

Mucormycosis, a dangerous complication of covid-19 disease: Documenting the occurrence in Iraq and a review of the literature

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ABSTRACT

Background: Mucormycosis, a rare, but severe angio-invasive disease that can have a catastrophic or fatal outcome. It is an opportunistic infection that has been mostly reported in immunocompromized and diabetic patients, and it commonly begins by invading the respiratory tract. The aim of this paper is to document the emergence of mucormycosis as a dangerous complication of covid-19 in Iraq and many countries in the world.

Materials and methods: On the first of June, 1,201,352 cases of covid-19 were reported by the Iraqi Ministry of Health, and 16375 patients died because of the disease. During, the first week of June, 2021, the death of Iraqi three patients having covid-19 disease complicated by mucormycosis was reported. At least 140 patients with covid-19 disease complicated by mucormycosis have been reported throughout the world including 100 patients from India, 18 patients from Iran, 11 patients from Turkey, 7 patients from the United States of America, 6 patients from Egypt, 2 patients from Spain, and one patient from each of the following countries, Brazil, Italy, Austria, France, Mexico, UK, and the United Kingdom. Most patients were males and the disease was documented in sixteen females.

Results: Sino/rhino-orbital mucormycosis with or without cerebral involvement was the most commonly reported type including 87 patients. Pulmonary mucormycosis was the second most common type, and was reported in five patients. Catastrophic outcome occurred in nineteen patients including patients ending with orbital exenteration in patients (14), and patients developed irreversible loss of vision (5). Forty patients with covid-19 with mucormycosis died including, 15 patients from India, eight patients from Iran, seven from Turkey, four deaths from USA, two deaths from Egypt, on death from Brazil, one death from Austria, one death from Mexico, and one death from the United Kingdom.

Conclusions: Mucormycosis is a rare disease that is generally associated with diagnostic difficulty and delay, high morbidity, catastrophic outcome, and mortality. Diabetes mellitus and use of corticosteroids increase the risk of the development of invasive mucormycosis which may appear during the course of the covid-19, or appear as a later complication. Hyperglycemia induced impaired chemotaxis and phagocytosis of neutrophils, steroid-induced immunosuppression, and covid-19 induced immune dysregulation associated with decreased numbers of T lymphocytes, CD8+T, and CD4+T cells were considered the important factors that led to the emergence of invasive mucormycosis as a catastrophic and fatal complication of covid-19 disease. Mucormycosis can be rapidly progressive, requiring immediate surgical and medical interventions. High index of suspicion can contribute to making an early diagnosis, and providing early aggressive management which can

improve survival. Upon suspicion of mucormycosis appropriate imaging is advised to determine extent of disease. First-line treatment is generally including the use of a high-dose liposomal amphotericin B. Other antifungal drugs that have been used include isavuconazole and posaconazole.

Keywords: Covid-19, dangerous complication, mucormycosis, mortality, Iraq, global.

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Introduction:

Mucormycosis, a rare, but severe angio-invasive disease that can have a catastrophic or fatal outcome. It is an opportunistic infection that has been mostly reported in immunocompromized patients, and it commonly begins by invading the respiratory tract. The disease is characterized by vascular invasion by hyphae, causing thrombosis and tissue necrosis. The causative fungus is an omnipresent organism belongs to the family of Zygomycetes. In normal individuals, it is a noninvasive saprophyte. Mucormycosis was first reported by Friedrich Küchenmeister (Figure-1) in 1855. Pulmonary mucormycosis was the first described by Julius Friedrich Cohnheim (Figure-2) in 1865, and by Paul Walther Fürbringer in 1876 (Figure-3). Cohnheim reported two patients with pulmonary mycosis caused by mucormycosis.



Figure-3: Paul Walther Fürbringer (August, 7, 1849-July, 21, 1930), a German physician

In 1884, Ludwig Lichtheim (Figure-4) reported the occurrence of infection with mucormycosis in rabbits and described two species, *Mucor corymbifera* (Lichtheimia) and *Mucor rhizopodiformis* (Rhizopus, respectively) [1-10].

In 1885, Arnold Paltau reported a patient having with systemic mucormycosis with involvement of sinus, brain and gastrointestinal tract, and called the condition “Mycosis Mucorina” [6].

In 1943, Gregory and colleagues reported three patients with mucormycosis of the central nervous system, and in 1946, Georgiade et al reported a diabetic patient with mucormycosis [7, 8].

