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Post Covid-19: Outbreak of Mucormycosis

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Abstract: ***The main aim of Corona is transmission of disease from person to person, and it had also been declared as a global pandemic which has caused disaster in the respiratory system of more than five million people and killed more than half a billion people across the world. Patients surviving from Covid-19 have lower immunosuppressive CD4+ T and CD8+ T Cells. And most of the patients are in severe need of mechanical ventilation. This is the reason for a longer stay in hospital for a particular patient. Gradually, these patients have been discovered to develop fungal co-infection. This infection is deadly leading to loss of hearing, loss of sight and eventually death. The fungal infection is referred to as Mucormycosis, the black fungus. The causative agent for this infection is Mucormycotina which is a member of Mucorales. Mucormycotina usually habitats in soil and decaying organic matter. The infection of Mucormycotina is associated with a wide range of human diseases including arthritis, gastritis, renal disorders and pulmonary diseases. This infection is closely associated with the mucous layer of skin, precisely cutaneous layer. This infection is present in the nasal and upper respiratory tract. In the lower respiratory tract these infections are difficult to diagnose and treat due to the lack of precise methods. It was found those neutroponia patients are more prone to this infection. This is caused by extensive use of chemotherapy resulting in impaired immunity. In recent times, in the case of pulmonary Mucormycosis, necrotizing pneumonia is a major symptom. A combination of antifungal and antimicrobial agents is being used for a higher clinical recovery in the Mucormycosis case.***
Keywords: Mucormycosis, The Black Fungus, Covid-19, Zygomycosis, Amphotericin-B.

I. INTRODUCTION

Mucormycosis (Black fungal disease) is also called zygomycosis or phycomycosis. In 1885, zygomycosis or phycomycosis was described by Genrallery The disease is caused by bacteria or virus-like that it is caused by fungus hence it is a fungal disease. An example of fungal disease is Rhizopus species, Mucour SP., Rizomucaor SP. These are present in soil and also in decaying matter. They play a vital role after the death of living organisms like plants or animals they feast on the dead body and they take all nutrients and put it into the soil. They play a vital role in circulation through the environment.

Fungus consists of different types of diseases cause they attack different tissue in our body. Based on where they attack that form of the disease occurs. But it is a rare disease cause, our immune system is sufficient for protection from this disease, After covid-19 infection, the immunity gets hampered hence our body becomes very weak. Hence due to weakness, our immune system is dropped, due to which the fungal disease starts to react to our body.

Infection of Mucormycosis is a form of life-threatening invasive fungal sinusitis that typically affects immunocompromised individuals with an impaired neutrophilic response. Patients can include those with uncontrolled diabetes mellitus, acquired immunodeficiency syndrome, immunosuppression, and hematological malignancies, and those who have undergone organ transplantation. Mucor is a saprophytic fungus; its spores exist widely in nature and are spread in soil, air, food, and decaying organic material. Because of the low virulence potential, it may be present in the nasal mucosa of healthy people as a commensal. If the patient becomes immunosuppressed, this fungus may germinate within the paranasal sinuses, and spread nearby structures. There are various possible reasons for this association, including the immunosuppression caused by Covid-19 infection and disease process, or the extensive use of steroids and broad-spectrum antibiotics in the management of Covid-19, leading to the development or exacerbation of a pre-existing fungal disease.

Mucormycosis is characterized by the presence of hyphal invasion of sinus tissue and a time course of fewer than four weeks. Clinically, rhinocerebral mucormycosis can present with atypical signs and symptoms similar to complicated sinusitis, such as nasal blockage, crusting, proptosis, facial pain and edema, ptosis, chemosis, and even ophthalmoplegia, with headache and fever and various neurological signs and symptoms of the intracranial extension are present.

Without early diagnosis and treatment, there may be a rapid progression of the disease, with reported mortality rates from intra-orbital and intracranial complications of 50–80%. An aggressive surgical approach has been shown to improve survival. Amphotericin-B deoxycholate remains the anti-fungal treatment of choice to start, with its liposomal preparations preferred because of decreased nephrotoxicity. In cases refractory or intolerant to amphotericin therapy, posaconazole is considered a suitable alternative option.

