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Research Article

Clinico-epidemiological Profile of COVID-19 Associated Invasive Fungal Rhinosinusitis Reported in the Teaching Hospital of Diwaniya, Qadisiya Province, Iraq: A Case Series

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I N F O

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A B S T R A C T

Introduction: With the current COVID-19 pandemic, the increasing use of glucocorticoids has resulted in more adverse effects and secondary bacterial or fungal infections.

Objective: To find out the clinic-epidemiological profile of patients having COVID-19 associated invasive fungal rhinosinusitis in Diwaniya teaching hospital- Qadisiya province - Iraq.

Method: Retrospective case series study of 24 patients with COVID-19 who were admitted to Alshafa centre in Al-Diwaniyah Province from 1st of May 2020 to end of August 2021. Patients were moderate to severe COVID-19 received treatment according to local guidelines. Patients who developed signs and symptoms of nose and paranasal sinuses disorder were seen by otolaryngologists and treated by a multidisciplinary team if invasive mucormycosis and its comorbidities were detected.

Results: Out of 24 patients, 8 were female and two patients were excluded because their histopathological examination hasn't confirmed acute invasive fungal rhinosinusitis. The average age was 54 years old, they all had diabetes, 2 patients had chronic kidney diseases, and 2 patients had malignancy (leukaemia). Furthermore, 19 patients were with severe SARS-COV-2 while 5 patients had moderate symptoms. All patients were confirmed COVID-19 positive by PCR test.

Conclusion: Invasive fungal infections of the nose and paranasal sinuses are highly lethal conditions with significant morbidity. Early recognition and high index of suspicion are needed in the case of COVID-19 patients who complain features of sinusitis with careful prescription of drugs that affect immune response in COVID-19 patients.

Keywords: Invasive Fungal Infection, Corona, Mucormycosis, Steroid

Introduction

Invasive fungal infections are characterised by tissue infiltration by fungal elements and necrosis. These forms are acute invasive fungal rhinosinusitis, chronic invasive fungal rhinosinusitis, and granulomatous fungal rhinosinusitis.[1]

Acute invasive fungal rhinosinusitis (AIFRS) is considered one of the most severe of the three mentioned types. This kind usually occurs in immunocompromised patients resulting in the rapid development of infection.

The medical treatment evolution of these comorbid diseases leads to an increase in the population of the immune-compromised patient in the community. However, increased survival has also resulted in a larger population at risk of exposure to invasive fungal rhinosinusitis.[2]

AIFRS is the most life-threatening and challenging manifestation of all others forms of rhinosinusitis of fungal aetiology with rapid disease progression, significant complications, and elevated mortality rate. The main predisposing condition for the development of AIFRS is an impaired immunity with an altered neutrophil response. Neutropenia is recognized when absolute neutrophil counts below 500 cells/ µL. Even though, some patients with poorly controlled diabetes mellitus also developed functional neutropenia despite normal neutrophils count which is also strongly associated with the development of AIFRS.[3]

Immune compromised patient is the result of a variety of medical disorders, including diabetes mellitus, organ transplantation, aplastic anaemia, acquired immunodeficiency syndrome, hematologic malignancies, and hemochromatosis. Iatrogenic immunosuppression with chemotherapy drugs and prolonged use of systemic steroids also make individuals susceptible to AIFRS. However, rare cases of AIFRS have been reported in the literature immune-competent patients.[4]

Histopathology for AIFRS shows a direct fungal invasion of the nose and paranasal sinuses mucosa, in particular, the hyphal forms that extend into the mucosa, submucosa, blood vessels, or bones of the sinonasal cavity. Additionally, areas of coagulative necrosis with a presence of mild inflammatory response also can be seen. Since the fungi involved in AIFRS tend to invade surrounding blood vessels, the resulting angioinvasion is eventually accompanied by vasculitis with thrombosis, eventually leading to tissue infarction and haemorrhage on histopathology.[5] Aspergillus species and the fungi in the order of Mucorales (e.g., Rhizopus, Rhizomucor, and Mucor) are the most commonly implicated species.[6]

Rapid disease progression has been reported with mortality rates of 50% to 80% due to intraorbital and intracranial complications when early diagnosis and optimal treatment are not established. Improving the immune response of the host is of utmost importance for survival. Surgical intervention is essential to stop or slow the progression of the disease (to allow time for the bone marrow to recover), to reduce fungal contamination, and provide tissue culture.[2]

Empirical treatment with a broad-spectrum antifungal agent (intravenous amphotericin B) is highly recommended before definitive identification of the causative fungi.[7]

With the current Coronavirus Disease 2019 (COVID19) pandemic, there has been a desperate search for therapeutic options for the various drugs that have been tried with varying degrees of success. However, the use of systemic glucocorticoids has been shown to improve survival in COVID-19. Unfortunately, the increasing use of glucocorticoids has resulted in an increase in the adverse effects of these drugs, particularly, in cases of secondary bacterial or fungal infections.[8]

This article presents the clinic-epidemiological profile of patients having COVID-19 associated invasive fungal rhinosinusitis in Diwaniya teaching hospital - Qadisiya province - Iraq.