In 1947, Philip Medford LeCompte (Figure-5) and William Meissner (Figure-6), reported what they considered, the fifth case of mucormycosis of the central nervous system in the USA, which occurred in association with hemochromatosis [9].



Figure-1: Gottlieb Heinrich Friedrich Küchenmeister (January 22, 1821-April 13, 1890), a German physician.



Figure-2: Julius Friedrich Cohnheim (July, 20, 1839-August, 15 1884), a German pathologist



Figure-4: Ludwig Lichtheim (December, 7, 1845- 13 January, 13, 1928), German physician

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Figure-5: Philip Medford LeCompte (October, 4, 1907-September, 1998)



Figure-6: William Meissner

They emphasized that the four previously reported patients had the triad of [9]:

- 1-Uncontrolled diabetes, with either coma or mental confusion.
- 2-Orbital infection.
- 3-Meningo-encephalitis, with the presence of large, non-septate, branching hyphae with a predilection for blood vessels walls.

In 1948, Roger Baker and Severance reported a 3-year old child in Texas who had acute lobular pneumonia caused by mucormycosis. They emphasized that the previously reported of cases mucormycosis in the American literature were acutely fatal and occurred in diabetic patients. They thought that the fungus cause necrosis and acute inflammation, multiply in blood vessel walls resulting in thromboses [10].

In 1949, Morris Moore and colleagues reported a 37-year old female patient who had acute colitis caused by mucormycosis. She developed ulcerative colonic lesions, and perforation of the bowel. The patient died because of generalized peritonitis. Lloyd and colleagues (1949), and Murphy and Bornstein (1950) reported pulmonary mucormycosis, and the case of Lloyd and colleagues was complicating pregnancy. Stratemeier (1950), Wadsworth (1951), and Bank (1951) reported mucormycosis of the central nervous system, ocular mucormycosis, and mucormycosis of the endometrium respectively. Nicod and colleagues (1952) reported the occurrence of mucormycosis in association with *Aspergillus fumigatus* infection. Kurrein emphasized that the case was unlike the previously reported patients, as there was no diabetes, and no obvious invasion of the eye and orbit. Bauer (1955) reported two diabetic patients died because of cerebral mucormycosis caused by *Rhizopus oryzae*. The paranasal sinuses were the possible portal of entry of the infection. They suggested that mucormycosis was emerging as a clinical syndrome consisting of uncontrolled diabetes mellitus, ophthalmoplegia, meningoencephalitis and, sinusitis [11].

In 1956, Roger Baker reported six cases of pulmonary mucormycosis, studied 10 cases of pulmonary mucormycosis previously reported in the literature including six patients from the old German literature and 4 patients from the American literature. Baker considered mucormycosis as a new disorder in the USA and attributed its emergence to the incidence to the use of antibiotics, cortisone, Adrenocorticotrophic hormone ACTH, and drugs used in leukemia. Baker reported that predisposing factors included diabetes mellitus in four patients, leukemia in two patients, multiple myeloma in one patient, cutaneous burns in one patient, infantile diarrhea in one patient, and there was no obvious predisposing factor in one patient In 1957, Roger Baker, and colleagues reported a patient with mucormycosis of the digestive tract. In 1971, Roger Baker studied 49 patients of mucormycosis including 39 patients with pulmonary mucormycosis [11].

Tedder et al (1994) reported 30 patients, and reviewed 225 patients previously reported in the medical literature.

Ninety two patients were diagnosed antemortem; 61% of them were treated with antifungal agents, 21% were treated surgically, and 18% received combined medical and surgical therapy. The mean age at presentation of the 255 patients studied by Tedder et al was 41 +/- 21 years. Associated diseases included leukemia or lymphoma (37%), diabetes (32%), chronic kidney failure (18%),organ transplantation (7.6%), and solid tumors (5.6%). The deaths in hospitalized patients included 65% of patients with isolated pulmonary mucormycosis, 96% of patients with disseminated disease, and 80% overall. 11% of the patients whom were treated surgically died, significantly lower than the 68% deaths in

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patients whom were treated medically ($p = 0.0004$). The most common causes of death included fungal sepsis (42%), respiratory insufficiency (27%), and hemoptysis (13%) [11].