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II. MECHANISM OF INFECTION IN MUCORMYCOSIS

A. Host defense against Mucormycosis

Experimental and clinical data clearly states that people who lack phagocytes or having impaired phagocytic function are at high risk of this black fungus disease. Considering the case of any neutropenic patients, they are at high risk for this disease. While it was found that patients with AIDS do not seem to have an increased risk of developing Mucormycosis. It was found that neutrophils are critical for inhibiting fungal spore proliferation. Further, mononuclear and polymorphonuclear phagocytes, with the generation of oxidative metabolite and cationic peptides, kills Mucorales. Mucormycosis is the infection caused by fungi belonging to the order Mucorales. Rhizopus oryzae [R. oryzae] is the most common organism isolated from patients and is responsible for 70% of all cases of mucormycosis. According to a recent study, the reaction of neutrophils to R. oryzae hyphae result in up-regulation of toll-like receptor 2 expressions and a robust proinflammatory gene expression with rapid induction of NF-kB pathway-related gene. It was found that the patients with Diabetic ketoacidosis [DKA], have the presence of hyperglycemia and low pH. Due to which phagocytes are dysfunctional and have impaired chemotaxis and defective intracellular killing.

According to clinical observation, immunocompetent animals on inhalation of Mucorales sporangiospores do not result in Mucormycosis infection. While animals with immunosuppression or with DKA die progressively due to pulmonary infection. Sporangiospores aim to germinate and form hyphae in the host. This germination is blocked by pulmonary alveolar macrophages harvested from the lungs. The pulmonary alveolar macrophages of immunocompetent animals can ingest and inhibit germination of R. oryzae sporangiospores. While pulmonary alveolar macrophages of immunosuppressive animals are unable to even prevent the germination of R. oryzae sporangiospores.

The exact mechanism by which phagocytes are impaired by ketoacidosis, diabetes mellitus, and corticosteroids is not determined yet. From further studies, it was found that phagocyte dysfunction alone cannot explain the incidence of Mucormycosis. Hence for infection Mucorales must possess unique virulence traits that enable the exploitation of immunosuppressive animals and physiologic impairment. The primary defense mechanism against cutaneous mucormycosis is our skin. According to recent observation, it was found that disruption of the skin barrier leads to an increased risk of developing mucormycosis. The mucormycosis agents are incapable of penetrating the skin barrier. However, cuts, burns, traumatic disruption of skin may lead to the deeper dive of infection into tissues. This organism originates from contaminated soil or water. Contaminated surgical dressings and nonsterile adhesive tape are the sources of primary cutaneous mucormycosis.

B. Host Pathogen Interaction

Mucormycosis infection causes extensive anti-invasion that results in vessel thrombosis and subsequent tissue necrosis. Necrosis of infected tissue can prevent the delivery of leukocytes and antifungal agents to the foci of infection. The important step in the pathogenic strategy of R. oryzae is to penetrate through endothelial cells or the extracellular matrix proteins lining blood vessels. According to studies R. oryzae can adhere to extracellular matrix laminin and type IV collagen. And also R. oryzae strains adhere to human umbilical vein endothelial cells in vitro and invade these cells by induced endocytosis.

Endocytosed R. oryzae damages endothelial cells and prevents endocytosis which evades the ability of an organism to cause endothelial cell damage. Glucose-regulated protein [GRP78] acts as a receptor that enables the penetration and damage of endothelial cells by Mucorales.

GRP78 is a member of the HSP70 protein family that is mainly present in the endoplasmic reticulum. The function of this protein is involved in various cellular processes which include protein folding and assembly, marking misfolded protein, serving as a sensor for endoplasmic reticulum stress, and regulating calcium homeostasis. It was found that animals with DKA-enhanced surface GRP78 expression had increased susceptibility to mucormycosis. While it is currently unknown whether anti-GRP78 immune serum can protect the neutropenic host from mucormycosis.

