22. Corzo-Leon DE, Chora-Hernandez LD, Rodriguez-Zulueta AP, et al. Diabetes mellitus as the major risk factor for mucormycosis in Mexico: Epidemiology, diagnosis, and outcomes of reported cases. Med Mycol 2018; 56:29-43.
23. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 2005; 41:60-66.
24. Legouge C, Caillot D, Chretien ML, et al. The reversed halo sign: pathognomonic pattern of pulmonary mucormycosis in leukemic patients with neutropenia?. Clin Infect Dis 2014; 58:672-678.
25. Liu Y, Wu H, Huang F, et al. Utility of 18F-FDG PET/CT in diagnosis and management of mucormycosis. Clin Nucl Med 2013; 38:370-371.
26. Nair V, Sharma RK, Khanna A, et al. Pulmonary mucormycosis diagnosed by convex probe endobronchial ultrasound-guided fine needle aspiration of cavity wall. Lung India 2017; 34:179.
27. Lass-Florl C. Zygomycosis: conventional laboratory diagnosis. Clin Microbiol Infect 2009; 15:60-65.
28. Jensen He, Salonen J, Ekfors To. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies. J Pathol 1997; 181:100-105.
29. Sandven PE, Eduard W. Detection and quantitation of antibodies against Rhizopus by enzyme-linked immunosorbent assay. APMIS 1992; 100:981-987.
30. Wysong DR, Waldorf AR. Electrophoretic and immunoblot analyses of Rhizopus arrhizus antigens. J Clin Microbiol. 1987; 25:358-363.
31. Jones KW, Kaufman L. Development and evaluation of an immuno diffusion test for diagnosis of systemic zygomycosis (mucormycosis): preliminary report. J Clin Microbiol 1978; 7:97-101.
32. Potenza L, Vallerini D, Barozzi P, et al. Mucorales-specific T cells emerge in the course of invasive mucormycosis and may be used as a surrogate diagnostic marker in high-risk patients. Blood 2011; 118:5416-5419.
33. Walsh TJ, Gamaletsou MN, McGinnis MR, et al. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis 2012; 54:55-60.
34. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica 2017; 102:433.
35. Cornely OA, Alastruey-Izquierdo A, Arenz D, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis 2019; 19:405-421.
36. Wiederhold NP. Pharmacokinetics and safety of posaconazole delayed-release tablets for invasive fungal infections. Clin Pharmacol 2016; 8:1.
37. Gebremariam T, Alkhazraji S, Soliman SS, et al. Anti-CotH3 antibodies protect mice from mucormycosis by prevention of invasion and augmenting opsonophagocytosis. Sci Adv 2019; 5:1327.
38. Gebremariam T, Alkhazraji S, Lin L, et al. Prophylactic treatment with VT-1161 protects immunosuppressed mice from Rhizopus arrhizus var. arrhizus infection. Antimicrob Agents Chemother 2017; 61:00390-00417.
39. Chatterjee P, Nagi N, Agarwal A, et al. The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence. Indian J Med Res 2020; 151:147.