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Post-COVID-19-Invasive Pulmonary Mycosis

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Abstract

COVID-19 has been associated with myriad manifestations as well as adverse outcomes. One of the less commonly reported consequences of COVID-19 is the occurrence of secondary infections in patients suffering acutely from COVID-19 or in those recuperating. Secondary invasive fungal infections (IFIs) have also been observed earlier in other viral infections such as influenza, parainfluenza, and respiratory syncytial virus infections. Severe lung damage and immunologic derangement resulting from SARS-CoV-2 infection predispose to superinfections. Risk factors for secondary IFI includes immunologic derangement and immunoparalysis resulting from SARS-CoV-2 infection, neutropenia, or lymphopenia, poorly controlled diabetes, structural lung disease fungal colonization, and drugs such as corticosteroids or immunomodulators given as therapies for COVID-19. Invasive aspergillosis following COVID-19 is most commonly described fungal infection but other non-*Aspergillus* fungal infections (including mucormycosis) has also been reported. Herein we describe two interesting cases of secondary infections developing in patients beyond the acute phase of COVID-19 who had similar presentations but with different diagnoses and requiring different management strategies. Patient in case 1 developed COVID-19-associated subacute invasive pulmonary aspergillosis (SAIA) and patient in case 2 had COVID-19 associated pulmonary mucormycosis (CAPM). We have also described the various postulated immune-pathogenesis of the super-added fungal infections in COVID-19 patients.

Keywords
- COVID-19
- mucorales
- aspergillosis
- immune dysfunction

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ملخص المقال باللغة العربية

الفطر الرئوي ما بعد الكوفيد-19

المؤلفون: سانيش سوين، كونال شارما، أنيميش راي، سورابي فياس، جاجانديب سينغ، موهيت جوشي، ديبالي جاين، إيماكولاتا أكزس، سانجيف سينها، نفيث وج.
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ارتبط مرض الكوفيد-19 بعدد لا يحصى من الظواهر بالإضافة إلى نتائجه السلبية. واحدة من النتائج الأقل شيوعاً لـ كوفيد-19 هي حدوث عدوى ثانوية في المرضى الذين يعانون بشكل حاد من المرض أو في أولئك الذين يتعافون منه. ولقد لوحظت الالتهابات الفطرية الثانوية الغازية في وقت سابق في حالات العدوى الفيروسية الأخرى مثل الإنفلونزا، نظيرة الإنفلونزا، وعدوى الفيروس التنفسي المتزامن. كما أن تلف الرئة الشديد والاضطراب المناعي الناتج عن عدوى كوفيد-19 يؤدي إلى الإصابة بالعدوى الفائقة.

تشمل عوامل الخطر للإصابة بمرض الالتهابات الفطرية الثانوية الغازية كل من الاختلال والشلل المناعي الناتج عن العدوى بكوفيد-19، ونقص في كل من العدلات واللمفاويات، ومرض السكري الذي لا يتم التحكم فيه بشكل جيد، والاستعمار الفطري لأمراض الرئة الهيكلية، والأدوية مثل الكورتيكوستيرويدات ومضادات المناعة الأخرى التي تُعطى كعلاجات لـ كوفيد-19. يعتبر داء الرشاشيات الغازي الذي يلي الإصابة بكوفيد-19 هو الأكثر شيوعاً للعدوى الفطرية، ولكن تم الإبلاغ أيضاً عن عدوى فطرية أخرى غير الرشاشيات (بما في ذلك فطر الغشاء المخاطي).

في هذا البحث نصف حالتين مثيرتين للاهتمام من العدوى الثانوية التي تطورت في المرضى بعد المرحلة الحادة من كوفيد-19 ولديهم أعراض تقديمية مماثلة ولكن بتشخيصات مختلفة ويتطلبون استراتيجيات علاجية مختلفة. كان المريض في الحالة الأولى مصاب بداء الرشاشيات الرئوي الغازي تحت الحاد المرتبط بـ كوفيد-19، أما المريض في الحالة الثانية فكان مصاباً بداء الغشاء المخاطي الرئوي المرتبط بـ كوفيد-19. لقد وصفنا أيضًا مختلف مسببات الأمراض المناعية المفترضة للعدوى الفطرية فائقة الإضافة في مرضى كوفيد-19.

الكلمات المفتاحية: كوفيد -19، مخاطية، داء الرشاشيات، ضعف الجهاز المناعي.

