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A Unique Triad of Invasive Sinusitis, Brain Abscess with Focal Cerebritis, and COVID-19

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 49-year-old
Final Diagnosis: Rhinosinusitis
Symptoms: Cough • fatigue • headache • seizure
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Rare coexistence of disease or pathology

Background: We present a case of invasive sinusitis with rhinocerebral infection in a patient who had mild symptoms of COVID-19 infection and did not receive any immunosuppressive therapies.

Case Report: A 49-year-old man with a history of uncontrolled diabetes presented to the hospital with multiple generalized tonic clonic seizures. He had recently been diagnosed with mild COVID-19 and was treated at home with supportive care only. He was found to have cerebritis in the right frontal lobe along with right fronto-ethmoid sinusitis. He underwent extensive testing with nasal endoscopy with gram stain and culture, cryptococcal studies, 1-3-Beta-D glucan, blood cultures, fungal CSF studies, Lyme disease, HIV, Fungitell assay, and galactomannan studies, which were all negative. He was started on i.v. antibacterial therapy with cefepime, vancomycin, and metronidazole along with amphotericin B. After 2 weeks, his repeat imaging revealed progression of cerebritis along with new early abscess. Given these findings, his antibiotics were changed to meropenem and the amphotericin B dose was increased. He was recommended debridement and sinus surgery but refused. During the course of treatment, he developed acute kidney injury and was switched to Posaconazole.
Unfortunately, the patient decided to leave against medical advice 6 weeks into admission. He was advised to continue Posaconazole and levofloxacin but he could only afford levofloxacin. He was then recommended long-term levofloxacin. He has since recovered, with resolution of cerebritis noted in follow-up imaging 1 year later.

Conclusions: Our patient had mild COVID-19 infection and presented with secondary infective complications, which are usually associated with an immunocompromised state, despite receiving no immunosuppressives. It is imperative that all clinicians treating COVID-19 be watchful for fungal or bacterial co-infections in patients with active SARS-CoV-2 infection, even if the presenting symptoms are mild, particularly if other risk factors are present.

Keywords: COVID-19 • Diabetes Complications • Diabetes Mellitus • Ethmoid Sinusitis • Invasive Fungal Infections • Seizures

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/933177

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Background

Severe Acute Respiratory Syndrome, caused by coronavirus 2 (SARS-CoV-2), is arguably the greatest public health emergency of this century [1]. It has been challenging to manage given its diverse presentations and associated complications. Patients with COVID-19 are on treatment that makes them immunosuppressed and hence more prone to developing opportunistic infections. This trend has also been observed in previous coronavirus infections such as the SARS-1 outbreak as well as in the MERS (Middle East Respiratory Syndrome) outbreak [2]. In this case report, we present a case of culture-negative invasive sinusitis, osteomyelitis, and rhinocerebral infection with cerebral abscess in a patient with mild COVID-19 but not on any targeted therapies.

This case highlights the imperative that all clinicians treating COVID-19 infection continue to be watchful for fungal or bacterial co-infections in patients with active SARS-CoV-2 infection, even if the presenting symptoms are mild, particularly if other risk factors are present.

Case Report

A 49-year-old man presented to the hospital with headache and multiple generalized tonic clonic seizures in June 2020. His past medical history was significant for uncontrolled diabetes for which he was not on any medications. He had arrived to the US from Guatemala in 1998. He lived in Alabama for 1 year for work and then moved to Rhode Island. He lived at home with his wife and 8 children. He had not traveled to any other countries since 1998. He worked at a pizza restaurant and denied drinking alcohol, smoking, and illicit drug use.

He was diagnosed with COVID-19 2 weeks prior to his presentation for seizures. He was managed at home with supportive care without any specific anti-COVID-19 therapies prior to his hospitalization. His major symptoms were cough, fatigue, and headaches. His SARS-CoV-2 (CDC-approved RT-PCR test) was repeated upon admission and found to be positive again. He did not have any significant hypoxia and did not have clinical features of COVID-19 pneumonia.

His chest X-ray was consistent with recovering COVID-19 pneumonia. He did not qualify for Remdesivir, steroids, Tocilizumab, or monoclonal antibodies cocktail. His respiratory status was stable throughout the course of illness and he had no significant oxygen requirements.