Francis Lee et al reviewed 87 cases of pulmonary mucormycosis reported in the medical literature during the period from 1970 to 2000. Fifty five patients were treated with antifungal drugs, mostly amphotericin B, and only seven patients were treated with an Azole. Survival rate in general was 44% and was higher in patients whom were treated with combined medical and surgical therapy. The main risk factors in the 87 patients studied included diabetes mellitus, hematological malignancies, kidney insufficiency, and organ transplantation. Some patients didn't have obvious immune defect. There was more involvement of the upper lobes. Air crescent signs on chest radiographs suggested pulmonary hemorrhage and predicted the death from hemoptysis. Fiberoptic bronchoscopy was considered as a useful diagnostic tool, and histopathological study was more sensitive than fungal cultures. The study of Francis Lee et al suggested that early diagnosis and early aggressive treatment can maximize chances for cure. Optimal management include the use systemic antifungal, surgical resection, and, when relevant control any associated disorders.

Prakash and Chakrabarti (2019) emphasized the higher occurrence of mucormycosis in the Asian continent. Main risk factors in Asia include diabetes mellitus, post-tuberculosis and chronic renal failure. The rhino-cerebral mucormycosis was most commonly reported in diabetic patients, while, pulmonary mucormycosis were reported in patients with hematological malignancy and transplant recipients. In normal individuals, cutaneous mucormycosis were commonly reported after trauma. Isolated renal mucormycosis in immuno-competent patients was surprisingly reported only from China and India. *Rhizopus arrhizus* is the most commonly isolated species throughout the world. *Apophysomyces variabilis* was predominantly reported from Asia and *Lichtheimia* species were commonly reported in Europe [11].

The aim of this paper is to document the emergence of mucormycosis as a dangerous complication of covid-19 in Iraq and many countries in the world.

Materials and methods

On the first of June, 1,201,352 cases of covid-19 were reported by the Iraqi Ministry of Health, and 16375 patients died because of the disease. 594927 received at least one dose of one of the available covid-19 vaccines.

On the first of June, 2021, the first death occurring as a as a complication of covid-19 disease was reported by health authorities in Iraq. The patient aged 51 years, and died in the city of Nasiriyah in the province of Thi Qar.

The second death occurring as a as a complication of covid-19 was reported on the second of June, 2021, and the patient was

a 78 old diabetic patient from Al-Anbar province but he died at the hospital of Al-Sulaymaniyah at the North of Iraq. The patient was diagnosed as having covid-19 disease three weeks before his death, and he was thought as being in his was of recovery but he was hospitalized and received the diagnosis of mucormycosis, , and died within ten days.

In addition, to his diabetes, the patient had chronic heart disease. On the fifth of June, 2021, a military man also died from mucormycosis as a complication of covid-19.

At least 140 patients with covid-19 disease complicated by mucormycosis have been reported throughout the world including 100 patients from India, 18 patients from Iran, 11 patients from Turkey, 7 patients from the United States of America, 6 patients from Egypt, 2 patients from Spain, and one patient from each of the following countries, Brazil, Italy, Austria, France, Mexico, UK, and the United Kingdom. Most patients were males and the disease was documented in sixteen females.

Results

Sino/rhino-orbital mucormycosis with or without cerebral involvement was the most commonly reported type including 87 patients from India, 18 patients from Iran, 11 patients from Turkey, Six patients, from Egypt, three patients from the United States, one patient from Mexico, One patient from Spain. Orbital mucormycosis was reported in ten patients from India,

Pulmonary mucormycosis was reported in five patients including two patients from India, one patient from Italy, one patient from Austria, and one patient from the United States.

Maxillary sinusitis caused by mucormycosis was in one patient from India, gastrointestinal mucormycosis was reported in one patient from Brazil, cutaneous mucormycosis at an old intravascular device site was reported in one patient from the United States, disseminated mucormycosis was reported in one patient from the United Kingdom, and musculoskeletal was reported in one patient from Spain mucormycosis.

The association of mucormycosis with aspergillosis was reported in one patient from France.

Most patients were diabetic, but the occurrence of mucormycosis was documented a previously healthy 33-year-old female from the Unites States.

The occurrence of mucormycosis in organ transplantation patients was reported in five patients including two patients from India, and two patients from Spain who had renal transplantation and one patient from the United States with heart transplantation.

Other associated disorders include acute myeloid leukemia which occurred in one patient from Austria.

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Catastrophic outcome occurred in nineteen patients including patients ending with orbital exenteration in patients (14 from India, six from Iran, and one patient from Egypt). Five patients from India developed irreversible loss of vision.

Forty patients with covid-19 with mucormycosis died including, 15 patients from India, eight patients from Iran, seven from Turkey, four deaths from USA, two deaths from Egypt, one death from Brazil, one death from Austria, one death from Mexico, and one death from the United Kingdom.

