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Coronavirus Pandemic

Finegoldia magna and *Mucorales* molds co-infection in a severe case of SARS-CoV-2 disease

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Abstract

Introduction: Rhino-orbito-cerebral mucormycosis has been reported as a sequela after coronavirus disease in immunocompromised patients with poorly controlled diabetes mellitus. Most cases have been identified in India, with only 19 reported elsewhere.
Methodology: We herein report the results of clinical, imaging, microbiological, and histopathological studies in an immunocompetent 67-year-old male with rhino-orbital infection by *Finegoldia magna* and *Mucorales* molds following severe SARS-CoV-2 disease associated with new-onset decompensated diabetes mellitus.
Results: Microbiological and histological studies confirmed the presence of both *Mucorales* molds and *Finegoldia magna*, which was successfully treated with antibiotics and a specific anti-fungal agent (Posaconazole).
Conclusions: Careful multidisciplinary follow-up of patients treated for severe SARS-CoV-2 disease is necessary for the timely diagnosis of complications such as uncontrolled diabetes mellitus and opportunistic infections.

Key words: COVID-19; SARS-CoV-2; mucomycosis; rhino-orbital infection.

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Introduction

Mucormycosis is a difficult-to-diagnose life-threatening infection caused by spores of molds of the order *Mucorales*. Urgent medical and surgical treatment is necessary, as it has a rapidly progressive and destructive clinical course. Maximizing survival rates requires a multidisciplinary diagnostic team, including radiology, surgery, laboratory, and pathology specialists. Mucormycosis has been reported as a complication of the 2019 coronavirus disease (COVID-19) mostly affecting men with uncontrolled preexisting diabetes mellitus, a recent meta-analysis has identified 101 cases of mucormycosis in people with COVID-19, of which 82 cases were from India and 19 from the rest of the world [1].

Finegoldia magna is a Gram-positive anaerobic commensal that colonizes the skin, mucous membranes, and other non-sterile body surfaces and is an important opportunistic pathogen. It can potentially cause life-threatening infections like necrotizing fasciitis [2] and toxic shock syndrome [3] among others [4].

To our knowledge, this is the first description of simultaneous infection by *Finegoldia magna* and *Mucorales* molds following severe SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2) disease.

Methodology

In October 2021 a 67-year-old male was admitted for treatment of moderately severe COVID-19 disease due to progressively diminishing arterial partial pressure of oxygen (pO2) levels and persistent fever (up to 39 degrees Celsius). History was significant for arterial hypertension, which was well controlled medically, with normal blood sugar levels at previous check-ups, and patient-reported nasal polypectomy 30 years prior. The patient received three doses of mRNA vaccine (the last dose was administered 10 days prior to the start of complaints). The reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 demonstrated a positive result. On hospital admission, empiric antimicrobial therapy was initiated following

Table 1. Patient treatment for COVID-19 infection and follow-up during the first and second hospital stay.

First in-hospital stay October 2021	First follow up (At-home treatment)	Second in-hospital stay November 2021	Second follow up (At-home treatment)
Ampicillin / Sulbactam 1000 mg TID	Doxycycline 100 mg BID	Cefoperazone / Sulbactam 1gr i.v BID	Cefpodoxime 200 mg BID for 10 days
Levofloxacin 500 mg BID	Pantoprazole 20 mg BID	Famotidine 20 mg TID	Famotidine 20 mg TID
Fluconazole 200 mg BID	Fluconazole 150 mg every other day	Insulin i.v.	Itraconazole 100 mg QD
Fraxiparin 0.6 mL s.c.	Fraxiparin 0.6 s.c.	Fraxiparin 0.6 mL s.c.	Fraxiparin 0.6 mL s.c. QD.
Dexamethasone 12 mg i.v	Dexamethasone 8 mg p.o.	Colchicum 0.5 mg QID	Colchicine 0.5 mg BID
		Human Albumin once daily	Acetylsalicylic acid 100 mg QD
		Citicoline 1 g i.v. BID.	Setagliflozin s.c. QD

the hospital's standard COVID-19 treatment protocol (Table 1). Additionally, the patient was started on Dexamethasone 12 mg I.V. daily and oxygen supplementing therapy at 12 L/min at which he demonstrated oxygen saturation of 88%. The chest X-ray demonstrated diffuse nonhomogeneous ground-glass opacities mostly in the left lung. Laboratory results were typical of acute-phase coronavirus disease (Table 2) and proteinuria (positive test strip). The following week the patient was discharged against the physician's recommendation and the patient received follow-up treatment (Table 1).

