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Research Paper

Features and evaluation of mucormycosis in COVID-19 patients from two referral hospitals in Iran

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ABSTRACT

Objectives: The present study aimed to assess the features, clinical characteristics, and species diversity among patients admitted to referral Hospitals for SARS-CoV-2 pneumonia and mucormycosis in Tehran, Iran, and the relationship between seasonal and species diversity was considered.
Methods: Confirmed COVID-19 patients with a positive reverse-transcriptase real-time (rRT-PCR) test for SARS-CoV2 were primarily included based on clinically suspected mucormycosis infection and confirmed by histopathology and mycology examination of biopsy specimens. The PCR technique was performed by the amplification of the high-affinity iron permease 1 (FTR1) gene for identification and discrimination between *Rhizopus arrhizus* and non- *Rhizopus arrhizus* isolates. In contrast, species identification of non-*Rhizopus arrhizus* was performed by sequencing of ITS rDNA region.
Results: Rhino-sino-orbital mucormycosis was identified in the majority of cases (n = 33), with 66 % and 34 % of the cases involving male and female patients, respectively. *Rhizopus arrhizus* was found to be the most prevalent (84.6 %), followed by *Mucor circinelloides* (7.6 %). *Rhizopus arrhizus* was the most prevalent species and present in all the seasons; however, *Mucor circinelloides* was only present in the autumn. The overall mortality of the total population was 24.6 % (16/ 65); the mortality rates occurring in patients diagnosed with rhino-sino-orbital infection and rhino-sinusal form were 21.4 % and 25 %, respectively.
Conclusion: CAM can be a serious complication of severe COVID-19, especially in patients with uncontrolled diabetes. It is important to monitor the epidemiology of mucormycosis to raise awareness of the disease and improve diagnosis, treatment and prognosis, particularly in the setting of pandemic.

1. Introduction

More than 670 million people had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide and 6.82 million related deaths as of 30 January 2023 (WHO), however many countries are still dealing with outbreaks of the coronavirus disease 2019 (COVID-19) and its complications. The virus causes hyperactivation of the cytokine response and consequent immune suppression. Corticosteroids, anti-interleukin-6 (IL-6), anti-interleukin-1 (IL-1), and inhibitors of the JAK-STAT pathway are usually used to modulate the immune system [1]. Immunological and clinical factors with the immune suppression caused by the SARS-CoV-2 can lead to fungal infections [2]. The fungal secondary infections increase disease severity and mortality, especially in patients with invasive mechanical ventilation [3]. Aspergillosis, candidiasis, and mucormycosis are the most commonly reported COVID-19-associated (CAM) fungal infections in COVID-19 patients [4,5]. Mucormycosis is a rare

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opportunistic and invasive infection caused by fungi in the order of Mucorales [6-8]. Potential risk factors for developing mucormycosis included uncontrolled diabetes mellitus, hematological malignancy, human immunodeficiency virus infection, immunocompromised hosts, solid organ and bone marrow transplantation, use of immunosuppressants (e.g., corticosteroids), treatment with deferoxamine, and extensive burns or major trauma [9]. Reports of mucormycosis in otherwise healthy individuals are very rare; however, the importance of mucoralean fungi infection has increased in recent years owing to the COVID-19 pandemic [10]. The present study aimed to assess the features, clinical characteristics, and species diversity among patients admitted to referral Hospitals for SARS-CoV-2 pneumonia and mucormycosis in Tehran, Iran, and the relationship between seasonal and species diversity was considered.

2. Materials and methods

Study design

A cross-sectional descriptive study with follow-up was conducted in two referral hospitals in Tehran, Iran, namely 700-bed Rasool Akram and 358-bed Amir A'lam from February 2020 to November 2021 on proven rhino-orbito-cerebral mucormycosis (ROCM) [11]. We included patients with mucormycosis during or within 12 weeks after a diagnosis of COVID-19 based on previous studies [2,12,13].

