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Relapse of COVID-19-associated mucormycosis in patients receiving posaconazole as maintenance treatment

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) has been associated with secondary fungal infections such as mucormycosis. We investigated the relapse rate of mucormycosis and its risk factors.

Methodology: A prospective study was conducted on COVID-19-associated mucormycosis (CAM) patients discharged from Imam Khomeini Hospital Complex, Tehran, Iran, from July 2021 to February 2022. Patients who received posaconazole as a step-down therapy were included and examined monthly for six months. A relapsing mucormycosis case was defined as a patient with new clinical or radiological symptoms, confirmed by observing aseptate hyphae in the histopathological examination or tissue culture. The characteristics of patients with and without relapse were analyzed and compared.

Results: Seventy-seven patients completed the six-month follow-up after discharge. Most patients were male (n = 46, 59.8%), with a mean age of 53.1 years (median 19-84). The most common underlying diseases were diabetes (52/77, 67.5%), hypertension (33/77, 42.8%), and cancer/chemotherapy (25/77, 32.4%). Seven patients (7/77, 9%) were reported as relapsing cases. There was no difference in demographic features and underlying diseases between the groups. A significant difference was seen in the mean duration of posaconazole consumption between patients with and without relapse (24 ± 4.4 days vs. 49.4 ± 4.3 days, respectively, $p = 0.015$). The primary orbital involvement was also significantly associated with relapse ($p = 0.04$).

Conclusions: Our findings showed a significant relapse of CAM (9%). A longer duration of posaconazole consumption and completion of treatment for initial orbital involvement in CAM patients are recommended for better patient management and prevention of relapse.

Key words: COVID-19; mucormycosis; relapse; posaconazole.

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Introduction

Coronavirus disease 2019 (COVID-19), an acute respiratory syndrome caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) virus, led to over 17 million deaths globally by early 2022 [1]. Among the various treatments studied, only systemic glucocorticoids significantly improved survival [2,3]. The wide and sometimes extensive use of glucocorticoids to treat COVID-19 led to the increased susceptibility of patients to secondary fungal infections, especially candidiasis, aspergillosis, and mucormycosis [4–8]. For example, the second wave of the COVID-19 epidemic in India was associated with an increase in the reported cases of COVID-19-

associated mucormycosis (CAM) [9]. Three important risk factors were identified that, when combined, could increase the incidence of sino-orbital mucormycosis. These included infection with SARS-CoV-2, steroid therapy, and uncontrolled diabetes mellitus [10].

Most of our information about epidemiology, diagnosis, and treatment of mucormycosis comes from case reports and case series [11–13]. These reports show that amphotericin B deoxycholate (d-AmB) was initially the only antifungal agent approved for the induction treatment of mucormycosis. However, this formulation had significant toxicity and was reported to cause renal injury. It was, therefore, replaced with lipid AmB formulations, such as liposomal AmB (L-AmB) [14]. The early administration of intravenous L-AmB together with surgical debridement of necrotic and infected tissues still remains the main method of treatment in CAM patients [15,16].

Unlike potent activity to other fungal infections, only few azole agents are active against mucormycosis. Posaconazole and isavuconazole are the only azoles that have been effective both *in vitro* and *in vivo*. While studies show no *in vitro* activity for voriconazole [17] and limited activity for itraconazole; posaconazole, and isavuconazole have been reported to show a fourfold increase in their *in vitro* anti-mucormycosis activity compared to itraconazole [18–20]. Although the fungicidal effect of posaconazole has been proven, AmB is considered to have a higher fungicidal rate than posaconazole [21]. A few studies have shown the therapeutic effect of azoles as the primary induction therapy in mucormycosis patients [22,23]; however, posaconazole and isavuconazole are currently not recommended as the first-line treatment for CAM cases [16]. Induction treatment with intravenous AmB should be continued until the mucormycosis patient is clinically stable. The patient can then switch to oral posaconazole or isavuconazole for maintenance therapy [24].

Despite effective surgical debridement and long-term antifungal treatments, mucormycosis recurrence is reported in clinical settings, especially in immunocompromised patients [25-27]. However, to our knowledge, there is no information on the relapse of CAM in the literature. We conducted this study to investigate the rate and causes of CAM relapse in discharged patients on posaconazole maintenance therapy.

Methodology

A prospective single-center study was conducted on CAM patients who were discharged from Imam Khomeini Hospital Complex affiliated with Tehran University of Medical Sciences, Tehran, Iran, from July 2021 to February 2022.