III. TYPES OF MUCORMYCOSIS

A. Rhinocerabral Mucormycosis

Rhinocerabral mucormycosis is a rare, invasive, and opportunistic fungal infection of the sinus and brain. Rhizopus Oryzae is responsible for approximately 60% of the mucormycosis cases in humans and around 90% for the rhinocerabral mucormycosis form of fungal infections. It is mainly seen in patients where the immune system is suppressed and is metabolically compromised. Patients like Diabetic patients, Neutropenic patients, Patients with hematologic malignancies, Increased serum iron symptoms, organ transplant patients are the mostly become host for Rhinocerabral mucormycosis.

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1) *Symptoms*

a) acial swelling on one side.
b) Headache, nosebleed.
c) Nasal or sinus congestion
d) Black lesions on nasal bridge or upper inside of mouth that quickly become more severe
e) Fever

2) *Diagnosis:* Early diagnosis of rhinocerabral mucormycosis play important role in appreciating the management of the patient. Using the compatible symptoms of the previous patient the initial treatment can be started. Fungal cultures can be used for more confirmation.

B. Pulmonary Mucormycosis

Pulmonary mucormycosis is a rare, life-threatening, and opportunistic infection of fungus. It causes the inhalation of fungi spores into the lungs, especially in bronchioles and alveoli. Due to this, there is a progression in pneumonia and endobronchial diseases. It typically affects neutropenia patients, diabetes mellitus, and immunocompromised patients, such as recipients of stem cells or organ transplants. It is mostly uncommon infection occurs in a person who has less immune response, immunocompromised persons. In 1876, the first case of pulmonary mucormycosis was described by Furbringer. The mortality rate of this infection is about 40-76%. This is a rare but dangerous disease because when you late in diagnosis there is a high rate of mortality and also there are limited available therapies.

1) *Symptoms*

a) The symptoms are typically nonspecific they may include fever, dyspnea, coughing, and chest pain.
b) The Main infection is on the lungs so hemoptysis commonly occurs with vascular invasion.
c) Then emphysema, pancost syndrome, Horner's syndrome, and bronchial perforation present in rare cases.
d) Rarer results include endobronchial lesions.

2) *Diagnosis:* For diagnosis, there are main 3 systems which are imagined feature, biopsy(bronchoscopy, CT guided percutaneous), and quantitative polymerase chain reaction. The most common method used to make the diagnosis of pulmonary mucormycosis is flexible fiberoptic bronchoscopy. There is also one antifungal therapy that is the recommended antifungal agent is liposomal amphotericin B. The cytokines therapy as adjunctive treatment is promising, but more clinical data are needed. Then combined medical therapy (combination of amphotericin B and caspofungin) show a superior effect on rhino-cerebral mucormycosis. But this is not applied to pulmonary mucormycosis cases to date.

3) *Management:* It is a dangerous but rare disease, so you can stay in a safe and clean environment there is less chance of infection. Control the blood glucose level because it majorly infects diabetic patients. Treatment of metabolic acidosis or tapering of immunosuppressive agents Boosting of Immunity is important. The combination of early surgical resection and antifungal therapy has a significant improvement in survival.

C. Gastrointestinal Mucourmycosis

Gastrointestinal mucormycosis is one type of mucormycosis. Most commonly the site of Gastrointestinal mucormycosis is the stomach followed by the small intestine(ileum) and large intestine (colon). The most common symptoms are omitted and fever. To diagnose these diseases use biopsy of suspected areas during endoscopy or surgery. Gastrointestinal is a rare type of mucormycosis. Mucormycosis consists of high mortality so it can't survive in neonates with gastrointestinal mucormycosis.

Gastrointestinal mucormycosis is ulcerating and necrotic. By historical examination, the gastrointestinal mucormycosis consist of irregular shape, broad size, septate to pauciseptate hyphae with right-angle branching. Gastric mucormycosis occurred due to contamination of wooden applicators that were used to mix drugs for patients with nasogastric feeding tubes. Maravi-Poma et al reported an outbreak of gastric mucormycosis associated with the use of wooden tongue depressors in critically ill patients.

