**INTRODUCTION**

For many years, mucormycosis was not a nationally notifiable disease in Iran until a growing number of COVID-19-associated mucormycosis (CAM) were reported in the second wave of coronavirus in parts of the world, especially in India.\(^1\) In addition to India, CAM was also reported in several countries with increased incidence including the United States, Pakistan, Syria, Brazil, and Iran.\(^3\) In Iran, in the fifth wave of COVID-19 with delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the summertime of 2021, CAM has seen a surge. At this time most of the Iranian population had not been vaccinated against sars-COV2.

Neutropenia, hematologic malignancies, steroid therapy, uncontrolled diabetes mellitus (DM) with or without ketoacidosis, and chronic kidney disease are among known risk factors for mucormycosis.\(^1\) It seems that in addition to known risk factors, there is some susceptibility in the post-COVID period.\(^4\)

The proposed mechanisms for the development of CAM include acute hyperglycemia, administration of corticosteroids, cytokine storm, insulin resistance, iron overload, and endothelial injury.\(^5\)

Genetic susceptibility has been reported as a risk factor for COVID-19 but not for CAM.\(^6\) Moreover, the role of environmental susceptibility has not been exactly understood.\(^1,7\) Herein, we report the cases of Father–Son CAM,
father (known case of DM) and his son (who did not have a previous history of DM) both infected with mucormycosis in the post-COVID period and both of them got visual impairment from the rapid progression of CAM with a relatively similar pattern after <3 days of initiation of the first symptom of CAM. Our observation suggests the possible role of genetics and environment in susceptibility to CAM.

2 | CASE HISTORY

2.1 | Case 1 (Father)

A 63-year-old man presented with facial, ocular, and dental pain. He had a history of DM, hypertension, and a recent history of real-time reverse transcriptase-polymerase chain reaction (RT-PCR)-confirmed pulmonary COVID-19 that was treated in an outpatient setting 18 days ago. He did not receive Remdesivir, Interferon, Tocilizomab, and antibiotic treatment.

On physical examination, the best-corrected visual acuity (BCVA) was finger count in the right eye and 20/80 in the left eye. Lateral gaze restriction, mild ptosis, and mild chemosis associated with periorbital erythema were noted on the right eye (Figure 1). The left eye examination was normal except nuclear sclerosis cataract.

On orofacial examination, necrotic ulcer on the hard palate and light touch sensation impairment was evident. On the first day of hospitalization, the fasting blood sugar serum level was 207 mg/dl.

Orbital computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed pansinusitis and destruction of the medial wall of right ethmoidal air cells (lamina papyracea) with the intraorbital extension of inflammatory tissue as signal changes and enhancement of intraocular fat and the medial rectus muscle (Figure 2).

Empirical antibiotic therapy consisting of meropenem and vancomycin (for coverage of possible hospital-acquired infection) in addition to systemic liposomal amphotericin B was started. The patient was put on intravenous liposomal amphotericin B 5 mg/kg/day after a clinical diagnosis of mucormycosis. Liposomal amphotericin B 3.5 mg/ml was administered to the patient via retrobulbar injection, three times daily.

2.2 | Case 2 (Son)

A 31-year-old man, the son of the aforementioned case, without a remarkable past medical history, got respiratory symptoms of COVID-19 1 day before his father. The chest CT scan was highly suggestive of COVID-19-induced pneumonia.

During the disease, he was treated with a course of 8 mg of intravenous dexamethasone daily for 5 days. Interferon, Tocilizomab, and antibiotics were not prescribed.

At the time of admission, he presented with headache, dental pain, and facial paresthesia. On physical examination, the BCVA was 20/20 in the right eye and no light perception (NLP) in the left eye. On ocular examination of the left eye, frozen eye, four-plus positive relative afferent pupillary defect (RAPD) and swelling of eyelids were obvious (Figure 3). The right eye examination was normal.

On the first day of hospitalization, FBS was 301 mg/dl and Hba1c was 6.1%. CT scan and MRI of the patient revealed pansinusitis as opacification of all paranasal sinuses associated with involvement of left periantral fat and masticator space without bony erosion indicating perivascular extension of invasive fungal sinusitis. Left-sided proptosis and involvement of intraconal/extraconal soft tissue, medial rectus muscle, and the optic nerve was seen. Also, perineural spreading along the left trigeminal nerve course was noted (Figure 4).

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3 | DISCUSSION

We present the first report of concomitant infection of CAM with ophthalmologic complications in Father–Son patients with severe COVID-19 who developed significant oculofacial disability in their treatment course. Both
patients met the criteria of the definition for CAM as evidenced by their clinical and radiological indicators.

There is no evidence that viral mutations in SARS-CoV-2 could explain the severe clinical phenotype variation nor the observed differences in the geographic distribution of COVID-19.8 In addition to age, sex, and immune system, host genetics can affect disease outcome as a major contributor to the differences observed in the host–pathogen relationship.9

The pooled prevalence of CAM increased 50-fold after the COVID-19 period.10 The simultaneous increase in the number of patients with mucormycosis and COVID-19 presented COVID-19 and its treatments as a possible risk factor for mucormycosis.5

In our report, the father had pre-existing DM and his son had no history of DM with short-term use of glucocorticoid and was newly diagnosed with hyperglycemia, which was detected after hospitalization.

The use of corticosteroids increased after the publication of the RECOVERY study; however, many COVID-19 patients receive corticosteroids without indications, even with higher doses and longer duration recommended in this study.5,11 Although one of the possible explanations for the rapid rise in mucormycosis infection in the second surge of COVID-19 in India was the overuse of glucocorticoids,12 all patients with steroid therapy do not develop CAM.