The study included patients who initially experienced COVID-19 and then developed mucormycosis within three months. COVID-19 was confirmed by a positive SARS-COV2 real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) assay on a nasopharyngeal sample. Proven cases of mucormycosis were identified based on the criteria provided by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) [28]. In order to determine the clinical picture of mucormycosis, the location and extension of the disease were evaluated based on clinical symptoms, radiological features, and endoscopic observation.

The patients included in the study had completed their hospital treatment with L-AmB as induction treatment alongside surgical debridement and were discharged on oral posaconazole as maintenance antifungal treatment (5 mL of posaconazole suspension with a fatty meal every 6 hours or 300 mg sustained release tablet/BID for the first day and then once a day, after hospitalization). Only patients who received posaconazole for more than one week were further followed up for outcome assessment. Patients were followed up monthly, either in-person or by phone by the medical team for six months. Any signs and symptoms of relapsing mucormycosis appearing in imaging, clinical presentations, and sinus endoscopy

Table 1. Baseline characteristics of treated COVID-19-associated mucormycosis patients discharged on posaconazole.

Characteristics	Patients with relapse n = 7	Patients without relapse n = 70	Total N = 77	*p* value
Age (mean)	61.1	52	53.1	0.33
Gender (male) n (%)	4 (57.1)	42 (60)	46 (59.8)	0.28
Diabetes n (%)	5 (71.4)	50 (71.4)	52 (67.5)	0.41
Hypertension n (%)	1(14.2)	32 (45.7)	33 (42.8)	0.33
Cancer/chemotherapy n (%)	2 (28.5)	23 (32.8)	25 (32.4)	0.18
Hospitalization days (mean ± SD)	43.1 ± 19.2	56.2 ± 22.3	54 ± 22.1	0.349
Posaconazole consumption days (mean ± SD)	24.0 ± 4.4	49.4 ± 4.3	49.5 ± 37.1	0.015*
Orbital involvement n (%)	5 (71.5)	37 (48.1)	43 (55.8)	0.04*
Treatment with pill n (%)	1 (14.2)	31 (42.8)	32 (41.5)	0.70

were recorded. A relapsing mucormycosis case was defined as a patient with new clinical or radiological symptoms of the infection, confirmed by observing aseptate hyphae in the histopathological examination or tissue culture. The patients were then divided into two groups: those with relapse and those without relapse. All the patients signed the informed consent form before participating in the study. The patients' data were reviewed by another group of the research team before statistical analysis. Any distorted information was corrected or removed. The finalized data was analyzed using IBM SPSS Statistics for Windows (IBM Corp. released 2016. version 24.0. Armonk, NY). Patients who experienced relapse of mucormycosis were compared with patients without relapse. The Shapiro-Wilk test was used to check the normality distribution of quantitative variables. The unpaired independent t-test was used to compare the mean variables between the two groups. The Chi square test was used to compare the qualitative variables. A p value of less than 0.05 was considered significant.

Ethical approval for this study was obtained from the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1401.034).

Results

A total of 101 proven CAM cases were identified, of whom 24 did not meet the inclusion criteria or were excluded during the follow-up. Seventy-seven patients on maintenance treatment with posaconazole were included in the study. Among them, 45/77 (59.8%) received oral suspension, and 32/77 (41.5%) took 300 mg tablets twice daily (BID). These patients were closely monitored for six months after discharge.

During the follow-up period, 7 patients (9%) exhibited signs of the disease and were considered as relapsing cases (Figure 1). The mean time of relapse after discharge was 60 (range 11-120) days. As presented in Table 1, most patients were male (n = 46, 59.8%) with a mean age of 53.1 years old (range 19-84). The most common underlying diseases were diabetes (52/77, 67.5%), hypertension (33/77, 42.8%), and cancer/chemotherapy (25/77, 32.4%), which were not significantly different between the group with relapse and those without relapse.