Method

A case series study was approved by the ethical committee of the University of Al-qadisiyah College of Medicine,informed consent obtained from patients with SARS-COV-2 who were admitted to Alshafa centre for COVID-19 in Diwaniya province from 1st of May 2020 to end of August, 2021. patients with PCR for covid 19 negative or nasal biopsy not shown invasive fungal rhinosinusitis were excluded from study. SPSS24 used in ststical analysis The total number of patients was 24, with moderate to severe COVID-19. The patients were admitted to this centre and received treatment according to local guidelines and to the condition of each case. The patients who had signs and symptoms of nose and paranasal sinuses disorder were seen by otolaryngologists. Full ENT examination, HbA1c, radiological studies, middle meatus nasal swab for culture and sensitivity were done. Tissue biopsies were taken from the suspected areas and sent for histopathological examination all patients suspected acute invasive fungal rhinosinusitis. The patients were treated by a multidisciplinary team with the aim of urgent treatment of invasive mucormycosis and its comorbidities. Medical treatment in form of systemic and topical (retrobulbar) antifungal amphotericin, surgical debridement by Sino nasal endoscopic and conventional procedures were done and individualised according to disease extension.

Results

24 patients were included in the study (8 of them were female) whereas two patients were excluded because

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the histopathological examination hasn't confirmed acute invasive fungal rhinosinusitis. The average age was 54 years old, they all have diabetes, 2 patients have chronic kidney diseases, and 2 patients have malignancy (leukaemic patient)as in Figure 3.

Furthermore, 19 patients were with severe SARS-COV2 while 5 patients have a moderate infection as shown in Figure 1. All patients were confirmed having COVID-19 by PCR test, nasal obstruction 23 patients (95.83%), headache 20 patients (83.3%) eye swelling 22 patients (91.66%), facial pain or swelling 16 patients (66.66%) and were the common presentation with other symptoms as reduced or no vision and toothache. Examination demonstrated, proptosis in 12 patients (50%), ptosis in 4 patients (16.66%), vision loss in 4 patients (16.66%), complete ophthalmoplegia in 5 patients (20.83%) and palate involvement 8 patients (33.33%) as shown in Table 1. 16 patients received steroids, all patients received broad-spectrum antibiotics, 10 patients were treated with Actemra (tocilizumab), 12 patients received remdesivir injections as in Figure 4, 21 patients developed acute invasive fungal sinusitis during admission, 3 after discharged Figure 2, 14 patients need admission to ICU, oxygen supplement modalities were 2 patients intubated, 12 patients on CPAP and 10 patients on face mask oxygen supplement Figure 5, three lost their vision in a single eye, one developed blindness in both eyes asresult of development of cavernous sinus thrombosis, two undergone orbital exenterating whileendoscopic orbital decompression were done for two cases one of them retained vision, three managed with medial maxillectomy, eight patients died from fungal infection despite their recovery from COVID-19 infection.

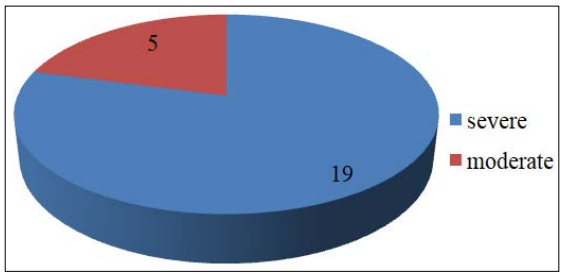

Figure 1.Severity of SARS-COV-2 Infection

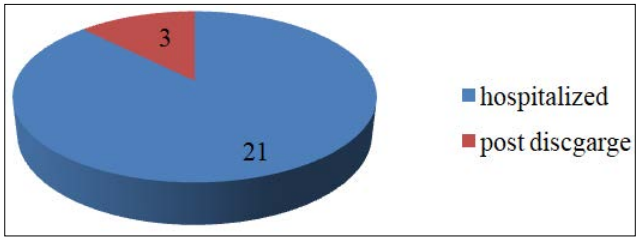

Figure 2.Time of Diagnosis of COVID-19 associated Invasive Fungal Infection

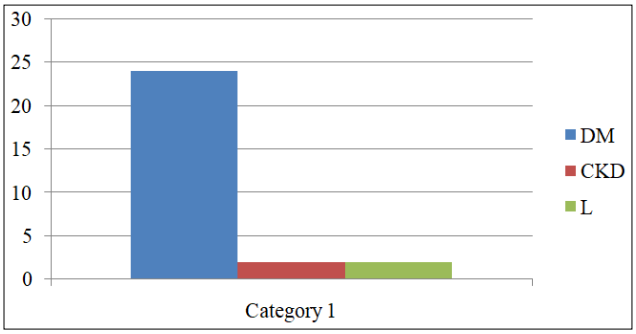

Figure 3.Pre-existing Diseases in COVID-19 associated Fungal Infection

DM: Diabetic; CKD: Chronic kidney diseases; L: Leukaemia

Table 1.Presentation and Clinical Findings

Clinical Finding	No. of Patients	Percentage
Nasal obstruction	23	95.83
Headache	20	83.3
Eye swelling	22	91.66
Facial pain or swelling	16	66.66
Proptosis	12	50
Ptosis	4	16.66
Loss of vision	4	16.66
ophthalmoplegia	5	20.83
Palate involvement	8	33.33