Upon arrival to the Emergency Department, he had a CT brain scan, which revealed signs of cerebritis. He underwent a lumbar puncture, which revealed 3-4 cells/mm^3 WBCs (white blood cells), 54 mg/dl protein, and 174 mg/dl glucose. Cerebrospinal fluid (CSF) culture, rapid meningitis panel, and Herpes Simplex Virus (HSV) titers were negative. He was hyperglycemic at the time, with blood glucose of 500 mg/dl and an HbA1c of 15%. His pH on venous blood gas was 7.33 with bicarbonate of 25 mEQ/L.

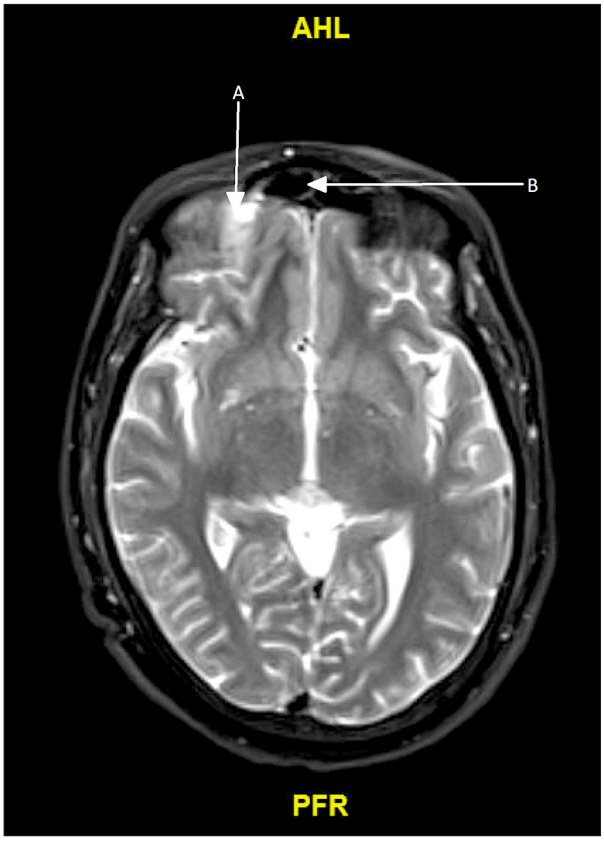

Figure 1. MRI with contrast, on admission. Right inferior frontal lobe T2/FLAIR hyperintensity with contrast enhancement (arrow A), immediately dorsal to the right frontal sinus (arrow B). There is associated leptomeningeal enhancement. Axial T2 fat-saturation (FS) gadoterate meglumine contrast.

He was started on Levetiracetam and underwent his first MRI, which revealed findings consistent with a small focus of cerebritis in the right frontal lobe with adjacent leptomeningeal enhancement (**Figure 1**) related to sinusitis of the right ethmoid and frontal sinuses (**Figure 2**). The Ear, Nose, and Throat (ENT) team were involved and the patient underwent a nasal endoscopy, which did not reveal any signs of fungal infection and only revealed scant purulent drainage suggesting a possible bacterial etiology.

Gram stain and cultures of the nasal discharge were negative. No fungal elements or Mucorales were seen on calcofluor white staining, and fungal cultures were negative. No

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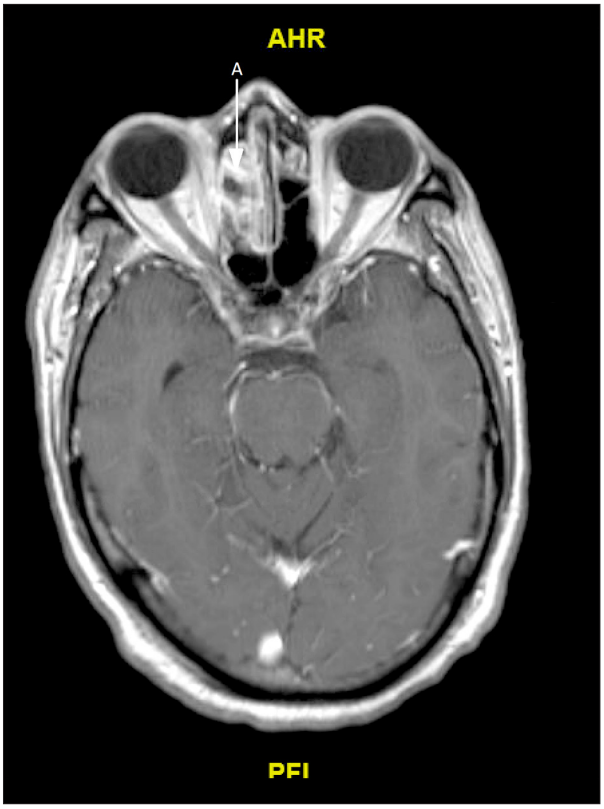

Figure 2. MRI with contrast, on admission. There is near complete opacification and post-contrast enhancement of the right ethmoid sinus (arrow A). Mucoperiosteal thickening is present. Axial T1 (gradient motion rephasing) post-gadoterate meglumine contrast.