For uncontrolled Diabetic Mellitus patients risk factor is more for gastrointestinal mucormycosis, Also, defect in phagocyte function, organ or steam transfer, iron overloaded these also involve in risk factors. In some cases, these diseases present in the primary condition of predisposing factors. In which some cases it consists of small intestinal involvement and some are esophageal involvement was all associated with additional lesions else where.

We report a patient with a history of rheumatoid arthritis who has developed gastrointestinal mucormycosis. To the best of our knowledge, this is the first such case reported in the literature.

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D. Dissemination Mucormycosis

Dissemination of mucormycosis has occurred when the infection spreads in the bloodstream which can affect another body part. It affects the brain, spleen, heart, and skin. It is a rare disease that is frequently seen in that patient who has a very serious health issue like have very low WBC count (neutropenia) which have cancer with blood, bone marrow, and lymph node (Hematologic malignancies) or patient who has done with organ transplantation. This disease is a non-infectious organ system and generally occurs in patients who have a very weak immune system. Most serious thing is that this disease is very dangerous to tyan other four types and very rare also, and has a mortality rate above 90%.

1) Symptoms

- Blood vomiting
- skin lesion on face
- In extreme cases body temp could rise
- Already sick from other diseases like diabetes.
- sometimes mental status of brain also changes

2) *Diagnosis and Prevention:* For testing, we can culture or direct we can detect the fungal infection through blood samples, CT scan, or MRI. In this case of organ transplantation, antifungal drugs should be given to the patient. Amphotericin B and Posaconzole are the two drugs approved for this treatment.

E. Cutaneous Micromycosis

1) Symptoms

- Fever
- Headache
- Reddish and swollen skin over nose and sinuses
- Dark scabbing in the nose by eye(s)
- Visual problems
- Eye(s) swelling
- Facial pain
- Coughing sometimes with bloody or dark fluid production
- Shortness of breath
- Diffuse abdominal pain
- Bloody and sometimes dark vomitus
- Abdominal distension

2) *Diagnosis:* Treatments for mucormycosis need to be fast because the patient has suffered significant tissue damage that cannot be reversed. Most people need both surgical and medical treatment Two main goals are the stop the further spread and medication for any debilitating underlying diseases. Amphotericin B (initially intravenous) is the usual drug of choice for antifungal treatment. The diabetic patients needed to control diabetes. If a patient undergoing treatment with steroids then it has to stop.

IV. CASE STUDY REPORTS

A. Case Study 1

In the laboratory, these fungi grow rapidly and have a black-brown fuzzy appearance. It was found that mucormycosis that cause human disease to grow well at normal body temperature and in acidic environments – the kind saw when tissue is dead, dying, or associated with uncontrolled diabetes.

1) *Covid 19 and Mucormycosis:* When our lungs are damaged and our immune systems suppressed, such as is the case in patients being treated for severe Covid-19, these spores can grow in our airways or sinuses, and invade our bodies tissues. Mucormycosis can manifest in the lungs, but the nose and sinuses are the most common site of mucormycosis infection. From there it can spread to the eyes, potentially causing blindness, or the brain, causing headaches or seizures.

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A recent summary of Covid 19 associated mucormycosis showed 94% patients has diabetes. When diabetes is poorly controlled, blood sugar is high and the tissues become relatively acidic – a good environment for Mucorales fungi to grow. This was identified as a risk for mucormycosis in India (where diabetes is increasingly prevalent and often uncontrolled) and worldwide well before the Covid-19 pandemic. Of all mucormycosis cases published in scientific journals globally between 2000-2017, diabetes was seen in 40% of cases.