Patient details

Confirmed COVID-19 patients with a positive RT-PCR test for SARS-CoV2 (targeting the *N* and *RdRp* genes) were primarily included based on clinically suspected mucormycosis and confirmed by histopathology and mycological examination of the biopsy specimens [14]. Radiological assessment was performed using MRI and CT scans. The COVID-19 infection was categorized based on world health organization (WHO) guidelines: mild, moderate, and severe. Patients with possible ROCM and a history of COVID-19 for more than 12 weeks have been excluded. Data on demographics, clinical characteristics, history of the underlying condition, hospital stay, clinical manifestations, radiological features, mycological findings, diagnostic method, treatments, and outcomes were collected. This study was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (IR.IUMS.REC.1400.1128). Informed and written consent was obtained from all patients.

Mycological examination

Direct examination of biopsy specimens was performed by mounting in 10 % potassium hydroxide. Subsequently, they were inoculated onto Sabouraud dextrose agar (SDA; Difco, Leeuwarden, The Netherlands) supplemented with 0.02 % chloramphenicol. The plates were incubated at 35 °C for 7 days to isolate Mucorales and initial identification was performed based on the macroscopic and microscopic characteristics. All identified isolates were suspended in a tryptic soy broth medium (TSB, Scharlau, Spain), containing 2 % peptone, 2 % glucose, and 20 % glycerol, at −80 °C for further analysis. Genomic DNA was extracted from biopsy tissues or 2-to 3-day-old cultures grown on 4 % Malt Extract Agar (MEA; Becton Dickinson) by using a DNA extraction kit (Add bio, Korea) with brief modification at the first step, which fungal elements or biopsy tissues were transferred to a tube containing acid-washed glass beads with 0.5 ml of kit lysis buffer. Then, the samples were homogenized for 10 min at maximum speed using a vortex adapter, followed by 1 h of incubation in a thermo-mixer at 68 °C and finally all steps run according to the instructions of the manufacturer and DNA was stored at −20 °C prior to use. Identification of *Rhizopus arrhizus* isolates was achieved by PCR amplification of the high-affinity iron permease 1 (*FTR1*) gene using the primers Rho3 (5'-GATCATGATCACTGCCAT-3') and Rho2 (5'-GCGGTWGAGACTCTGTARCYA-3') as previously described [15]. Briefly, the amplification was performed with an initial cycle of 5 min at 95 °C for primary denaturation, followed by 35 cycles of the 30 s at 94 °C, 30 s at 68 °C, and 1 min at 72 °C with a final extension step of 10 min at 72 °C. The PCR products were analyzed in 1 % agarose gels with producing fragments ranging from 465 bp [15]. In contrast, species identification of non- *Rhizopus arrhizus* was carried out by sequencing the ITS-rDNA region. Briefly, the PCR amplification of the ITS-rDNA region was performed using the universal primers, namely ITS1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS4 (5'-TCCTCCGCTTATTGATATGC-3'). Sequence data were aligned manually using MEGA 5.05 and BioEdit (Version 7.0.9, Alignment, BioEdit Sequence 2011) software packages. Sequencing was performed on an ABI 3730 automatic sequencer (Applied Biosystems, Foster City, CA). Sequence data were adjusted using the SeqMan of Lasergene software (DNAStar Inc., Madison, WI, USA) and compared with the GenBank database and submitted to GenBank database (http://blast.ncbi.nlm.nih.gov/Blast.cgi).

Statistical analysis

All data were analyzed in SPSS software (Version 19.0, IBM Corporation, Armonk, NY, USA). Data were presented as percentages, frequencies, or median and IQR.