Two weeks after leaving the hospital the patient complained of tingling and pain in the maxilla as well as double vision and loss of muscle tone in the left arm. Ophthalmic examination demonstrated eccentric proptosis, weak adduction, conjunctival hyperemia and chemosis of the right eye, and slight proptosis of the left eye, which was otherwise unremarkable. Visual acuity was 20/30 in both eyes. Neurological examination demonstrated bradypsychia, confusion, muscle weakness in the left forearm, normal reflexes, and no meningeal symptoms.

A computed tomography (CT) scan of the brain and chest was performed. There were no obvious ischemic areas in the brain and no bony erosion of the sinuses (Figure 1A). Chest CT findings included subacute and chronic phase opacities in both lungs.

Laboratory results are shown in Table 2. Blood glucose levels were 33.3 mmol/L. The patient was re-admitted to the COVID-19 department due to a persistent positive RT-PCR result. Blood glucose was managed with intravenous insulin, dexamethasone was discontinued and empirical therapy in accordance with the second hospital's standard COVID-19 treatment protocol was initiated (Table 1) with follow-up therapy.

Two weeks after discharge from the second hospital the patient underwent magnetic resonance tomography (MRT) which showed diffuse nonhomogeneous polypoidal thickening of sinus mucosa, changes similar to the dark sinus sign with a hypointense T2 mass in the superior right ethmoidal sinus, protruding into the right orbit. Right orbit demonstrated proptosis with medial and superior oblique muscles hyperintense enlargement in fluid-attenuated inversion recovery (FLAIR) with contrast material retention (Figure 1B). The MRT

Table 2. Laboratory results of the patient in the course of COVID-19.

	October	November	Follow-up November	Reference ranges
Leucocytes	9.8×10^9/L	17.3×10^9/L	6.32×10^9/L	$3.5\text{-}10.5 \times 10^9$/L
Lymphocytes	1.7×10^9/L	0.6×10^9/L	1.86×10^9/L	$1.3\text{-}3.9 \times 10^9$/L
Neutrophils	6.1×10^9/L	15.1×10^9/L	4.64×10^9/L	$2\text{-}7 \times 10^9$/L
Thrombocytes	103×10^9/L	191×10^9/L	267×10^9/L	$130\text{-}440 \times 10^9$/L
Fibrinogen	3.9 g/L	7.6 g/L	8.5 g/L	2-4 g/L
Ferritin	851.89 ng/mL	2307 ng/mL	309.7 ng/mL	22-322 ng/mL
cRP	130.87 mg/L	101.7 mg/L	67.12 mg/L	0-9 mg/L
Fasting glucose	7.84 mmol/L	33.3 mmol/L	6.1 mmol/L	3.5-6.1 mmol/L
Protein	56.95 g/L	57 g/L	63 g/L	64-86 g/L
Albumin	36 g/L	31.70 g/L	37.70 g/L	35-52 g/L
Creatinine	86 µmol/L	118 µmol/L	79 µmol/L	62-115 µmol/L
Urea	6.14 mmol/L	18.0 mmol/L	6.5 mmol/L	2.5-8.2 mmol/L
Sodium	141.0 mmol/L	129 mmol/L	136 mmol/L	135-155 mmol/L
Potassium	3.9 mmol/L	3.85 mmol/L	3.65 mmol/L	3.5-5.5 mmol/L
Troponin	N/A	0.021 ng/mL	N/A	0 - 0.04 ng/mL
LDH	261.81 U/L			140-280 U/L
D-dimer	N/A	0.21 mg/L	1206.0 ng/mL	0-0.55 mg/L;
ALAT	33.0 IU/L	N/A	123.7IU/L	0-41 IU/L