Case Presentation

Case A

A 45 year old male patient, non-smoker, diabetic on oral medications with uncontrolled sugars (HbA1c-10.4), presented with intermittent low-grade fever, progressive shortness of breath and cough with minimal expectoration for 28 days. The patient was previously hospitalized around 1.5 months back with sever COVID-19 pneumonia and had received steroids for 7 days. On examination, the heart rate was 80 per minute, blood pressure was 122/78 mm Hg, respiratory rate of 18 per minute with a saturation of 95% on room air. Bilateral scattered rales were heard on auscultations, whereas the rest of systemic examination was normal. On current admission, a chest radiograph showed bilateral lower zone opacities. Subsequently, high-resolution computed tomography (HRCT) chest revealed patchy areas of consolidation in the right middle lobe and both lower lobes along with bilateral subpleural areas of ground glass opacities (►**Fig. 1A**). Keeping a strong differential of infectious etiology, broncho-alveolar lavage (BAL) was done. BAL for bacterial etiology (Gram stain and bacterial culture) and tubercular etiology (acid fast bacilli and Genexpert) came out to be negative. Interestingly, BAL for potassium hydroxide (KOH) mount showed septate hyphae with acute angle branching and the fungal culture subsequently grew *Aspergillus fumigatus* (►**Fig. 1B**). Narrowing down our differential to pulmonary aspergillosis a serum antibody (IgG *Aspergillus* ELISA) against *Aspergillus* was sent, which was positive. Given the clinical scenario of a subacute (1–3 months), insidious respiratory pathology, which was fulfilling the European Respiratory Society (ERS) 2014 diagnostic criteria for pulmonary aspergillosis, a diagnosis of subacute invasive pulmonary aspergillosis (SAIA) was made. With a given back drop of a recent severe COVID-19 disease, which may have predisposed to this infection, a final diagnosis of COVID-19-associated SAIA was kept and the patient was started on voriconazole. The patient showed steady improvement, and the last follow-up 6 months from treatment initiation showed clinico-radiological improvement.

Case B

A 55-year-old woman, recently diagnosed diabetic on oral anti-diabetic agents, with past history of severe COVID-19 pneumonia (2 months ago), now presented with complaints of cough with expectoration and streaky hemoptysis for 25 days. An initial chest radiograph, showed a cavitary lesion on the right upper zone. On further evaluation, a HRCT chest revealed a large thick-walled cavity in the right upper lobe with air fluid level and surrounding ground glass opacities (►**Fig. 1C**). The patient underwent BAL to further evaluate the cause for rapidly evolving (< 12 weeks) cavitary lesion. Ziehl–Neelsen (ZN), Genexpert, Gram staining, and bacterial culture was negative. However, KOH mount showed broad aseptate hyphae with wide-angled branching suggestive of mucormycosis. Polymerase chain reaction (PCR) for detection of *Mucorales* performed on the BAL sample using commercially available MucorGenius kit (Pathonostics, The Netherlands), was also positive. A diagnosis of COVID-19-associated pulmonary mucormycosis (CAPM) was made and the patient was started on liposomal amphotericin-B at the dose of 5 mg/kg. After 2 weeks of amphotericin-B therapy,