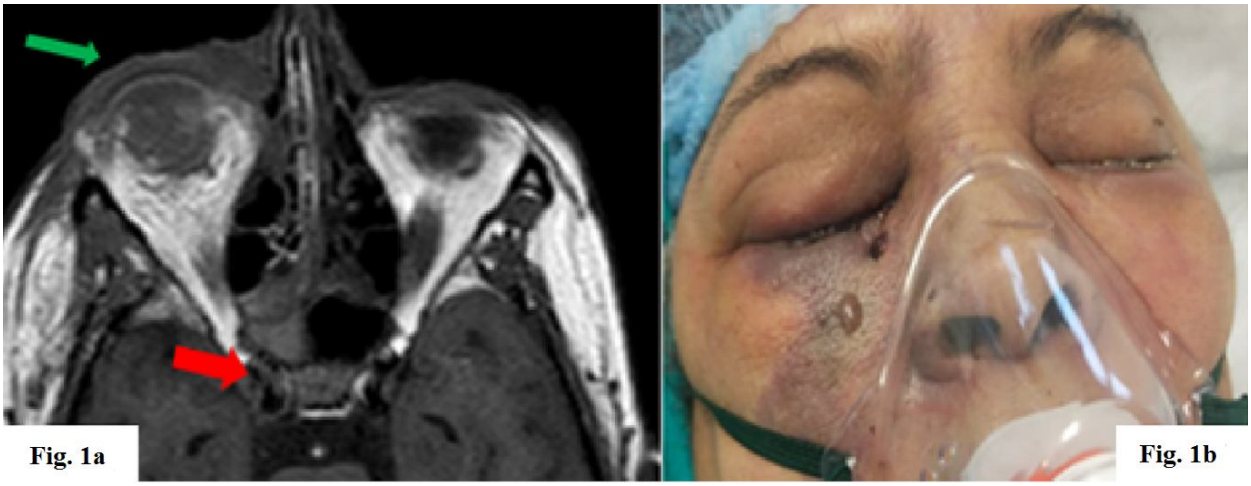

Fig. 1a Fig. 1b

Fig. 1a MRI of Patient which reveals right pre and post-septal orbital cellulitis with endo-ophthalmitis and Fig. 1b Complete ophthalmoplegia of the right eye, and blood-tinged black discharge from the nostril

A case study performed by the SP Medical College, Bikaner, Rajasthan, India on a 68-year-old female who has diabetes and recovered from CVOVID 19 pneumonia, After a negative report of RT-PCR, shifted to post COVID ICU. After a couple of days, she developed a headache, right eye swelling, and drooping of the right upper eyelid. On examination, It was found that there was lid edema, loss of vision, proptosis, and complete ophthalmoplegia of the right eye, and blood-tinged black discharge from the nostril. MRI revealed right pre and post-septal orbital cellulitis with endo-ophthalmitis, right cavernous thrombosis, multiple lacunar infarcts, and pansinusitis (Fig. 1a) Histopathological examination of nasal scraping revealed mucormycosis, and Rhizopus arrhizus was grown on sabouraud dextrose agar culture. She was started on intravenous liposomal amphotericin B and broad-spectrum antibiotics and steroid was tapered. She progressively deteriorated, required inotropes and infection also spread to her left eye (Fig.1b). Debridement could not be done due to hemodynamic instability and the patient succumbed on day 8 despite all measures.

B. Case Study 2

A 28-year-man presented with weakness and fever in August 2019. He was diagnosed with Acute Myelomonocytic Leukemia, based on blood investigations followed by bone marrow examination with immunophenotyping and cytogenetic evaluation.

1) *Treatment:* He gives the treatment with 7:3 Induction chemotherapy (Cytarabine 100 mg/m2 for 7 days and Daunorubicin 60 mg/m2 for 3 days) which was then Daunorubicin 60 mg/m2 for 2 days) and then completed 3 cycles of followed by 5:2 chemotherapy (Cytarabine 100 mg/m2 for 5 days and consolidation with high dose Cytarabine (3 g/m2). Within a period of fewer than 6 months of completion of treatment, he relapsed and presented with hyperleukocytosis (blood leukocyte count of 172 × 109/L). He was advised to salvage chemotherapy followed by consolidation with a hematopoietic stem cell transplant. Salvage chemotherapy consist of FLA- IDA chemotherapy (Fludarabine 30 mg/m2 for 5 days, Idarubicin 10 mg/m2 and cytarabine 2 g/m2 .for 5 days. The cytopenic period after chemotherapy was adequately supported with antibiotics, antifungals, blood products, and Granulocyte Colony Stimulating Factor (GCSF). Antifungal prophylaxis was done with oral Posaconazole suspension 200 mg three times daily. On day +20 post-chemotherapy during the peak cytopenic period, he developed abdominal distension with obstipation. Computed Tomography (CT) imaging of the abdomen revealed dilated small bowel loops. Conservative management measures failed hence he underwent laparotomy and 7.5 cm of obstructed small bowel was resected. Histopathology of the resected bowel revealed angio-invasive mucormycosis (Figure 1). He was then started with intravenous liposomal amphotericin B 3 mg/kg daily. Upon completion of Amphotericin B for a course of 14 days followed by oral Posaconazole 300 mg once daily.