Results

During the study period, a total of 65 patients with a history of SARS-CoV-2 pneumonia were admitted to referral Hospitals due to mucormycosis. The median age of patients was 51.7 years (range of age 5−85 years), and 47(72.3 %) patients were male. The male population was slightly younger (median 52.5 years, IQR 40.3−60) than the female one (median 57.5 years, IQR 51−65.7). At least one underlying comorbidity was present in 70.8 %. The prevalent underlying condition included diabetes mellitus (50.8 %; *n* = 33) and hypertension (16.9 %; *n* = 11). Of the 33 patients diagnosed with diabetes, 22 (66.6 %) were male (male to female ratio of 2: 1) with ages that ranged from 35 to 85 years. Among the diabetic patients, hypertension and ischemic heart disease were concomitantly associated in 8 and 6 cases, respectively and 17 cases had no underlying diseases. Epidemiological and clinical characteristics are detailed in Table 1. A total of 47 patients received systemic corticosteroids for the treatment of COVID-19 and 72.3 % (*n* = 47) and 20 % (*n* = 13) of patients had a history of severe and moderate COVID-19, respectively. We categorized the patients with CAM into four distinct groups based on the main localization of mucormycosis; 1) rhino-sinusal, 2) rhino-sino-orbital, 3) rhino-orbito-cerebral, and 4) systemic. Rhino-sino-orbital mucormycosis was identified in the majority of cases (*n* = 33), with 66 % and 34 % of the cases involving male and female patients, respectively. The median age of patients diagnosed with rhino-sino-orbital mucormycosis was 55 years, and diabetes was the most commonly diagnosed concomitant disease, occurring in 22 (68.7 %) of these patients. 21 out of 28 patients were male and diagnosed with rhino-sinusal mucormycosis. However, 4 (6.2 %) and 1(1.5 %) patients were included in rhino-orbito-cerebral and systemic groups, respectively (Fig. 1). Generally, headache (*n* = 21, 32.3 %), swelling of organs (*n* = 15, 23.1 %), and loss of visual acuity (*n* = 11, 16.9 %) were the most frequently encountered signs and symptoms of infection. The culture was performed in 65 cases with positive and negative culture results obtained in 18 (27.7 %) and 47 (72.3 %) cases respectively. *Rhizopus arrhizus* was the most prevalent (*n* = 55, 84.6 %), followed by *Mucor circinelloides* (*n* = 5, 7.6 %). Two *Mucor* isolates have not been identified to the species level based on DNA amplification of ITS and three isolates remained unknown. 47.7 % (*n* = 31), 44.6 % (*n* = 29), 6.2 % (*n* = 4), and 1.5 % (*n* = 1) of cases were reported in autumn,

Table 1
Demographical, comorbidities and symptoms of 65 COVID-19-associated mucormycosis (CAM) cases.

Epidemiological and clinical characteristics of patients		
	All patients (n = 65)	p- value
Patient characteristics		
Age-Median (range of age), in years	51.7 (5–85)	
Male sex, n (%)	47 (72.3 %)	0.021
Comorbidities	**Nr of cases (%)**	
Diabetes mellitus	33 (50.8)	
Hypertension	11 (16.9)	
Ischemic heart disease	9 (13.8)	
Aplastic anemia	2 (3.1)	
Hypothyroidism	2 (3.1)	
Kidney transplant	1 (1.5)	
Acute myeloid leukemia	1 (1.5)	
No underlying diseases	17 (26.2)	
Symptom at admission	**Nr of cases (%)**	
Headache	20 (32.3)	
Swelling of organs	15 (23.1)	
Loss of visual acuity	11 (16.9)	
Parasthesia	8 (12.3)	
Facial paralysis	6 (9.2)	
Facial pain	5 (7.7)	
Dental loosening	5 (7.7)	
Dizziness	3 (4.6)	
Nasal obstruction	3 (4.6)	
Fever	1 (1.5)	
Laboratory values at admission	**Nr of cases (%)**	
White blood cell count <4000 cell/uL	7(10.7)	
C-reactive protein > 5 mg/dL	65 (100)	
Erythrocyte sedimentation rate >35mm	39 (60)	

