International Journal of Otorhinolaryngology and Head and Neck Surgery
Singla S et al. Int J Otorhinolaryngol Head Neck Surg. 2021 Jul;7(7):1187-1192
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937

DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20212459

Case Report

Post COVID-19 acute invasive fungal rhinosinusitis caused by *Scedosporium apiospermum*: a covert pathogen

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Received: 06 June 2021
Accepted: 21 June 2021

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ABSTRACT

Immune dysregulation caused by COVID-19 and the presence of risk factors such as diabetes, steroid therapy and immune-modulatory drugs significantly increase the risk of secondary invasive fungal infections. *Scedosporium apiospermum* is an emerging pathogen and is rarely reported as a cause of fungal rhinosinusitis. This was a previously unreported case of post COVID-19 acute invasive fungal rhinosinusitis caused by *S. apiospermum* with rare complications of cranial nerve palsies and ruptured mycotic intracranial aneurysm.

Keywords: *Scedosporium*, Fungal rhinosinusitis, Mycotic aneurysm, Secondary infections, COVID-19

INTRODUCTION

Critical COVID-19 illness takes a huge toll on the host's immune system. Such immunosuppressed status predisposes patients to serious secondary invasive fungal infections (IFI), the most prevalent ones being aspergillosis and candidiasis.[1] *S. apiospermum* is an emerging fungal pathogen that is ubiquitous in nature and commonly found in soil, sewage and polluted water bodies. Scedosporidiosis has a wide spectrum of clinical presentation ranging from colonization of damaged respiratory tract to localized invasive infections and even disseminated disease on occasion. The fungus is refractory to therapy by several anti-fungal agents and is increasingly being recognized as a cause for severe life-threatening infections in immunocompromised individuals.[2,3] Fungal rhinosinusitis (FRS) caused by *Scedosporium* species is not a commonly reported entity.[4-6] Furthermore, its association with COVID-19 is hitherto unknown. Here, we presented a unique case of *S. apiospermum* acute invasive fungal rhinosinusitis (AIFRS) in the background of past COVID-19 illness with atypical presentation of central nervous system (CNS) complications in a geriatric diabetic patient.

CASE REPORT

A 75 year old male patient presented to the neurology outpatient department (OPD) with a complaint of severe headache of one month duration (day 0). There was longstanding history of diabetes and hypertension (>20 years) being managed with oral medication. The patient gave a history of influenza-like illness (ILI) two months prior to day 0, for which admission to a local healthcare facility needed to be done. A nasopharyngeal swab sample was collected at that time to test for SARS CoV2 by RT-PCR and it was reported as positive. Intravenous (IV) remdesivir (200 mg single dose on first day followed by 100 mg once daily for the next 4 days) therapy was initiated in view of the patient's geriatric age and co-morbidities. Subsequent deterioration in oxygen saturation due to acute respiratory distress syndrome

(ARDS) led to administration of IV dexamethasone (6 mg once daily) and 3 doses of IV tocilizumab (400 mg each dose). The patient was shifted to the intensive care unit (ICU) and high flow nasal cannula was applied for managing oxygen saturation. Uncontrolled blood sugar levels of 500-600 mg/dl were recorded and the same were managed with insulin adjusted as per sliding scale. The patient was discharged in stable condition after 20 days of admission.

The patient developed sudden onset headache in the left temporal region 5-6 days after discharge. It was severe enough in intensity to disturb sleep. The pain did not get relieved with non-steroidal anti-inflammatory drugs. This symptom continued for almost a month and was accompanied by left eyelid ptosis that began two weeks prior to day 0.

The patient was referred to our institution with the above complaints. On examination, he was found to be conscious and oriented. Vitals were stable. Except for CNS, the rest of the systemic examination was unremarkable. Cranial nerve examination showed left third cranial nerve (CN) palsy. On day 3, there was development of fourth and sixth CN palsies, resulting in vertical diplopia.