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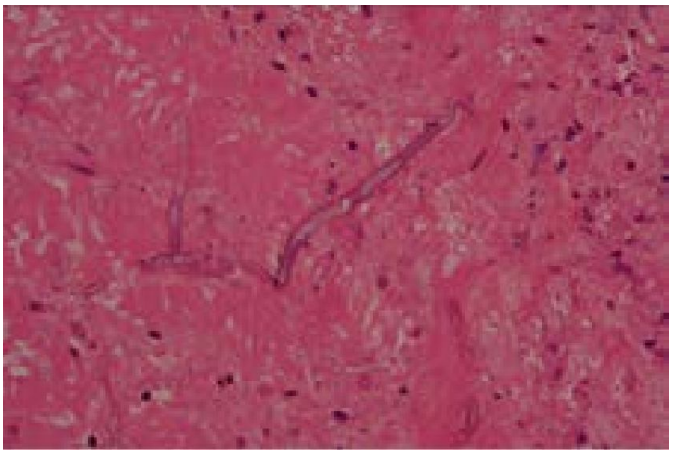

Fig. 2 Gastric biopsy showing Angio-invasive Mucormycosis

Post salvage bone marrow examination, done on Day+35 post-FLA IDA chemotherapy, he was in complete remission (Both morphology and measurable residual disease status). Since he had a matched sibling, he was recommended allogeneic peripheral blood stem cell transplantation. The conditioning chemotherapy regimen was Fludarabine 30 mg/m2 for 5 days along with Treosulfan 14 g/m2 for 3 days. Antifungal prophylaxis was started with oral Posaconazole suspension 200 mg three times daily. Post-transplant, during the neutropenic phase, he was restarted on intravenous liposomal Amphotericin B 3 mg/kg daily from Day+5 to Day+12 for a period of 8 days with successfully prevented the recurrence of Mucormycosis. Upon count recovery, liposomal Amphotericin B was stopped and oral Posaconazole suspension 200 mg three times daily was restarted.

C. Case Study 3

A 32-year-old male, burned wound at the right side of chest and arm was contact with electricity.

1) *Treatment:* The patient gets to debridement at private hospital and antibiotic courses. After testing ZN staining was negative, Gram stain showed few pus cells and IV Antibiotics are administered by the burn part sensitivity but no improvement. Then there seen three zones of subcutaneous necrosis gangrenous changes in overlying skin and inflammatory changes in surrounding tissue. Then perform KOH tube which then revealed the presence of Aseptate hyphae suggestive of Mucormycosis, and inj. Amphotercin B 0.75 mg/kg body weight BD as given. On POD 3, by the surgery wound is cleaned and subcutaneous necrotic material completely removed the skin was healed by antifungal medication.

Fig. 3 Electric burn wound over right arm and chest wall.