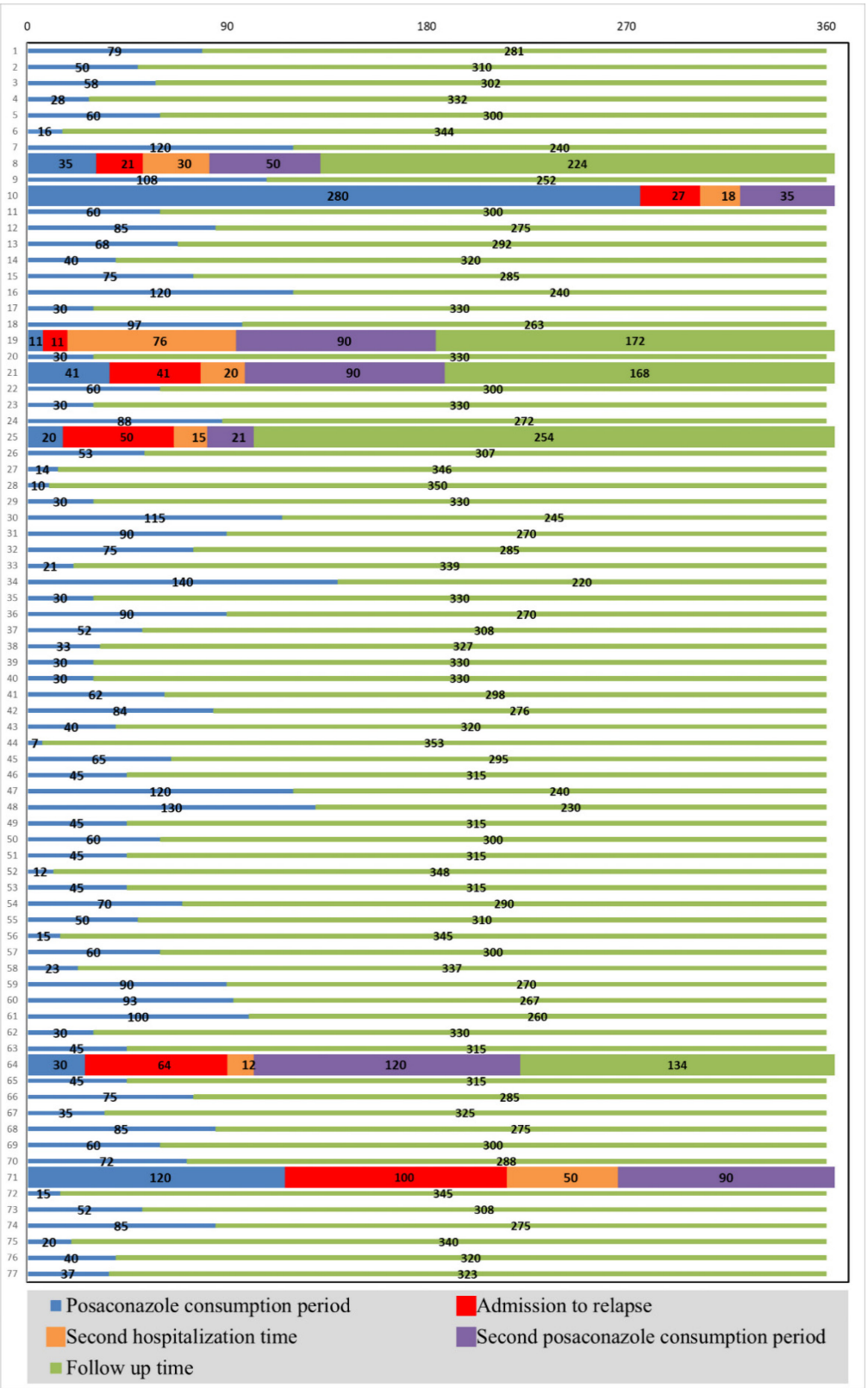
The mean hospitalization period of the patients was 54 days (range 18-183) for mucormycosis management. Despite the numerical difference, there were no statistically significant differences in hospitalization period between the two groups (56.2 vs. 43.1 days in no relapse and relapse group, respectively). The mean duration of posaconazole consumption was 49.5 ± 37.1 days, which was significantly different between the group with relapse and those without relapse (24 ± 4.4 vs. 49.4 ± 4.3 days, respectively, $p = 0.015$). Five out of 7 patients (71.4%) with relapsing mucormycosis and 37 out of 70 patients (41.8%) without relapse were suffering from rhino orbital mucormycosis (ROM), indicating that ROM was significantly associated with relapsing ($p = 0.04$). Among the patients in the relapse group, one person had a relapse for the second time, which was also related to the ROM. In terms of the type of treatment (pill vs suspension), there was no significant difference between the two groups (pill: 1/7, 14.2% for the relapse group and 31/70, 42.8% for other patients).