Discussion

Salil Mehta and Abha Pandey from Mumbai, India were probably the first to report the emergence mucormycosis as a serious complication of covid-19 disease. They reported a 60-year-old male diabetic patient who developed rhino-orbital mucormycosis during treatment of covid-19. The patient received parenteral meropenem, oral oseltamivir, and parenteral methylprednisolone. He presented with orbital cellulitis associated with soft tissue swelling apparent on Magnetic resonance imaging in the right pre-septal, malar, and pre-maxillary and retrobulbar regions with paranasal sinusitis. A nasal biopsy showed broad aseptate filamentous fungal hyphae indicative of mucormycosis, which was confirmed later on culture.

Mehta and Pandey suggested that the excessive use of steroids/monoclonal antibodies/broad-spectrum antibiotics may contribute to the development/exacerbation of mucormycosis [11].

Monte Junior from Sao Paulo, Brasil and his colleagues, were probably the first to report the emergence of mucormycosis as a fatal complication of covid-19 disease in Brazil. They reported an 86-year-old male with covid-19 who was hospitalized with acute diarrhea, cough, dyspnea, and fever of 5 days duration. After five days, he developed melena and acute anemia requiring transfusion of three units of red blood cells. Esophago-gastroduodenoscopy showed two giant gastric ulcers with necrotic debris and a deep hemorrhagic base without active bleeding. Biopsies established the diagnosis of mucormycosis. The patient died 36 hours after the esophago-gastroduodenoscopy.

Pulmonary mycoses are generally classified into endogenous mycoses (actinomycosis, moniliasis, and geotrichosis), endogenous-exogenous mycoses (cryptococcosis, aspergillosis, and mucormycosis) and texogenous mycoses (nocardiosis, coccidioidomycosis, histoplasmosis, North American blastomycosis).

Daniela Pasero from Italy and her colleagues were probably the first to report the emergence mucormycosis as a serious complication of covid-19 disease in Italy. They reported the first patient with covid-19 complicated by extensive cavitary pulmonary mucormycosis.

Christoph Zurl from Austria and his colleagues were probably the first to report the emergence mucormycosis as a dangerous fatal complication of covid-19 disease in Austria. They reported report a 53-year old male who had secondary acute myeloid leukemia who died from covid-19 postmortem autopsy examination established the diagnosis of pulmonary mucormycosis caused by *Rhizopus microsporus* [11].

Anne-Pauline Bellanger from France and her colleagues were probably the first to report the emergence mucormycosis as a serious complication of covid-19 disease in France. They reported mucormycosis caused by *Rhizopus microsporus* occurring in association with *Aspergillus fumigatus* infection in a patient with severe covid-19 disease.

Mrittika Sen and her colleagues from India reported six males observed during the period from first of August to December, 15, 2020, who had covid-19 complicated by rhino-orbital mucormycosis. Two of the patients were diabetic. The six patients received systemic corticosteroids for the treatment of covid-19. The patients received intravenous liposomal amphotericin B plus posaconazole and required endoscopic sinus debridement of necrotic tissue. Two patients of the six required orbital exenteration. Treatments of the six patients were considered successful.

Salomon Waizel-Haiat from Mexico and his colleagues were probably the first to report the emergence mucormycosis as a serious complication of covid-19 disease in Mexico. They reported a 24-year-old female patient who had new onset diabetic ketoacidosis and developed covid-19 complicated by acute fatal rhino-orbital mucormycosis.

Anubhav Kanwar and his colleagues from Alabama, USA reported a 56-year-old male patient who was hospitalized for covid-19, and treated with methylprednisolone and tocilizumab, but he died following developing mucormycosis pneumonia caused by *Rhizopus azygosporus*.

Moorthy et al from Bangalore, India reported 18 patients who had covid-19 complicated by maxillofacial/rhino-cerebro-orbital fungal infections including 16 patients with mucormycosis, one patient with aspergillosis, and one patient had a mixed fungal infection. 16 patients were treated with steroids for covid-19 treatment and sixteen patients were diabetic and 15 of them received steroids. Loss of vision was observed in twelve patients including seven underwent orbital exenteration. Eleven patients survived, six died and one could not be followed [11].

Alekseyev et al from Denver, USA reported a 41-year-old male with type 1 diabetes mellitus who developed covid-19 pneumonia complicated by rhinocerebral mucormycosis. He was treated with steroids, hydroxychloroquine, cefepime and three surgical debridements for the rhinocerebral mucormycosis. The pneumonia improved during hospitalization, and treatment of rhinocerebral mucormycosis was considered successful.