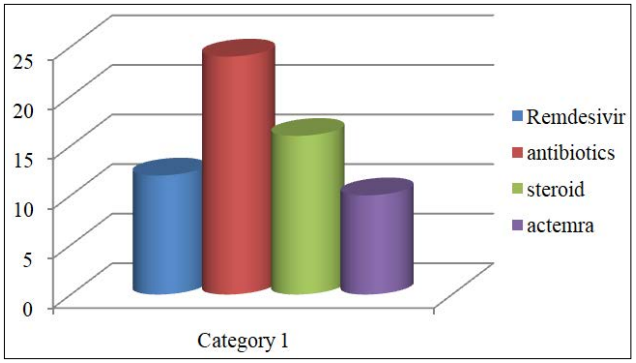

Figure 4.Drugs used During Hospitalisation

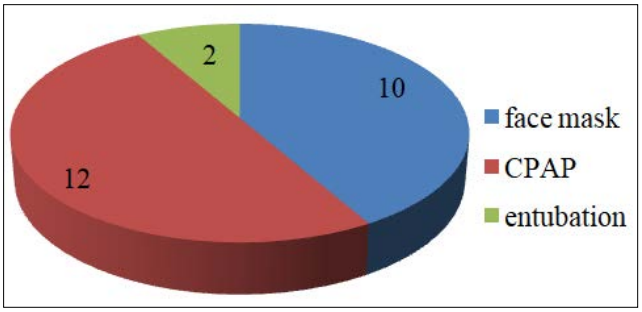

Figure 5.Oxygen Supplement Modality

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Discussion

Mucormycosis is a rare and fatal fungal infection caused by the Mucoraceae family, which belongs to the Phygomycetes or Zygomycetes class.[9] This fungus is generally found as the commensal of the nasal mucosa and can germinate in the nasal cavity and sinuses and invade the roof of the mouth, eye sockets, and brain, often causing death, in immunosuppressive conditions such as diabetes, ketoacidosis, solid organ transplant, severe burns, etc.[10]

Since the end of 2019, the emergence of the COVID-19 pandemic so far, no effective treatment was approved apart from trial treatment of steroids, oxygen supplement, and tocilizumab. Although the use of steroids is associated with the risk of secondary infection such as fungal infection.

In this study, all patients are diabetics and received broad-spectrum antibiotics (in the mentioned centre, unfortunately, all our patients either received levofloxacin with ceftriaxone or meropenem which are broad-spectrum antibiotics and associated with a high incidence of opportunistic infection). Half of them received remdesivir while ten received tocilizumab.

The treatment included control of blood sugar, liposomal amphotericin, surgical debridements (in form conventional endonasaldebridement, endoscopic under local anaesthesia, medial maxillectomy, orbital decompression and orbital exoneration).

The mortality rate was 33.33% (8/ 24) in comparison to 50-80% mortality rates from intra-orbital and intracranial complications have been reported by Gillespie MB et al.[2] which may be due to early recognition of fungal rhinosinusitis because otolaryngology doctors had regular duty in COVID-19 care centre due to shortage of doctors during the pandemic.

It is believed that the emergence of new cases of rhino-orbital invasive fungal rhinosinusitis is due to multifactorial aetiology including uncontrolled diabetes, corticosteroids therapy and broad-spectrum antibiotics overuse while the role of prescription of an interleukin-6 (IL-6) receptor antagonist Actemra (tocilizumab) and the use of antiviral agents as remdesivir needs further investigation and studies to establish their role.[11] A lot of supplements such as Zinc are practised in different countries without causing a notable increase in mucormycosis cases. For all eukaryotes, zinc is an essential micronutrient and is a key factor in pathogenic fungus such as Aspergillus, Candida, and others' pathogenicity and growth, and in our country, it's given as part of multivitamins and other supplements in the daily required dose and not routinely given in a high dose of the isolated supplement so its role in the development of invasive fungal rhinosinusitis cannot established. regarding steroid therapy patients given dexamethasone injections 6 mg per day for ten days as WHO recommends the use of steroids in hypoxemic COVID-19 patients to decrease the inflammatory response, although steroids side effects such as decrease leucocytes phagocytic activity, impaired immune response, development of hyperglycaemia and opportunistic infection, there us is a double sword in COVID-19 patients.

Although the role of coronavirus infection in impairment of host immunity and the development of diabetes due to virus effect on the pancreas which in result leads to spikes of opportunistic infection still needs to be established.[12]

Conclusion

Invasive fungal infections of the nose and paranasal sinuses are highly lethal conditions with significant morbidity, early recognition and high index of suspicion is needed in COVID-19 patients who complain of severe headache, facial pain, or other features of sinusitis with careful prescription of drugs that affect immune response in COVID-19 patients. Finally, more studies are required to establish if there is a direct relationship between COVID-19 and invasive fungal rhinosinusitis as its role is neither rejected nor accepted till now.

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Conflict of Interest: None

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