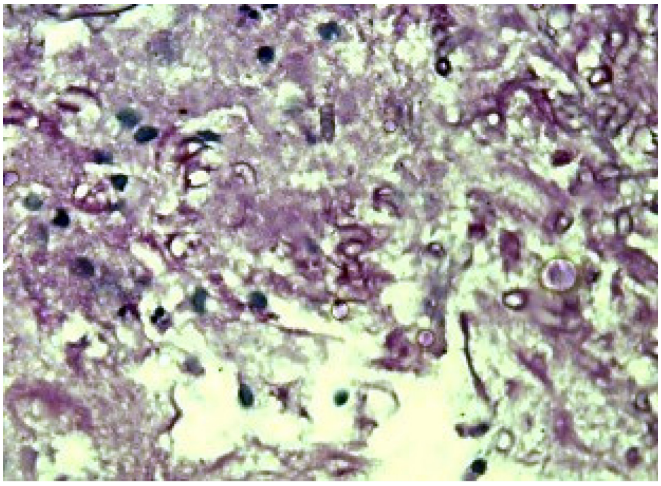
findings were interpreted as either benign tumor, mucormycosis, or diffuse bacterial sinusitis.

At this point, laboratory results (Table 2) demonstrated gradual D-dimer elevation. Double vision continued to be a concern for the patient, but no weakness in the left arm was noticed.

Results

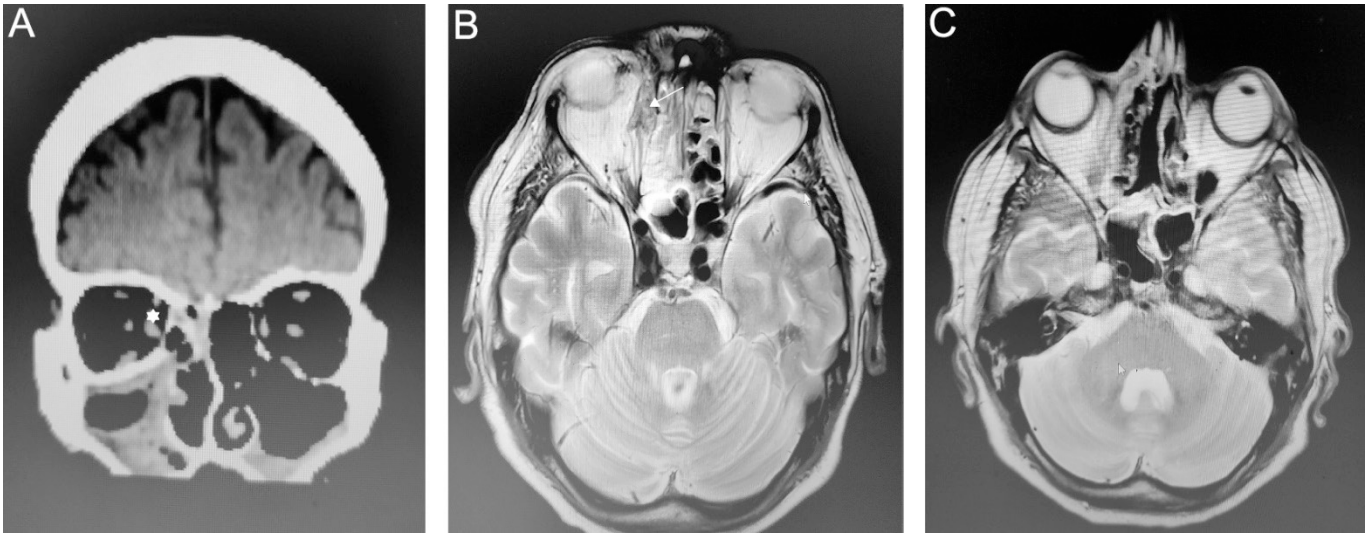
Due to the inconclusive results from the MRT, two months after the first positive SARS-CoV-2 test an exploratory biopsy was undertaken in the Department of Dental, Oral and Maxillofacial Surgery under local and intravenous anesthesia. General anesthesia was contraindicated due to the pulmonary changes and a thorough debridement could not be performed. Microbiology methods included standard culture for aerobic, anaerobic organisms and yeasts and demonstrated significant *Finegoldia magna* growth, which was susceptible to Cefotaxime and Amoxicillin-clavulonic acid. Histological findings included microabscesses, diffuse edema, and granulomatous inflammation, interpreted as osteomyelitis with mycotic colonies demonstrating as non-pigmented hyphae showing tissue invasion that was PAS + GMS + stained with haematoxylin-eosin (HE), periodic acid-Schiff stain (PAS), and Grocott-Gomori's methenamine-silver stain (GMS) (Figure 2). The diagnosis was supported by the results of direct microscopy of clinical specimens, stained with the fluorescent brightener calcofluor white. This confirmed the presence of Mucormycetes in the biopsy. Culture of specimens for genus and species identification, as well as application of immunohistochemistry, were not available due to the rarity of the disease.