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Dallalzadeh et al from California, USA reported the death of two diabetic covid-19 patients because of rhino-orbital-cerebral mucormycosis. Both patients were treated with steroids, and developed ketoacidosis.

Mekonnen et al from University of California, San Francisco reported a patient with covid-19 who developed acute invasive fungal rhino-orbital mucormycosis.

Werthman-Ehrenreich from University at Buffalo, New York, reported a previously healthy 33-year-old female who developed covid-19 and complicated by mucormycosis and orbital compartment syndrome. The patient presented with altered mental status and proptosis.

Sarkar et al from India reported ten diabetics patients observed during October and November, 2020, who had covid-19 complicated by orbital mucormycosis. Four patients had diabetic ketoacidosis on admission, and another five patients developed diabetic ketoacidosis after receiving intravenous dexamethasone for covid-19 disease. Four patients received also an injection of remdesivir for covid-19, and nine patients required ventilatory support. All patients received liposomal amphotericin B for mucormycosis. Four patients died within one month of the diagnosis, five patients survived, but developed irreversible vision loss. One patient had favorable outcomes.

Krishna et al from London, United Kingdom reported a young obese Asian male who was hospitalized because of severe covid-19 pneumonitis associated with an acute anterior cerebral artery territory infarction. He developed recurrent episodes of vasoplegic shock and multi-organ dysfunction. Autopsy established the diagnosis of disseminated mucormycosis.

Sharma et al from Jaipur, India reported 23 patients who had covid-19 disease complicated by ethmoidal sinusitis caused by mucormycosis. Intra-orbital extension was occurred in 43.47%, and intracranial extension occurred in 8.69 %. 21 were diabetic and twelve of them had uncontrolled diabetes. All patients received steroid for covid-19 disease.

Veisi et al from Iran two patients, a 40-year old female and a 54-year male who had covid-19 complicated by rhino-orbitocerebral mucormycosis in one patient and rhino-orbital mucormycosis in the other patient. Mucormycosis appeared during steroid treatment. One of the patients experienced bilateral visual loss and complete ophthalmoplegia of the right eye, while the other patient experienced loss of vision, proptosis, orbital inflammation, and complete ophthalmoplegia on the left side [11].

The patients rejected orbital exenteration and were treated with amphotericin B and endoscopic sinus debridement with irrigation with diluted amphotericin B on daily basis. One patient died and treatment was successful in the other patient.

Saldanha et al from, India reported a patient who had covid-19 disease complicated by orbital apex syndrome caused by

mucormycosis of nose and paranasal sinus. The patient required emergency endoscopic sinus surgery.

Revannavar et al from India reported a middle-aged diabetic female who had covid-19 presented by the features of left-sided mucormycosis pansinusitis and incidentally found to be positive for covid-19 test. On presentation, she had fever, hyperglycemia without ketosis left-sided facial pain, complete ptosis, total left ophthalmoplegia, and a reduced visual acuity (6/36). CT and MRI brain established the diagnosis of pansinusitis on the left side with acute infarction of the parieto-occipital region on the left side. She received amphotericin B and antibiotics, and after one week, CT brain revealed improvement in mucosal thickening and sinusitis.

Garg et al from, India reported 55-year-old diabetic male patient who had end-stage kidney disease, and developed covid-19 disease complicated by pulmonary mucormycosis, 21 days after hospitalization. The patient was treated successfully with 5 g of liposomal amphotericin B, and was discharged 54 days after admission.

Maini et al from India reported a patient with covid-19 who developed sino-orbital mucormycosis caused by *Rhizopus oryzae* on 18th day after recovery. On presentation, the patient had chemosis and pain in the left eye. Magnetic resonance imaging and functional endoscopic sinus surgery established the diagnosis of mucormycosis. Initial treatment was conservative with intravenous fluconazole and amphotericin B followed by surgical debridement. Treatment was successful with minor residual deformity.

Sai Krishna et al from India reported 50-year-old male who had uncontrolled type 2 diabetes who developed covid-19 disease complicated by mucormycosis of the right maxilla. He presented with a firm, non-tender swelling over the right side of the midface of months duration. Oral examination showed an area of alveolar necrosis in the right posterior maxillary area and swelling affecting the hard palate.