Relevant baseline laboratory investigations revealed a hemoglobin value of 13.40 gm/dl (normal 13-17 gm/dl), mild leucocytosis 11920/µl (normal 4000-11000/µl) but normal differential cell count, elevated C-reactive protein (CRP) at 23.70 mg/l (normal <5.0 mg/l), Erythrocyte sedimentation rate (ESR) of 40mm/hour (normal 0-14 mm/hour). Diabetes was found to be uncontrolled with a glycosylated hemoglobin of 8.1%. Kidney and liver function tests were within normal limits. Viral markers were negative. Screening for autoimmune disorders was also negative.

Magnetic resonance imaging (MRI) with contrast of the brain was done which revealed few tiny acute lacunar infarcts in the frontal cortex and minimal thickening of left cavernous sinus suggestive of sequelae to an inflammatory disorder, granulomatous infective or non-infective. Mucosal thickening was seen in bilateral sphenoid sinuses and bilateral posterior maxillary sinuses. The contents appeared centrally hyperintense on T1 and hypointense on T2 weighted images suggesting chronic inspissated secretions and/or fungal sinusitis. Computed tomography (CT) scan of the paranasal sinuses (PNS), face and orbits revealed mucosal thickening in the right sphenoid sinus causing complete opacification. Mild hyperdense contents were seen in it, raising the possibility of fungal sinusitis. Tiny focal defects suggestive of bone erosion were reported in the right sphenoid sinus (Figure 1).

Based on radiology reports, clinical features and symptom duration of fewer than 4 weeks, a probable diagnosis of AIFRS was conceived. Empirical liposomal amphotericin B (300 mg OD) was commenced.

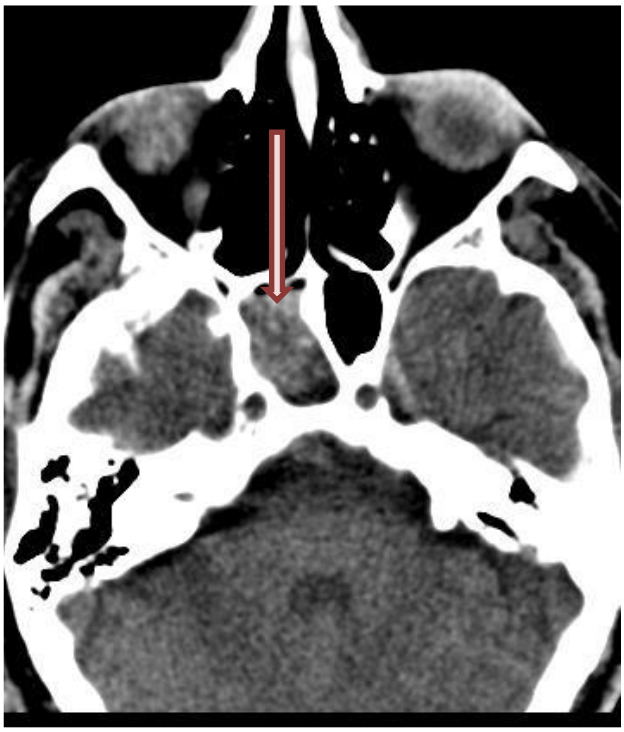

Figure 1: Non-contrast CT scan of the PNS demonstrating mucosal thickening and opacification of the right sphenoid sinus with hyperdense material (arrow) indicating fungal rhinosinusitis.

Functional endoscopic sinus surgery (FESS) of the right sphenoid sinus was performed on day 7. Biopsy specimens were sent for histopathological examination (HPE) and microbiological diagnosis.

The KOH mount of the biopsy revealed hyaline (non-pigmented) thin, septate, branching hyphae. HPE revealed mainly necrotic tissue infiltrated by fungal hyphae and spores.

Fungal culture showed rapidly growing white cottony colonies which turned to olive gray in color in 3-4 days (Figure 2).

The lactophenol cotton blue (LPCB) preparation showed septate hyphae giving rise to conidiogenous cells. Conidia were oval, unicellular, brown and annellidic in origin. Based on microscopic characteristics, a diagnosis of *S. apiospermum* was made (Figure 3).