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Fig. 4 3 zones of subcutaneous necrosis

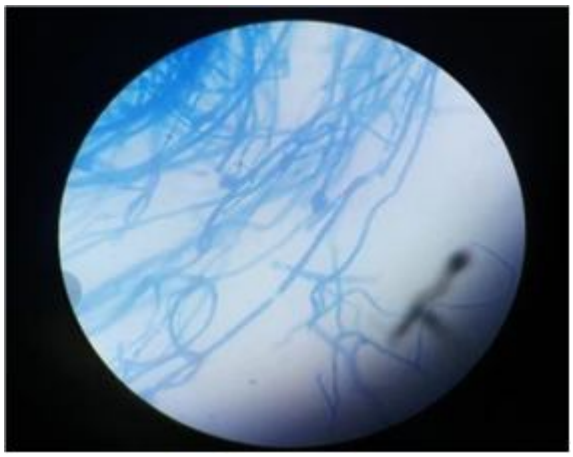

Fig. 5 KOH mount showing aseptate hyphae

V. DISCUSSION

World facing with COVID 19 pandemic, a new health issue appears to be quickly reaching the potential of an outbreak in India. Mucormycosis is a rare but deadly black fungus infection that occurs in COVID 19 recovering patients. It is caused by exposure to mucor mould which is commonly found in soil, plants, manure, and decaying fruits and vegetables.

As many as 28.252 cases of Mucosmycosis are found in India, the majority of these cases from Maharashtra and Gujrat states. Out of the total cases, 86% have a history of COVID 19, and 62.3% a history of diabetes.

Its attack on the sinuses, the brain, skin, and the lungs and can be life-threatening in diabetic or severely immunocompromised individuals, such as people with HIV/AIDS and cancer patients. Patients infected with black fungus in most cases have symptoms of a stuffy and bleeding nose, swelling of and pain in the eye, drooping of eyelids and blurred, and finally, loss of vision. There could be black patches of skin around the nose.

Data received from Doctors says that the earlier mortality rate was 54% now it reduced to 50%. It may be reduced by the use of steroids, a life-saving treatment for severe and critically ill COVID 19 patients. The steroid helps in the reduction of inflammation in the lungs for COVID 19 and appears to help some of the damage that can happen when the body's immune system goes into overdrive to fight off the coronavirus. But they also reduce immunity and push up blood sugar levels in both diabetics and non-diabetic Covid-19 patients. It's thought that this drop in immunity could be triggering these cases of Mucormycosis. Doctors say most of their patients admitted late, when they are already losing vision, and doctors have to surgically remove the eye to stop the infection from reaching the brain.

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In some cases, doctors in India say, patients, have lost their vision in both eyes. And in rare cases, doctors have to surgically remove the jaw bone to stop the disease from spreading. An anti-fungal intravenous injection which costs 3,500 rupees ($48) a dose and has to be administered every day for up to eight weeks is the only drug effective against the disease.

One report from SGPGI Lucknow institute says that, as compared to men women have less mucormycosis infection due to the presence of the hormone estrogen. This hormone active in women between 14 to 50 age and most women infected were above age 50.

Among all 5 types of mucormycosis Rhino orbital mucormycosis is a major fungal opportunistic infection that occurs in post-COVID 19 patients. The patients with weak innate immunity to fight the external invading pathogens have naturally occurring fungus found as a rhino-orbital cerebral infection. An early diagnosis treatment with a quick, Well organized, multidisciplinary approach has been crucial to saving both the life and sight of the patient. Rhino-orbital mucormycosis is a known viral infection caused by immune-compromised patients. Its severity increases due to uncontrolled diabetes mellitus, COVID 19 infection, and the use of steroids. As reported world literature mucormycosis has been severe life-threatening pre-COVID 19 eras with 315 cases from 12 tertiary centers in India over a year and 9 months period with identifiable risk factors for 90-day mortality

VI. CONCLUSIONS

Mucormycosis is rare but it is a burden on immunosuppressed patients. The mechanism of infection of Mucormycosis is still not understood completely, hence finding a cure for this disease is still a challenge. Serious consideration must be given to the association between Coronavirus and Mucormycosis of the paranasal sinuses. The two main factors of infection are uncontrolled diabetes and overuse of steroids. Several methods are developed for the cure of the Mucormycosis, but they are more time-consuming. These methods may include injection of antifungal agents, surgical interventions, and timely dosage of antifungal therapy. The approach to Mucormycosis is way easier by using Immunologic and Metabolic profiling. A high degree of clinical inspection is required to diagnose Mucormycosis. Early diagnosis and timely management are necessary to improve outcomes in Mucormycosis.