Increased blood sugar and suppression of the immune system are suggested mechanisms to increase the incidence of CAM as a result of corticosteroid therapy.1 This suppression usually occurs in prolonged use of glucocorticoids but whether short-term treatment is also a risk factor, is a matter of controversy. It seems other factors including genetic susceptibility should be considered.

Diabetes elevates the risk of CAM via four possible important mechanisms: (1) inhibiting the action of iron sequestrating proteins which elevates serum iron which is necessary for mucural growth; (2) up-regulating the expression of Glucose Regulator Protein 78 (GRP78) and spore coating protein family (CotH3) which serve as a receptor and ligand for fungal endocytosis; (3) impairment of neutrophilic phagocytosis and chemotaxis; (4) weakening of oxidative and nonoxidative pathways.13

There are some reports that some CAM patients do not have known risk factors for CAM.14,15 Moreover, most of the cases of CAM have been reported from limited countries like India, Iran, Mexico, and Egypt.16 Hence, we can hypothesize that other factors including environmental and genetic factors may play a role in susceptibility to CAM. It is not yet known exactly whether environmental factors predispose to COVID-19 or not but it seems that factors like contaminated air and humid climate may play a role in CAM infection.5,7,14 In our study, these two cases have the same environment which suggests the environment is a possible risk factor for CAM.

4 CONCLUSION

Genetic susceptibility has not been introduced as a risk factor for CAM. The infection of a father and his son with CAM is a rare and severe complication in the post-COVID phase, especially when the son had no definite risk factor for CAM, which can present genetics and environment as possible risk factors for CAM.

AUTHOR CONTRIBUTIONS

Mohsen Pourazizi, Bahram Eshraghi, Roya Azad: Contributed to the conception and design of the study, establishment of the diagnosis, and revising the manuscript critically for important intellectual content. Kimia Afshar, Iman Mohammadbeigy: Contributed to the collection of the case information, interpretation of data, and drafting of the manuscript. All authors approved the final version of the manuscript and agreed on all aspects of the work.

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None.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data used to support this study’s findings can be obtained from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (IR.ARI.MUI.REC.1401.028).

CONSENT

Written informed consent was obtained from the patients to publish this report in accordance with the journal’s patient consent policy.

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REFERENCES

1. Narayanan S, Chua JV, Baddley JW. Coronavirus disease 2019–associated mucormycosis: risk factors and mechanisms of disease. Clin Infect Dis. 2021;74:1279-1283.

2. Patel A, Kaur H, Xess I, et al. A multicentre observational study on the epidemiology, risk factors, management and outcomes of mucormycosis in India. Clin Microbiol Infect. 2020;26(7):944.e9-944.e15.

3. Hoenigl M, Seidel D, Carvalho A, et al. The emergence of COVID-19 associated mucormycosis: a review of cases from 18 countries. Lancet Microbe. 2022;3:e543-e552.

4. Hoang K, Abdo T, Reinersman JM, Lu R, Higuita NIA. A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient. Med Mycol Case Rep. 2020;29:22-24.

5. Dilek A, Ozaras R, Ozkaya S, Sunbul M, Sen EI, Leblebicioglu H. COVID-19-associated mucormycosis: case report and systematic review. Travel Med Infect Dis. 2021;44:102148.

6. Chamnanphon M, Pongpanich M, Suttichet TB, et al. Host genetic factors of COVID-19 susceptibility and disease severity in a Thai population. J Hum Genet. 2022;67:295-301.

7. Pourazizi M, Mohammadi R, Abtahi-Naeini B. COVID-19 associated mucormycosis and anbarnesa: concerning about important source of spores. Iran J Public Health. 2022;51(1):223-225.

8. Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: implications for risk, severity, and outcomes. FASEB J. 2020;34(7):8787-8795.

9. Hussain S, Riad A, Singh A, et al. Global prevalence of COVID-19-associated mucormycosis (CAM): living systematic review and meta-analysis. J Fungi. 2021;7(11):985.

10. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2020;384(8):693-704.

11. Hussain S, Ryad A, Singh A, et al. Global prevalence of COVID-19-associated mucormycosis (CAM): living systematic review and meta-analysis. J Fungi. 2021;7(11):985.

12. Vare AA, Yellambkar S, Farheen A, Nandedkar V, Bhomse SS, Shah R. Incidence, cumulative mortality and factors affecting the outcome of COVID-19-associated mucormycosis from Western India. Indian J Ophthalmol. 2021;69(12):3678-3683.

13. Jose A, Singh S, Roychoudhury A, Khoklakiya Y, Aarya S, Roychoudhury S. Current understanding in the pathophysiology of SARS-CoV-2-associated rhino-orbito-cerebral mucormycosis: a comprehensive review. J Maxillofac Oral Surg. 2021;20(3):1-8.

14. Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R. Epidemiology and pathophysiology of COVID-19-associated mucormycosis: India versus the rest of the world. Mycopathologia. 2021;186(6):739-754.

15. Eshraghi B, Hosseini NS, Mohammadi R, et al. From bilateral periorbital necrotic wound to fungal brain abscess: a complicated case of COVID-19-associated mucormycosis. Case Rep Infect Dis. 2022;2022:3821492.

16. Guzmán-Castro S, Chora-Hernandez LD, Trujillo-Alonso G, et al. COVID-19-associated mucormycosis, diabetes and steroid therapy: experience in a single centre in Western Mexico. Mycoses. 2022;65(1):65-70.

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