Graphium eumorphum anamorph characterized by olive brown hyphae cemented together to form synnemata, terminating in a brush of slender conidiogenous cells was also observed at the edge of the colonies in later stages of incubation (Figure 4).

Confirmation of the identity of the fungal isolate was done by Matrix-Assisted Laser Desorption/Ionisation-Time of Flight mass spectrometry on Vitek MS system (bioMérieux, l'Etoile, France).

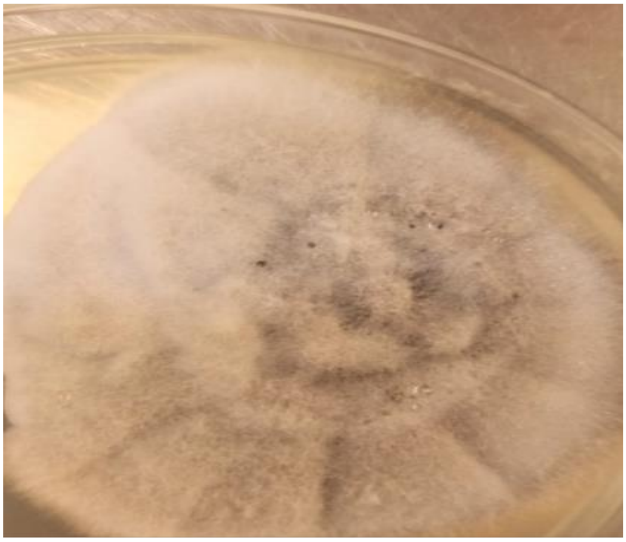

Figure 2: (Color print) downy olive-gray colored colony of *S. apiospermum* on potato dextrose agar.

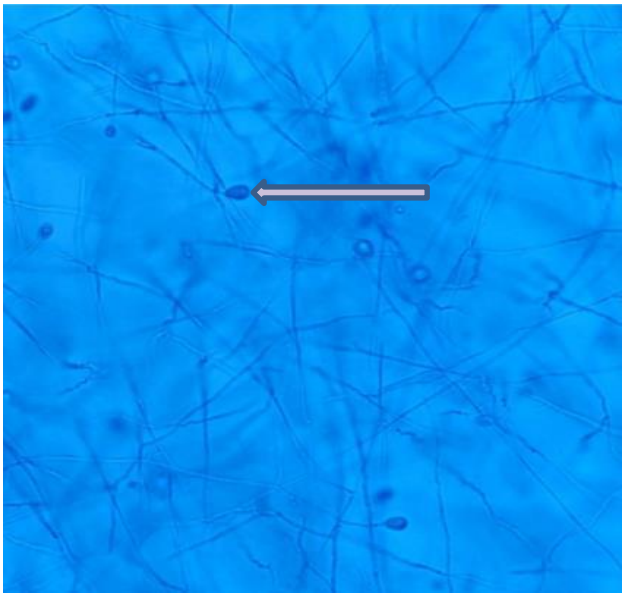

Figure 3: (Color print) lactophenol cotton blue stained mount showing hyaline, thin, septate hyphae and oval annelloconidia (arrow) of *S. apiospermum* (magnification, ×400).

Post FESS, on day 8, the patient developed right upper limb weakness, slurred speech, inability to follow commands with Broca's aphasia and right upper motor neuron facial palsy.

MRI and CT scan of the brain showed interval massive acute subarachnoid hemorrhage (SAH) in the suprasellar, prepontine and perimedullary cisterns and cortical sulci of both the cerebral hemispheres. Acute intra-ventricular hemorrhage (IVH) was present in all the ventricles (Figure 5).