Figure 2. PAS + GMS + mycotic colonies in the biopsy specimen, interpreted as Mucormycetes (× 200)



An empirical broad-spectrum treatment with oral Posaconazole 300 mg QD was initiated in January 2022 three months after the first positive COVID-19 test. The patient demonstrated improvement in double vision with regression of all signs of inflammation. Laboratory results improved with the return of fasting glucose to normal levels without treatment, with no elevation of C-reactive protein (CRP), D-dimer, ferritin, fibrinogen, etc. Follow-up MRT scans did not show any

Figure 1. Imaging results with sinu-orbital focus.



A: CT scan during re-hospitalization demonstrating generalized sinusitis, no bony erosion, and no obvious ischemic areas in the brain. Discreet thickening of the medial rectus muscle (asterisk); **B:** MRI following discharge demonstrating hypointense T2 mass in the superior right ethmoidal sinus, protruding into the right orbit, similar to the dark sinus sign (white arrow), asymmetrical eccentric right proptosis, diffuse thickening of sinus mucosa; **C:** Follow-up MRI after surgical excisional biopsy and specific antifungal treatment showing a reduction in the protruding mass' size, in exophthalmos, and in diffuse sinus mucosa thickening

progression of the disease with a significant reduction of the protruding mass between the ethmoidal sinus and right orbit (Figure 1C and D).

Pulmonary involvement due to mucormycosis was ruled out based on repeated chest CTs and ultrasounds. All respiratory volumes were reduced with a tendency for improvement but did not reach normal levels.

Discussion

We herein present an immunocompetent patient with simultaneous *Finegoldia magna* infection and Mucormycosis following SARS-CoV-2 disease. Recent literature reports an association between COVID-19 and mucormycosis usually in immunosuppressed patients with poorly controlled diabetes mellitus. In our case the patient did not have a history of conditions leading to immune compromise, nor did he have a history of diabetes mellitus.

Finegoldia magna has been reported to cause tumor-like lesions, imaging of which could be misleading. A recent case report by Basu *et al.*[5] presents a patient with known substance abuse (alcohol) suspected of having disseminated malignancy with multiple tumor-like visceral masses that were consequently diagnosed as multifocal *Finegoldia magna* infection. *Finegoldia magna* as a commensal in the sinonasal mucosa is known to cause infection only in immunocompromised states. In the presented case the patient was not immunocompromised apart from the SARS-CoV-2 infection and corticosteroid treatment associated with hyperglycemia. This leads us to believe that there are several factors that can lead to immune suppression associated with SARS-CoV-2 infection.

Firstly, current treatment guidelines for moderate and severe COVID-19 infection include systemic Dexamethasone in doses 6-12 mg [6,7]. A study by the RECOVERY Collaborative Group concluded that "in patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support" [8]. However, other studies did not reach the same conclusion and early initiation of corticosteroid therapy could be potentially harmful [9]. Application of corticosteroids could lead to various side-effects, steroid-induced diabetes mellitus, and opportunistic infections among others [10].

Treatment with broad-spectrum antibiotics could also lead to opportunistic yeast and fungal infections. Our patient received several different antibiotics. Interestingly, the generalized sinusitis did not show a positive treatment response prior to the excisional biopsy, even though microbiology demonstrated a bacterial infection with susceptible *Finegoldia magna*.