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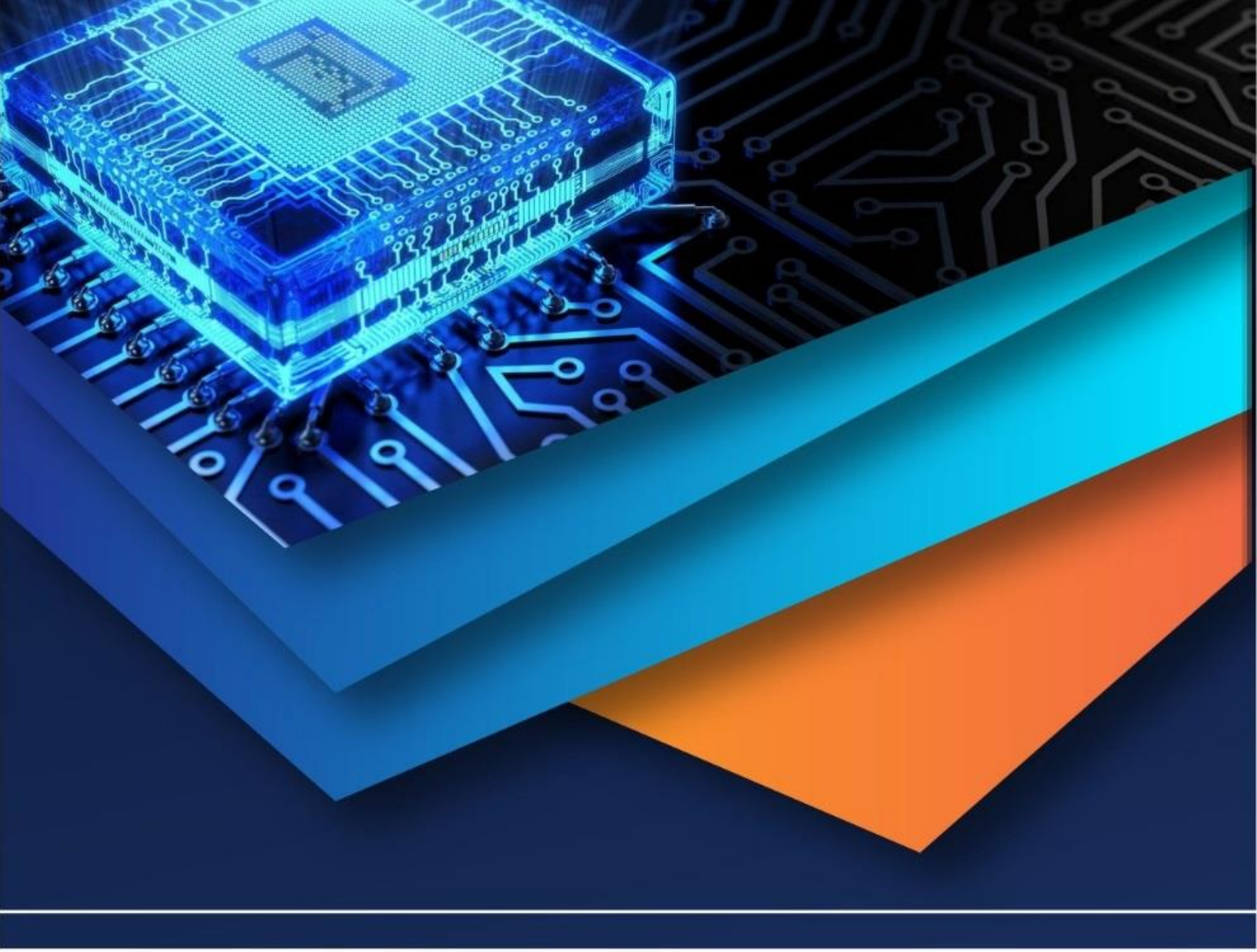

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