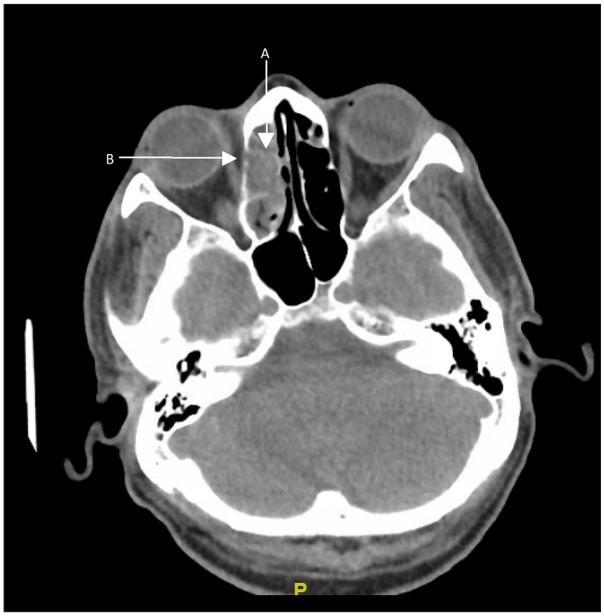

Figure 3. CT Sinus without contrast, Day 3. There is complete opacification of the anterior right ethmoid air sinus (arrow A) with extension into the right superior medial orbit. There are bony erosions of the medial wall of the right orbit (arrow B). Standard Sinus, no contrast.

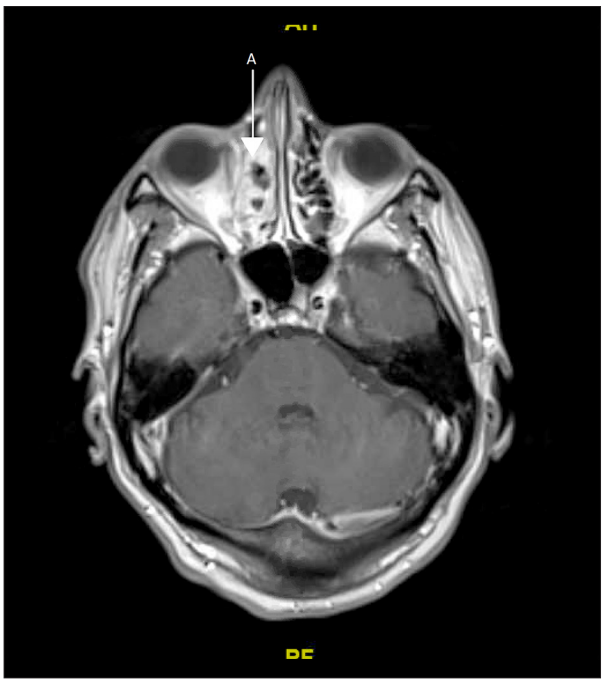

Figure 4. MRI with contrast, Week 3. Redemonstrated complete opacification of the anterior right ethmoid air cells (arrow A) with viscous material. Axial T1 (gradient motion rephasing) post-gadoterate meglumine contrast.

invasive fungal disease or necrosis was seen in nasal endoscopy. Cryptococcal studies, (1,3)-Beta-D glucan (BDG), fungal CSF studies, galactomannan studies, Lyme, HIV, and blood cultures were also negative.

He was initially started on broad-spectrum antibacterial therapy with i.v. cefepime, i.v. vancomycin, and i.v. metronidazole.

A repeat MRI was performed 3 days later, which showed slight progression of cerebritis. CT sinuses revealed bony erosions of medial wall of right orbit, right fovea ethmoidalis, right cribriform plate with extensive opacification of anterior right ethmoid air cells, and partial opacification of the right frontal sinus (**Figure 3**).