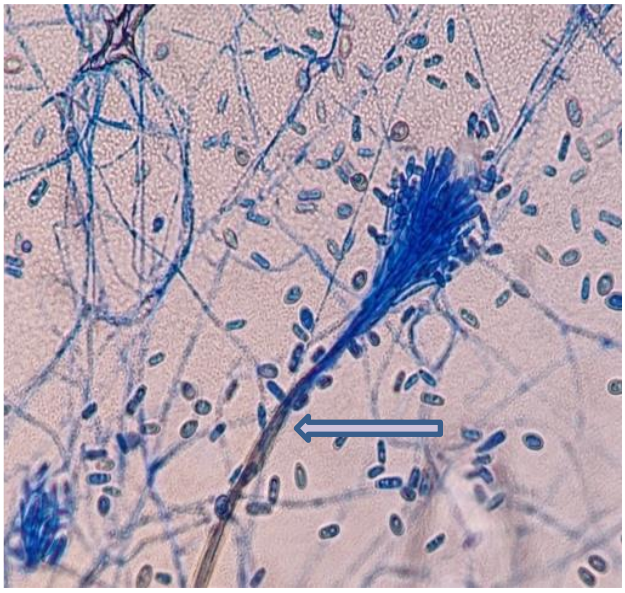

Figure 4: (Color print) lactophenol cotton blue stained mount showing brown-pigmented hyphae forming synnemata (coremia) of graphium stage of *S. apiospermum* (magnification, ×400).

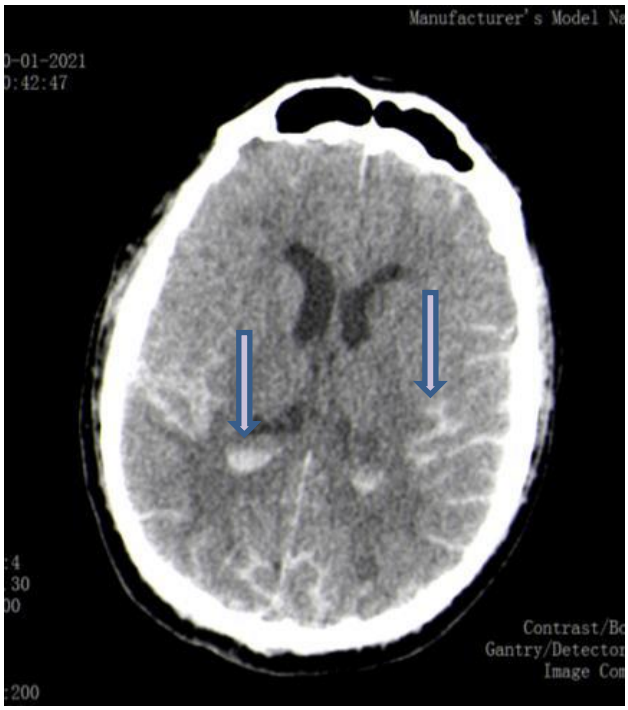

Figure 5: Non-contrast CT scan of the brain showing extensive SAH and IVH (arrows).

CT angiography revealed a fusiform dissecting aneurysm (probably mycotic in origin) in the cavernous segment of the left internal carotid artery (ICA) (Figure 6).