Second, COVID-19 has been associated with changes in blood glucose levels. A meta-analysis by Chen *et al.* provides evidence that severe COVID-19 is associated with increased blood glucose [11]. In this case report the patient's serum glucose levels gradually elevated reaching a maximum of 33 mmol/L, which was not managed in a timely manner, possibly due to his premature discharge. This highlights the importance of close follow-up with complete blood work and blood glucose monitoring of patients after COVID-19 infection, especially receiving corticosteroid treatment.

Thirdly, COVID-19 itself pathologically alters the immune response. There is evidence that plasma levels for a wide range of cytokines are elevated in patients with severe COVID-19 patients [12]. These include interleukin 1 beta (IL-1beta), interleukin 6 (IL-6), tumor necrosis factor (TNF), monocyte chemoattractant protein 1 and 2 (MCP-1 and -2), involved in the recruitment and activation of monocyte-macrophages to name a few. The dysregulation of the T-cell mediated immune response in severe COVID-19 includes reduced levels of circulating CD4 + and CD8 + T cells associated with hyperactivation phenotypes (Th17 and cytotoxicity). Persistent peripheral lymphopenia is also related to a greater risk of secondary bacterial infections [13,14]. It is worth noting that some recent findings point to the possible involvement of CD147 as an alternative gateway to SARS-CoV-2, favoring the direct invasion of T cells and consequent lymphopenia. Further research is needed into the immunopathology of SARS-CoV-2 in order to expand our knowledge of autoimmune phenomena rising after COVID-19 disease.

What is even more notable is that our patient had received three mRNA vaccine doses and completed the vaccination cycle shortly before the onset of SARS-CoV-2 infection. This could also have an effect on immunopathology and the timeline of the immune response after vaccination. Even though vaccination reduces the risk of infection, mortality/morbidity due to COVID-19, there is insufficient data about the rates of complications following vaccination.

Another aspect of the disease is the hypercoagulability states seen in COVID-19 patients. There are several explanations for this phenomenon - "thromboinflammation" – activation of the immune system leads to activation of the coagulation cascade either through complement factors, pathogen-associated molecular mechanisms, endothelial injury

mediated by cytokine inflammation [15]. Recent data points to endotheliopathy in COVID-19 [16]. Initially, the symptoms of diplopia, weak adduction of the right eye, loss of muscle tone in the left arm, and tingling sensations could be interpreted as stroke symptoms, which were ruled out based on neurological examination, CT scans, and laboratory results. Stroke has been reported to have a higher incidence among COVID-19 patients, younger age, fewer cerebrovascular risk factors, and higher morbidity/mortality rates [17].

Interestingly, D-dimer in our patient was initially normal and elevation was observed only after the start of the rhino-orbital infection. Mucormycosis could lead to infectious thrombosis of vessels with necrosis of tissues and explain the elevated levels of D-dimer late in the course of SARS-CoV-2 infection.

All of these factors can lead to a rise of atypical infections in COVID-19. In our case, the generalized sinusitis with thickened mucous membrane was suspected of having a bacterial origin, despite the continuous lack of effect of antimicrobial therapy. However, *Finegoldia magna* is by far the least possible culprit. The findings of osteolysis with a protruding mass in the right medial aspect of the orbit were indications of Mucormycosis. All of these clinical findings necessitated the exploratory biopsy in order to establish the correct diagnosis.

Finally, improvement in our patient was observed after three months of antifungal medication specific for Mucormycosis, which leads us to believe that the main cause of the symptoms was indeed Mucormycosis infection.

Conclusions

In conclusion, careful multidisciplinary follow-up is needed for patients after severe COVID-19 in order to have timely diagnosis of life-threatening complications such as opportunistic infections, regardless of their vaccination status.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rozaliya Hristova, Alexandrina Vlahova, Maria Christova, Konstantin Stamatov, Pavel Stanimirov. The first draft of the manuscript was written by Rozaliya Hristova and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

Approval was obtained from the ethics committee of Medical University Sofia. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Informed consent

Informed consent was obtained from the participant included in the study. The participant has consented to the submission of the case report to the journal.

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