summer, winter, and spring, respectively (Fig. 1). Interestingly, *Rhizopus arrhizus* was prevalent and present in all seasons; however, *Mucor circinelloides* was only present in the autumn. Of the 65 cases, 92 % (n = 60) of the patients were under a form of anti-fungal therapy. Of which, 59 were prescribed with amphotericin B and one was prescribed with voriconazole. As well as, one patient was treated with amphotericin B in combination with voriconazole. 94 % (61of 65) of patients were treated with a combination of surgery and antifungal therapy, resulting in the survival of 78.7 % (48 of 61) of the patients in this group. Three patients underwent surgery only, and the survival rate within this group was 33.3 % (one of three). One patient did not receive any treatment. The median length of hospital stay and the median duration of ICU stay were 38 and 30.5 days, respectively. The median interval time between the onset of COVID-19 and the first symptoms of mucormycosis was 20 days. The overall mortality of the total population was 24.6 % (16/ 65), with the mortality rate occurring in patients diagnosed with rhino-sino-orbital infection and rhino-sinusal form 21.4 % and 25 %, respectively.

3. Discussion

COVID-19 is considered a new public health concern threatening worldwide [16]. Recently, less attention has been paid to opportunistic infections, which could be due to COVID-19 and its consequent long-term hospitalization of patients, and increased workload in healthcare [17]. The current study reported features, clinical characteristics, and the relationship between seasonal and species diversity in COVID-19 patients with mucormycosis, as an opportunistic infection, in two academic Iranian hospitals. In the current study, we reported 65 patients who were affected by COVID-19 pneumonia throughout twenty months and we found a 24.6 % mortality rate. The main results are as follows: diabetes (50.8 %) and systemic corticosteroid (72.3 %) therapy were present in large proportions of patients. Rhino-sino-orbital mucormycosis was the most frequent presentation of the disease (49.2 %). The most CAM cases were reported in autumn, *Rhizopus arrhizus* was the most prevalent species and present in all the seasons, and amphotericin B therapy and surgery were the predominant treatment strategies. Hoenigl et al. reported a male bias in the development of CAM, [17] and in the present study, a significant proportion of the patients were male (72.3 %). It is interesting to note that we found a significant difference in the male to female ratio between patients diagnosed with rhino-sinusal mucormycosis (male to female ratio of 3: 1) and patients diagnosed with rhino-sino-orbital mucormycosis (male to female ratio of 2: 1). However, no significant differences were found in the mortality rates between male and female patients. The reasons for differences in the population of mucormycosis between sexes remain unknown, but it may be due to gender difference in Covid-19 patients. The major risk factors for mucormycosis in patients with COVID-19 are uncontrolled diabetes, followed by the use of corticosteroids, and hypertension [12,18]. In the current study, the most commonly identified underlying