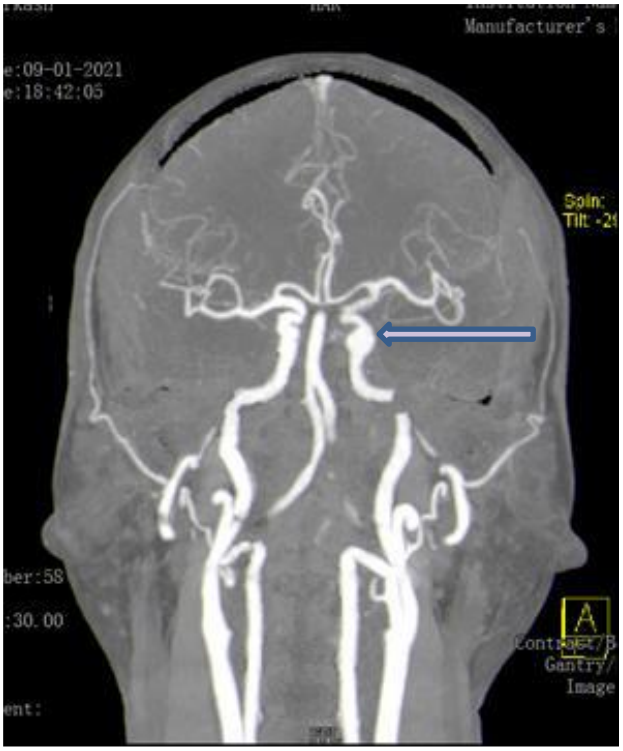

Figure 6: CT angiogram depicting fusiform mycotic aneurysm in the cavernous segment of left ICH (arrow).

Due to the likelihood of ruptured aneurysm, digital subtraction angiography was conducted and endovascular parent artery occlusion of left ICH was done. As a result of ongoing hemorrhagic stroke, plan for surgical debridement of fungal mass was deferred.

The patient was intubated and admitted to the ICU for further care. Based on culture findings, IV voriconazole was started (300 mg twice a day on the first day followed by 200 mg twice daily). Studies show that voriconazole (median MIC50 of 0.25 g/ml) has the most potent activity against *S. apiospermum*. Amphotericin B shows limited *in vitro* antifungal activity (median MIC50 of 4 g/ml).[2] Empirical IV meropenem (1 gm thrice daily) was also administered. Routine surveillance cultures of blood, urine and respiratory samples did not yield any growth of pathogenic organisms. The patient continued to be on mechanical ventilation and deteriorated, requiring inotropic support towards the end. On day 12, the patient had a sudden cardiac arrest and despite best efforts could not be revived.

DISCUSSION

COVID-19 renders a large number of infected individuals susceptible to opportunistic fungal infections. Globally, most reports of secondary IFI are those of COVID-19 associated pulmonary aspergillosis (CAPA) and a handful are those of rhino-orbital mucormycosis.[1,7] In India, although there have been media reports and published cases of secondary IFI since mid-2020, the threat of COVID-19 associated fungal infections emerged in a big way only after the second wave of the pandemic. The etiological spectrum of IFI in our country has been largely dominated by COVID-associated mucormycosis which was declared as a notifiable disease by the government of India due to the massive spurt in cases.[8,9] Paradoxically, reports in media and even those from scientific agencies focused solely on mucormycosis which was labeled as black fungus, a misnomer, while the actual dematiaceous (or melanised/black) fungi which though less common, but equally dangerous as agents of secondary IFI, were overlooked.

White et al reported an incidence of invasive fungal infections of 26.7% with aspergillosis comprising 14.1% of the cases and candida 12·6%. Patients with invasive fungal diseases had higher mortality (53% with versus 31% without).[10] Chowdhury et al from New Delhi, India reported *Candida auris* bloodstream infections in 10 patients, of whom six died (60%).[11] Similarly, high incidences of IFI have been observed in Pakistan (23/147, 15.6%) and Italy (30/108, 27.7%) with significant morbidity and mortality.[12,13]

COVID-19 is known to cause immune dysregulation through various mechanisms like cytokine storm, hyper-inflammatory response and coagulopathy. This leads to damage of respiratory tract epithelium lining, ciliary dysfunction, lung injury and ARDS. Overproduction of IL-6 by alveolar macrophages leads to CD4+ lymphopenia followed by B-cell lymphopenia. Innate immunity is also affected due to depletion in the natural killer (NK) cell count due to the rapidly multiplying virus.[14]

The increased propensity for fungal and bacterial superinfections in critically ill COVID-19 patients is further worsened by factors such as old age, comorbidities, mechanical ventilation, parenteral nutrition, broad-spectrum antibiotic treatment, indwelling lines and catheters, corticosteroid therapy, prolonged hospitalization and so on during the course of treatment. The use of tocilizumab, an IL-6 receptor monoclonal blocking agent, in severe COVID-19 cases has been shown to further exacerbate the situation.[1,15]

Studies have demonstrated that SARS-CoV-2 binds to ACE-2 receptors which are overexpressed in islet cells of the pancreas, qualifying it as a diabetogenic virus that can cause severe instability in the blood glucose levels of diabetes patients, inflammatory imbalance and increased likelihood of secondary infections.[16] The double threat of COVID-19 and diabetes as in the present case, provides a conducive environment for IFI to take root.