The biopsy showed thick-walled aseptate fungal hyphae with right-angled branching in P.A.S. stain. In addition to insulin, the patient was treated successfully with intravenous liposomal amphotericin B 250 mg, and surgical resection followed by oral posaconazole 300 mg.

Arana et al from Barcelona, Spain reported two renal transplant recipients who developed covid-19 disease complicated by rhino-sinus and musculoskeletal involvement, respectively [11].

The first patient was a 62-year diabetic male who was treated with non-invasive mechanical ventilation for six days, intravenous dexamethasone 6 mg daily for 10 days, ceftriaxone 1 g four times daily, azithromycin 500mg four times daily.

After improvement, he developed left maxillary sinusitis. Endoscopic debridement was performed, and culture of a swab showed voriconazole-resistant *Rhizopus oryzae* and

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caspo fungin-resistant, but was sensitive to posaconazole and isavuconazole.

The patient was treated successfully with amphotericin B and an azole (initially isavuconazole and subsequently posaconazole), and six surgical debridement procedures, including a total left maxillectomy over two months. The dose of prednisone was reduced to 2.5 mg and tacrolimus level was maintained between 6-8 ng/ml.

The second patient reported by Arana et al was a 48-year old male. His covid-19 disease was treated with hydroxychloroquine, azithromycin and lopinavir/ritonavir, and anticoagulation with prophylactic low weight heparin. Because of worsening of respiratory failure, tocilizumab 400 mg was given. Tacrolimus and mycophenolate were withdrawn, while prednisone was continued at a daily dose of 20 mg. Three weeks following hospitalization, the patient developed musculoskeletal mucormycosis caused by *Lichtheimia ramosa*, and developed pain and enlargement of lower right limb.

The patient required fasciotomy and surgical debridement of the necrotic muscles. The patient was treated successfully with liposomal amphotericin B 5mg / kg 4 times daily, isavuconazole 200 mg three times daily, and two more surgical debridements followed by three months with isavuconazole.

Nehara et al reported five diabetic patients (4 females and one male) from the north-western part of India who had covid-19 disease, treated with intravenous steroid and complicated by bilateral sinusitis and orbital cellulitis on one side, with the development of rhinocerebral mucormycosis in three of them.

The disease was caused by *Rhizopus* species, and in four patients, was caused by *Rhizopus arrhizus*. On presentation, all the patients had headache, facial swelling, proptosis on one side, ophthalmoplegia, and reduced vision.

Three patients had palatal involvement, three patients had cavernous sinus thrombosis on one side and one patient had several lacunar infarcts. The five patients received intravenous amphotericin B and one patient required debridement. One patient improved, two patients were still hospitalized, and two patients died.

Bayram et al from Kayseri City, Turkey reported that of 32,814 covid-19 patients hospitalized during the period from March 2020 and December 2020, eleven patients (9 males and 2 females; mean age of 73.1 ± 7.7 years) who had severe disease and received steroids developed rhino-orbital mucormycosis. Eight patients had uncontrolled type 2 diabetes [11].

The mean time period between the diagnosis of covid-19 disease and the diagnosis of rhino-orbital mucormycosis was 14.4 ± 4.3 days. Seven patients (63.6%) had orbital apex syndrome, and four patients (36.4%) had orbital cellulitis on presentation. Endophthalmitis occurred in 54.5% of patients, two of them developed retinoschisis.

All patients had CT scan/MRI evidence of sino-orbital involvement, and three patients had cerebral involvement on presentation. All patients received intravenous and retrobulbar liposomal amphotericin B, and required radical debridement of the affected sinuses. Intravitreal liposomal amphotericin B were used in patients with endophthalmitis. Seven patients died.

Khatri et al from New York, USA reported a heart transplant recipient male who developed covid-19 two months after heart transplant which was complicated by cutaneous mucormycosis at an old intravascular device site three months after the diagnosis of covid-19. He received convalescent plasma therapy for covid-19.

Mucormycosis was treated with extensive surgical interventions, and broad-spectrum antifungal therapy, but the patient died despite treatment.

Karimi-Galougahi et al from Iran reported a 61-year-old female who had covid-19 complicated by rhino-orbital mucormycosis. She received remdesivir, interferon-alpha, and systemic corticosteroid for covid-19, and discharged after two weeks of hospitalization. One week later, she developed right hemifacial pain without sino-nasal symptoms.

Thereafter, she developed right-sided proptosis, frozen eye, complete loss of vision, fixed mydriasis, right hemifacial numbness, chemosis, and a black eschar on the skin over the right lateral nasal wall, and malar and periorbital areas.