The patient was reevaluated by ENT given worsening cerebritis and presence of bony erosions into sinuses and orbit despite antibiotic therapy. ENT tentatively planned for endoscopic sinus surgery in 1 week due to his active SARS-CoV-2 infection. In the meantime, he was started on 5 mg/kg i.v. liposomal amphotericin B for suspected fungal rhinosinusitis given his history of poorly controlled diabetes. Neurosurgery

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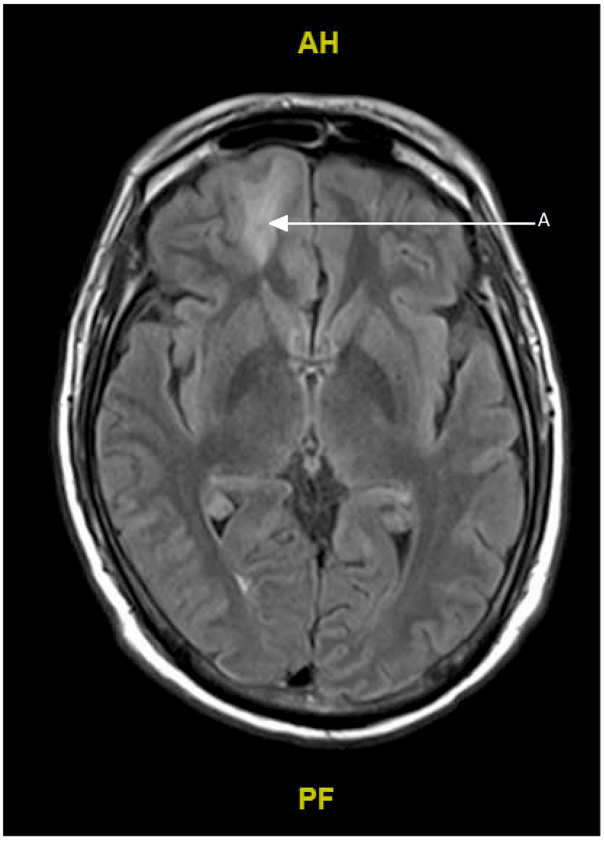

Figure 5. MRI with contrast, week 3. Interval increased abnormal T2/FLAIR signal in the right inferior frontal lobe (arrow A) with peripheral contrast enhancement, worsened compared to prior imaging. Axial FLAIR gadoterate meglumine contrast.

advised that stereotactic biopsy for pathogen, aspirational biopsy, or open craniotomy for washout would all carry a greater risk of morbidity than a repeat ENT biopsy done after a 48-h antibiotic hiatus.

Testing for SARS-CoV-2 (CDC-approved RT-PCR test) was repeated again 1 week into admission prior to planned endoscopy and was negative (approximately 3 weeks after the initial positive result). Unfortunately, the patient adamantly refused endoscopic surgical evaluation, citing clinical improvement. Amphotericin B and i.v. antibiotics were continued empirically with serial radiological follow-up.

A third MRI (**Figure 4**) done after 2 weeks of antifungal and antibacterial therapy showed persistent fronto-ethmoid sinusitis along with further progression of cerebritis. There was also concern for new early abscess formation with persistent pachymeningeal enhancement (**Figure 5**).

Given these findings, the antibiotics were changed from cefepime, vancomycin, and metronidazole to meropenem at 2 gm i.v. every 8 hs, and liposomal amphotericin B was increased to 10 mg/kg as the patient started to report blurry vision. He was counseled again regarding need for debridement and sinus surgery (maxillary antrostomy, anterior ethmoidectomy) for source control and culture data, but he continued to refuse despite the risks of invasive fungal disease.

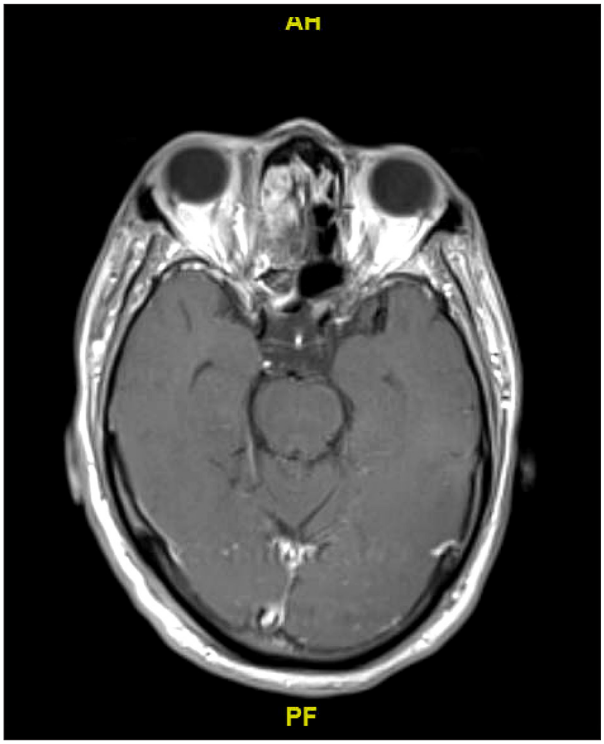

Figure 6. MRI with contrast, week 5. Persistent right ethmoid sinusitis fairly unchanged from prior studies. Axial T1 (gradient motion rephasing) post-gadoterate meglumine contrast.