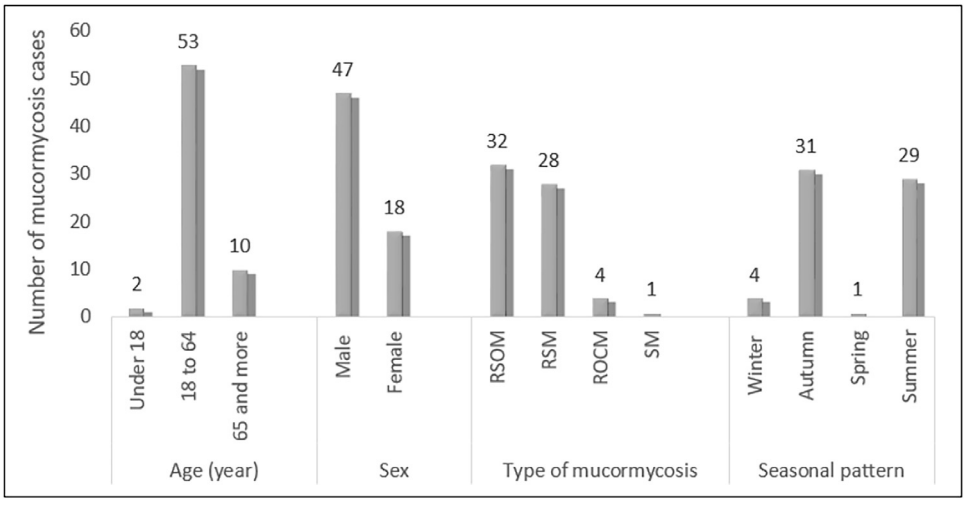

Fig. 1. Distribution of 65 COVID-19-associated mucormycosis (CAM) cases by age groups, sex, infection type, and seasonal pattern. RSOM: Rhino-sino-orbital mucormycosis, RSM: Rhino-sinusal mucormycosis, ROCM: Rhino-orbito-cerebral mucormycosis, SM: Systemic mucormycosis.

conditions were uncontrolled diabetes and systemic corticosteroid treatment. In addition, involvement of the sinuses, including rhino-sino-orbital and sinus infections, was observed in the majority of infections in 92.3 % of these patients with the predominant underlying disease in this group identified as uncontrolled diabetes. In diabetic patients should be immediately implemented the use of novel medical imaging and molecular techniques to improve early diagnosis and successful treatment of mucormycosis. Diagnosis of mucormycosis was confirmed by histopathology, microscopy, and culture (27.7 %). Histological hallmarks in tissue samples included the presence of broad, irregularly branching and non-septate fungal elements. *Rhizopus arrhizus* was the most common agent, followed by *Mucor circinelloides*, in contrast with a study by Nazari et al., [19] who reported *Rhizopus, Mucor,* and *Lichtheimia* species as the most commonly isolated pathogens in COVID-19 patients. However, *Apophysomyces* was the second most familiar species causing mucormycosis in India [20]. The weather pattern in Tehran is categorised by four seasons, namely a cold winter (an average low of 2 °C and high of 9 °C), spring (temperatures typically range from 1 °C to 28 °C), hot dry summer (an average daily high temperature above 30 °C) and cool autumn (from November 24 to March 8 with an average daily high temperature below 14 °C) (https://weatherspark.com). In recent study, a seasonal variation exists with a maximum reported in autumn. The positive mucormycosis cases were most frequently detected in autumn (47.7 %), which is in line with the results obtained for mucormycosis [21]. The increased incidence of mucormycosis in autumn with increasing humidity has also been described in Mediterranean countries [13,22,23]. It seems that differences in humidity and seasonal temperature influence the airborne spore concentration of Mucorales, which leads to an increase in the prevalence of mucormycosis [24]. Also, the prevalence of mucormycosis in a particular season could be related to a new wave of COVID-19. However, the impact of seasonal weather conditions on the incidence of mucormycosis remains unknown. Further studies are highly required to assess the impact of climatic conditions on the incidence of mucormycosis. For many decades, amphotericin has been a mainstay of antifungal therapy for the treatment of mucoralean infections, despite its toxicity [25,26]. Therefore, lipid amphotericin B formulations remain the primary treatment, which was also shown in the current study with 90.7 % of patients receiving liposomal amphotericin B. Because rapid vascular invasion can lead to tissue necrosis and infarction, penetration of antifungal agents to the site of infection may be impaired. Amphotericin B monotherapy may therefore be insufficient for the treatment of mucormycosis in patients with COVID-19, and control of the underlying disease and surgical excision of necrotic tissue is often necessary for successful treatment [27]. Therefore, there is an urgent need for the efficacy of new antifungal drugs and new combinations of existing agents to be further explored in the laboratory and clinical trials. Finally, CAM can be a serious complication of severe COVID-19, particularly in patients with uncontrolled diabetes. It is important to monitor the epidemiology of mucormycosis to raise awareness of the disease and improve diagnosis, treatment and prognosis, particularly in the setting of pandemic.

Declaration of competing interest

All authors report no potential conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.mycmed.2024.101480.

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