Although, she had no fever or respiratory symptoms, she tested positive for covid-19. It was also found that she had hyperglycemia without ketoacidosis. Sino-nasal endoscopy showed widespread necrosis of the mucosa of the lateral nasal wall on the right side, inferior and middle turbinates, and septum. In addition to insulin and systemic anti-fungal drugs, she required extensive debridement of necrotic tissue, and right eye exenteration. Examination of tissue specimens and sino-nasal secretions established the diagnosis of mucormycosis.

Ravani et al from Gujarat, India reported that of 31 patients (Mean age of 56.3 years) with rhino-orbital mucormycosis observed during the period from September 2020 to mid-March 2021, nineteen patients (61.2%) had positive for covid-19.

The most common symptom was reduced vision (80.64%) and ophthalmoplegia (77.4%). The most common imaging diagnoses were orbital cellulitis (61.29%) and pansinusitis (77.4%). All patients received intravenous liposomal amphotericin B for an average 18.93 days. Four patients required exenteration. Twenty-eight patients achieved recovery and were alive on follow-up, while three patients died [11].

Raksha Rao and her colleagues from Karnataka, India reported a 66-year-old diabetic male who had covid-19, treated with

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systemic steroids, and his illness was complicated by orbital infarction syndrome caused by rhino-orbital mucormycosis. On presentation, he had loss of vision in the left eye of sudden onset, total ophthalmoplegia and diffuses opacification of the retina.

Manar Ashour from Cairo, Egypt and her colleagues were probably the first to report the emergence of mucormycosis as a dangerous and fatal complication in Egypt. They reported six patients (3 males and 3 females) who had covid-19 disease complicated acute invasive rhino-orbital-cerebral sinusitis, and resulted in the death of two patients.

The first patient was a 65-year-old diabetic female who was hospitalized because of covid-19 disease which was complicated by invasive rhino-orbital-cerebral sinusitis mucormycosis. In the second week after hospitalization, she developed rapidly progressive edema of the right upper eyelid, chemosis of the conjunctiva, reduced vision, complete ophthalmoplegia on the right side and black nasal crusts. CT-MRI imaging showed ethmoidal and maxillary sinusitis on the right side, with orbital infiltration affecting the right optic nerve, right cavernous sinus partial thrombosis with secondary vasculitis of the cavernous segment of the internal carotid artery, and right posterior watershed acute infarctions. The patient was successfully treated with surgical debridement and postoperative amphotericin B for two weeks and followed by itraconazole.

The second patient was a 67-year-old diabetic male with chronic renal disease who had covid-19 disease complicated by invasive rhino-orbital mucormycosis with right orbital panophthalmitis. On presentation he had rapidly progressive reduction of right eye visual acuity, conjunctival chemosis, mild orbital proptosis, nasal crusts, and respiratory distress. He received amphotericin B, but the patient died without performing surgical debridement.

The third patient was a 42-year-old diabetic male who had a recent cerebral infarction and developed covid-19 disease complicated by invasive rhino-orbital mucormycosis with by right paralytic esotropia, right nasal black crusts, and bilateral oroantral fistulae. The patient was treated successfully with amphotericin B and endoscopic surgical debridement, but he required palatal reconstruction.

The fourth patient was a 63-year-old diabetic female patient who had covid-19 disease complicated by rhino-sinusitis caused by mucormycosis, with the development of left upper eyelid edema, decreased visual acuity, left ophthalmoplegia, and blackish nasal crusts. The patient was treated successfully with endoscopic surgical debridement and postoperative systemic antifungal.

The fifth patient was a 41-year-old diabetic female patient who was hospitalized because of covid-19 disease which was complicated by invasive rhino-sinusitis caused by

mucormycosis, with erosions of the nasal septum, hard palate, maxillary sinus wall pterygoid plates, and clivus [11].

On the fourteenth day of hospitalization, she developed progressive facial edema. She was treated successfully with surgical debridement and amphotericin.

The sixth patient was a 50-year-old diabetic male who had covid-19 complicated by invasive rhino-sinusitis caused by mucormycosis with development of left panophthalmitis. He had left painful orbital proptosis, reduction of vision, total ophthalmoplegia, blackish nasal crusts, septal ulceration and, septal perforation. The patient required surgical endoscopic debridement and left orbital enucleation. The patient died on the fifteenth day of hospitalization after significant progression of the left frontal-temporo-parietal infarctions.