During the course of treatment, he developed acute kidney injury and was switched to Posaconazole delayed-release tablets (300 mg every 12 h on the first day, then 300 mg once daily) with food.

Another MRI (**Figure 6**) was performed at around 5 weeks, which showed stable disease. The patient was then continued on Posaconazole and meropenem.

The patient's blood glucose levels had become better controlled throughout his stay with insulin administration. He was started on insulin glargine 100 unit/ml subcutaneously at 16 units nightly along with a corrective dose of insulin lispro 100 unit/ml subcutaneously at 2 units administered for every 50 mg/dl over 150 mg/dl 3 times a day. He was also given a diabetic diet while admitted. All of these interventions had led to his blood glucose ranging from 100 mg/dl to 220 mg/dl throughout his admission.

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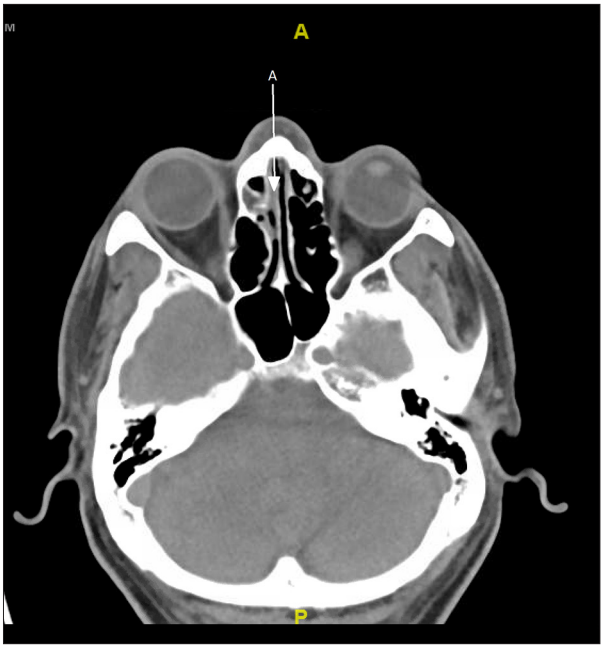

Figure 7. CT face without contrast, week 52. Mucosal thickening of ethmoid air cells (arrow A). Resolution of prior opacification of ethmoid sinus. Axial face soft tissue, no contrast.

Unfortunately, the patient decided to leave against medical advice 6 weeks into admission. He was advised to continue Posaconazole and levofloxacin on discharge along with strict diabetic control. In total he received 5 weeks of liposomal amphotericin B and 1 week of Posaconazole. He could not afford Posaconazole due to its high cost and only took levofloxacin. His blurry vision continued to improve until discharge and Ophthalmological review did not suggest any invasive fungal disease in the eye.

He was followed up by ENT and Infectious Diseases as an outpatient, and a repeat CT of the brain 2 weeks after discharge revealed improvement in cerebritis and sinusitis. Infectious Diseases advised him to continue levofloxacin for at least 1 year.

The patient was readmitted in June 2021 following a fall from a ladder, and the CT face (**Figure 7**) showed continued improvement of the osteomyelitis lesions and he was still taking levofloxacin. He was still asymptomatic and was assessed to have made a great recovery from his initial presentation.

Discussion

The patient in our case had mild symptoms of COVID-19 and presented with secondary infective complications, likely bacterial (sinuses and cerebral but not pulmonary), which might be related with an immunocompromised state. This patient had a predisposition for secondary infections due to his underlying diabetes. There is not enough clinical data to know if SARS-CoV-2 infection can predispose to opportunistic infections without immunosuppressive therapies [3]].

It is difficult to ascertain whether the sinusitis was acute or chronic. The area was contiguous with the small area of frontal cerebritis and surrounding leptomeningeal enhancement. This focal infection is consistent with the lumbar puncture findings. Numerous rigid nasal endoscopies did not demonstrate any evidence of invasive fungal sinusitis, but he was given empirical therapy due to his increased risk.