Invasive fungal rhinosinusitis due to *Scedosporium* species is not widely reported. In a study by Montone et al in a total of 400 FRS cases, amongst those with aspergilloma, only 5% were found to be due to this particular mold.[17]

Researchers from India found that only 6 cases of FRS due to *S. apiospermum* have been published in literature to date while globally less than 30 cases of FRS due to *Pseudoallescheria boydii* (teleomorph of *S. apiospermum*) have been reported.[4,6]

We conducted a thorough online PubMed and Google Scholar review with the search terms fungal superinfections, fungal rhinosinusitis, scedosporium, scedosporidiosis and COVID-19, to identify any such FRS cases. Our search did not yield any case report demonstrating that opportunistic filamentous fungi like *Scedosporium* species have caused IFI in COVID-19 patients. In saying so, we believe this is the first-ever reported case in published literature of *S. apiospermum* acute invasive FRS in a patient with post COVID-19 status.

The occurrence of two uncommon sequelae of FRS also makes this case remarkable, the presence of multiple CN palsies and a fungal intracranial aneurysm. Our patient presented with headache, ptosis and diplopia which are hallmarks of CN deficits (CN III, IV and VI). Studies have elucidated the pathogenesis of CN palsy in sphenoid sinusitis wherein an extension of the inflammatory process from sphenoid sinus to the nerve sheath directly or via bony erosions, compression of the nerve by an expanding fungal mass or mucosal edema and ischemia of the nerves due to vasculitis are some of the likely mechanisms. CN VI is suspected to be the most commonly involved nerve followed by CN III.[18]

There are scarce reports of mycotic intracranial aneursyms due to *Scedosporium* species in literature. The angioinvasive nature of this species lends itself to promoting vascular complications.[2,19] A fusiform shape, intimal inflammation visible on contrast MRI and ensuing rupture of the cavernous segment aneurysm were indicative of mycotic (fungal) etiology in the present case. Confirmation of the diagnosis could not be achieved as postmortem examination was not done.

In most cases of AIFRS (as in ours), the acute fulminant course of the disease is an exacerbation of pre-existing chronic or allergic fungal rhinosinusitis.[20] AIFRS is known to have a poor prognosis and mortality rates of more than 70% have been reported especially in cases of *Scedosporium* species infection.[5]

In the reported case too, mortality may be attributed to a combination of factors such as immune dysregulation due to diabetes, recent past history of COVID-19, the ensuing medical management, the angioinvasive property of *Scedosporium* species and its refractoriness to antifungals.

CONCLUSION

In conclusion, we report the first case of post COVID-19 *S. apiospermum* invasive fungal infection in the form of AIFRS with probable extension into the CNS and intracranial hemorrhage. Secondary fungal infections associated with COVID-19 are increasing in incidence due to the rampant use of corticosteroids, monoclonal antibodies and invasive medical devices. Although IFI due to Aspergillus species and Mucorales have been more commonly reported in association with COVID-19, other hyaline fungi such as *Scedosporium* species which are refractory to antifungal therapy, must also be a part of the differential diagnoses. The propensity of these fungi to transform from mere colonizers to invasive pathogens in patients with depleted immunity should not be underestimated.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Hena Butta of department of microbiology, Indraprastha Apollo hospitals, Sarita Vihar, New Delhi for confirming the identity of the fungal isolate in Vitek MS system (bioMérieux, l'Etoile, France).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Singla S, Singh V, Bansal A, Sharma JP, Wadhwa T, Sarma S. Post COVID-19 acute invasive fungal rhinosinusitis caused by Scedosporium apiospermum: a covert pathogen. Int J Otorhinolaryngol Head Neck Surg 2021;7:1187-92.