Discussion

We studied the treated CAM patients discharged on posaconazole from Imam Khomeini Hospital Complex, Tehran, Iran, and reported the relapse rate of mucormycosis and its associated risk factors in these patients. Imam Khomeini Hospital Complex is Iran's largest teaching and referral hospital, treating a high number of patients with COVID-19 and fungal infections. The CAM patients in our study were followed up on oral posaconazole after responding well to hospital treatment (L-AmB and surgical treatment). Besides being used as maintenance and salvage therapy in mucormycosis patients [29,30], posaconazole is also suggested as prophylaxis in preventing CAM in high-risk individuals [31]. However, posaconazole prophylaxis is not recommended by the Iranian national protocol for CAM and was therefore not used in our patients [16].

We found that 9% of CAM patients followed for six months had a relapse while on maintenance treatment with posaconazole. In a retrospective study on rhinocerebral mucormycosis cases from India who were followed up for one year, 20% of patients had a relapse [32]. In another report from a hospital in India the incidence of recurrent cases requiring revision surgery was about 20% [33]. This suggests that mucormycosis relapse appears to be more frequent among non-COVID-19 patients in India, where conditions like diabetes and malignancies are more prevalent. Although the recurrence rate in cases of mucormycosis is high, it has been emphasized that aggressive resection and appropriate medical treatment can be the only effective treatment [34]. Most patients in our study received posaconazole as step-down therapy in the form of suspension, while approximately 40% received it in the tablet form.

Figure 1. Clinical timeline of patients with COVID-19-associated mucormycosis.



The x-axis represents the days of the year. The y-axis represents the number of studied patients, comprising seven patients with relapse (thick bars with timelines) and seventy patients without relapse (thin bars).

Neither form was associated with a higher relapse rate. Posaconazole has been shown to be well tolerated by patients and has demonstrated activity against the Mucorales, both *in vitro* and *in vivo* [29,35]. After the introduction of the posaconazole suspension, concerns about its oral bioavailability led to the development of sustained-release tablets and an intravenous infusion formulation [36]. Some studies have considered posaconazole tablets as a preferred option for antifungal prophylaxis based on factors such as absorption, serum levels, and tolerance; however, our findings indicate that posaconazole suspension was as effective as the tablet in relapse prevention [36–38].

The period of initial hospital treatment for CAM may extend over several weeks [39]. In our study, the average initial admission period for CAM patients was nearly eight weeks, which was not significantly related to the relapse rate.

There is no standard approach to diagnosing clinical recurrence of mucormycosis; however, exacerbation of immunosuppression, uncontrolled hyperglycemia, relapse of leukemia, and low serum levels of antifungal agents have been mentioned as risk factors [40]. In our study, patients' demographic features and the type of underlying diseases were not associated with the relapse rate. Relapse was more likely in patients who had primary orbital involvement and received a shorter course of posaconazole (> 3 weeks vs. > 7 weeks). The incomplete treatment of primary orbital mucormycosis in our patients can be considered as a source for relapse.

Our study presented valuable insights into the relapse rate in CAM patients and the related risk factors for the first time. However, it had some limitations. We did not perform standard antifungal susceptibility tests for Mucorales, as they are not routinely recommended [41]. Additionally, we were unable to perform serial monitoring of serum drug concentrations recommended for oral posaconazole treatment due to its unavailability in Iran [40]. Other limitations of our study include the retrospective evaluation of the patients' hospitalization and the relatively short follow-up period (compared to a one-year follow-up). Despite these limitations, the information provided by our study can be helpful in the management of CAM patients and in reducing the relapse rate.

Conclusions

Our findings showed a significant relapse rate of 9% for CAM. Although this rate of relapse was not related to the demographic features, underlying diseases of patients, and the type of posaconazole they used (suspension vs. tablet); it was significantly associated with initial orbital involvement and a shorter duration of posaconazole consumption. It seems that orbital involvement is a critical factor affecting treatment success. A longer duration of posaconazole consumption and completion of treatment for initial orbital involvement in CAM patients can be recommended for relapse prevention.

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Authors' contributions

Conceptualization, MS, SK; data curation, FP; formal analysis, HKS, MS; methodology, HKS, AT; project administration, AS, ESF; supervision, CM, ZR; visualization, MD; writing-original draft, SK, KA, AT; writing-review and editing, MS, AT.

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