The absence of hyphae should not dissuade clinicians from the diagnosis of mucormycosis when the clinical picture is highly suggestive. Tissue necrosis, often a late sign, is a hallmark of mucormycosis, resulting from angioinvasion and vascular thrombosis [4].

One review of case reports of mucormycosis in patients with COVID-19 included 101 cases, 80% of whom had pre-existing diabetes mellitus, and 76% of whom had received glucocorticoids for the treatment of COVID-19 [5].

Serum tests, such as the (1, 3)-beta-D-glucan assay and the *Aspergillus* galactomannan assay, are being used increasingly in patients suspected of having an invasive fungal infection, but they were all negative in our case. This is important to remember that agents of mucormycosis do not share these cell wall components and neither test is positive in patients with mucormycosis [6].

Extensive use of steroids, monoclonal antibodies, and broad-spectrum antibiotics can lead to the development or exacerbation of a pre-existing fungal disease, but this was not the situation with our patient.

Overall mortality from rhino-orbital-cerebral mucormycosis ranges from 25% to 62%, with the best prognosis in patients with infection confined to the sinuses. The prognosis is especially poor for patients with brain, cavernous sinus, or carotid involvement, although some patients with these complications have been cured of the infection. The outcome in patients with pulmonary mucormycosis is worse than for patients with rhino-orbital-cerebral involvement, with mortality rates as high as 87% [7].

It is impossible to know whether this patient's COVID-19 was contributory to his illness or merely coincidental. While COVID-19 has been linked to encephalopathy and viral encephalitis, there have been no cases of COVID-19-related cerebritis or sinusitis. Perhaps, the patient's severely immunocompromised state from untreated diabetes made him susceptible to bacterial or possible fungal infection, or even both.

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While the patient fit the picture of the typical host for invasive fungal infection, we unfortunately did not collect Mucorales or fungal element on any culture. There was evidence of purulence but no necrosis on direct visualization (although this was a rigid endoscopy and no OR exploration was done). We also had evidence of bony erosions and osteomyelitis on imaging as well as a brain abscess, and he responded to 6 weeks of antifungal and prolonged antibiotic therapy. If the patient had allowed a tissue sample or bone biopsy, it would likely have been diagnostic.

Fungal co-infections associated with active SARS-CoV-2 infections are atypical presentations which have been reported more frequently recently. Although it had first been highlighted early on during the COVID-19 pandemic, it has remained largely under-diagnosed and under-reported [8].

Most cases have been identified as pulmonic infections in patients undergoing high-dose steroid therapy for ongoing SARS-CoV-2 infections. The immunocompromised state along with steroid use predisposes them to serious complications from this fungal co-infection. In our case, although the patient did not receive high-dose steroids, he was found to be profoundly hyperglycemic upon admission due to uncontrolled diabetes, which would predispose him to developing a fungal infection.

Our case highlights how even patients who only exhibit mild symptoms of COVID-19 can also present with serious complications related to their immunocompromised state. A definitive fungal diagnosis was not obtained despite extensive testing with nasal endoscopies, (1,3)-Beta-D glucan, Fungitell, galactomannan, and cryptococcal studies.

However, given the SARS-CoV-2 infection, pre-existing diabetes, and the rapid progression of his disease process, it was difficult to rule out the possibility of a fungal co-infection. His initial scans revealed a rhinosinusitis of his ethmoid and frontal sinus, which had also extended into his cerebrum. This would explain his initial presentation of seizure along with his headaches and subsequent blurry vision.

The lumbar puncture result was not suggestive of a bacterial co-infection and the patient had clinically worsened despite initial broad-spectrum antibiotic therapy. Once the patient was given a therapeutic challenge of antifungal agents, he showed gradual recovery, however slowly, in 2 weeks.

An endoscopic nasal sinus surgery would have provided a definitive histopathologic sample for confirmation of a fungal organism, but the patient refused the procedure, citing improvement. Fungal infection was strongly suspected but never proven, although a fastidious bacterial organism cannot be ruled out.

Conclusions

It is imperative that all clinicians treating COVID-19 continue to be watchful for fungal or bacterial co-infections in patients with active SARS-CoV-2 infection, even if the presenting symptoms are mild, particularly if other risk factors are present.

Acknowledgements

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Institution Where Work Was Done

Rhode Island Hospital, Providence RI, USA.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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