Hari Shankar Meshram et al from Gujarat, India reported two renal transplant recipients with who developed post-covid-19 mucormycosis. The first patient was a 47-year diabetic male, before transplanted 17 years ago. He developed mild covid-19 disease for 7 one week. After discharge, he developed invasive sinusitis of left orbital, left pre-maxilla and infra-temporal fossa cellulitis with minimal dural enhancement in the left middle cranial fossa.

On presentation, he had swelling over the face and a black nasal discharge. The patient required left maxillectomy, left orbital exenteration, left zygotomy, removal of the nasal septum, and palate reconstruction with temporal flap. However, the patient died on the 51st day from the onset of covid-19.

The second patient was a 25-year diabetic male, transplanted before two years who developed pulmonary mucormycosis ten days after improvement of covid-19 disease. He developed fever, cough, and black expectoration, and was treated with amphotericin, but died on the 49th day from the onset of covid-19 disease.

Pakdel et al from Iran reported 15 patients (10 male, 5 females), aged 14-71 years, who had covid-19 complicated by rhino-orbital mucormycosis.

The median time between covid-19 disease and diagnosis of mucormycosis was seven (range: 1-37) days. Thirteen patients (86%) were diabetic, seven (46.6%) were treated with intravenous corticosteroid.

Five patients (33%) required orbital exenteration, and seven (47%) patients died from mucormycosis. Six patients (40%) were treated with combined anti-fungal therapy and none of them died [11].

Conclusions

Mucormycosis is a rare disease that is generally associated with diagnostic difficulty and delay, high morbidity, catastrophic outcome, and mortality.

Diabetes mellitus and use of corticosteroids increase the risk of the development of invasive mucormycosis which may

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appear during the course of the covid-19, or appear as a later complication. Hyperglycemia induced impaired chemotaxis and phagocytosis of neutrophils, steroid-induced immunosuppression, and covid-19 induced immune dysregulation associated with decreased numbers of T lymphocytes, CD8+T, and CD4+T cells were considered the important factors that led to the emergence of invasive mucormycosis as a catastrophic and fatal complication of covid-19 disease.

Mucormycosis can be rapidly progressive, requiring immediate surgical and medical interventions.

High index of suspicion can contribute to making an early diagnosis, and providing early aggressive management which can improve survival. Upon suspicion of mucormycosis appropriate imaging is advised to determine extent of disease.

First-line treatment is generally including the use of a high-dose liposomal amphotericin B. Other antifungal drugs that have been used include isavuconazole and posaconazole.

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References

1. Cohnheim J. Zwei fälle von mykosis der lungen. Virchows Arch Path Anat 1865; 33:157. <https://doi.org/10.1007/BF02134954>
2. Furbringer P. Beobachtungen uber lungenmycose beim menschen. Arch Pathol Anat Physiol Klin Med 1876:66330-65.
3. Podack, M. Zur Kenntniss des sogenannten Endothelkrebses der Pleura und der Mucormycosen, im menschlichen Respirationsapparate. Deutsches Arch. F klin Med 1899; 63, I-73.
4. Lang FJ, Grubauer F. Über Mucor- und Aspergillusmykose der Lunge. Virchows Arch F path. Anat 1923: 245: 480-512.
5. Wätjen. Pathologisch-anatomische Demonstrationen. Klin Wchnschr 1929; 8: 280.
6. Paltauf A. Mycosis mucorina. Virchows Arch F Path. Anat 1885; 102: 543-564.
7. Gregory JE, Golden A, Haymaker W. Mucormycosis of the central nervous system: a report of three cases. Bull Johns Hopkins Hosp 1943; 73:405-419.
8. Georgiade N, Maguire C, Crawford H, Pickrell K. Mucormycosis and palatal sloughs in diabetics. Plast Reconstr Surg (1946). 1956 Jun; 17(6):473-6. Doi: 10.1097/00006534-195606000-00008. PMID: 13349496.
9. Lecompte PM, Meissner WA. Mucormycosis of the Central Nervous System Associated with Hemochromatosis: Report of a Case. Am J Pathol 1947 Jul; 23(4):673-7. PMID: 19970953.

10. Baker RD, Severance AO. Mucormycosis, with report of acute mycotic pneumonia. Am J Pathol 1948 May; 24(3):716. PMID: 18859399.

11. Al-Mosawi AJ. Mucormycosis: An emerging dangerous complication of Covid-19 disease. Scholars' Press, June 2021 (ISBN: 13: 978-613-8-95508-5, ISBN-10: 613895 5080).

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