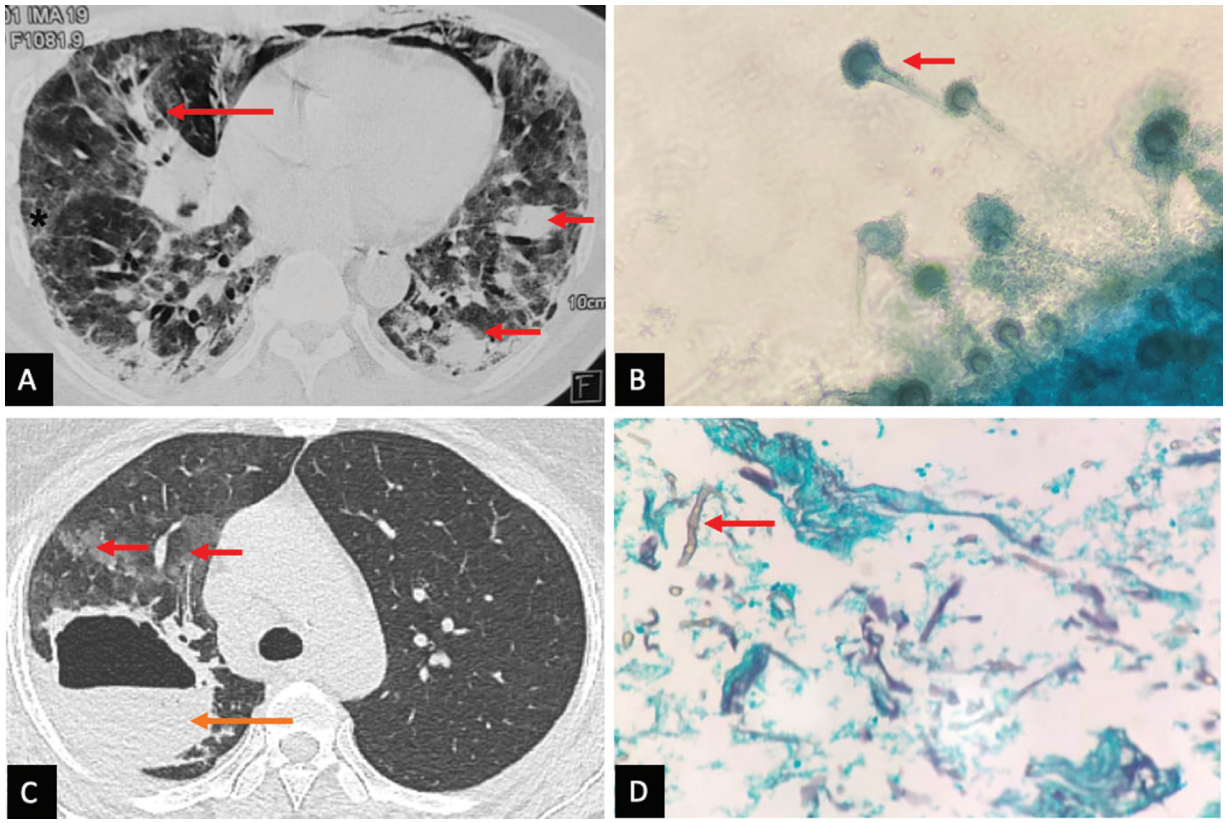

Fig. 1 (**A**) Axial CT image showing patchy areas of consolidation in the right middle lobe and both lower lobes in posterior basal segments (arrow). There are subpleural areas of ground glass opacities also seen bilaterally (asterisk). Mediastinal emphysema is noted anteriorly. (**B**) Lactophenol cotton blue mount showing typical morphology, suggestive of *Aspergillus fumigatus* (arrow). (**C**) Axial CT image showing a thick-walled cavity with air-fluid levels (orange arrow) involving the right upper lobe with surrounding areas of patchy and peribronchial ground glass opacities (arrow). (**D**) Gömöri methenamine silver staining of post lung resection sample showing broad aseptate hyphae with wide-angled branching (arrow).

she underwent a sub-lobar resection of right upper lobe with wedge resection of the right lower lobe. Mucor was also confirmed on the post resection sample of the lungs via broad aseptate hyphae with wide-angled branching on Gömöri methenamine silver staining (►**Fig. 1D**). Postoperatively, the patient was continued on amphotericin-B for 2 weeks with subsequent switch to posaconazole and showed marked clinical improvement. Currently, the patient is doing well and is under regular follow-up.

Discussion

Invasive fungal infections associated with COVID-19 pneumonia is a well-known entity. COVID-19-associated pulmonary aspergillosis (CAPA) has been widely reported across many countries. Although the exact pathophysiology is unclear, immune dysregulation following ARDS, immunosuppressing effect of commonly used drugs for treating COVID-19 (corticosteroids, tocilizumab), direct mucosal damage to the respiratory epithelium by virus and early fungal colonization have all been implicated for the same.[1] While CAPA is a well-established phenomenon, which comprise invasive aspergillosis in COVID-19 patients, COVID-19-associated SAIA is new and an uncommon etiology. Swain et al in a recent prospective study have described 10 patients with COVID-19-associated SAIA.[2] SAIA (previously known as chronic necrotizing or semi-invasive pulmonary aspergillosis) is a slowly progressive form of invasive aspergillosis typically seen in mildly immunocompromised conditions, which progress over 1 to 3 months. The immunocompromising conditions include diabetes mellitus, chronic obstructive lung disease (COPD), radiation therapy, HIV infection, non-tuberculous mycobacterial infection (NTM), connective tissue disorder, and low-dose corticosteroid therapy (5–20 mg every other day).[3] Radiological features in SAIA are variable, which include cavitation, nodules, or consolidation.[4] The diagnosis of SAIA is based on the presence of IgG antibody against *Aspergillus* in blood with subacute progression of the disease with characteristic radiology, typically in a mildly immunocompromised patient.[5] Biopsy may or may not be done for diagnosis that demonstrates fungal hyphae invading lung parenchyma. Oral triazole therapy is recommended for SAIA, preferably voriconazole typically for 9 months or more as in other form of chronic aspergillosis. Patients are to be clinically and radiologically followed up. Surgery may be indicated in patients not responding or deteriorating on systemic antifungals.

Mucormycosis relate to the infections caused by the order Mucorales, with most frequently reported pathogens includes *Rhizopus, Mucor, Lichtheimia* (formerly of the genera *Absidia* and *Mycocladus*), *Rhizomucor, Cunninghamella, Apophysomyces,* and *Saksenaea*.[6] COVID-19-associated mucormycosis (CAM) commonly involves paranasal sinus, orbit and brain with pulmonary involvement being relatively infrequent.[7] Multiple mechanisms has been put forth to explain the recent rise in the incidence of mucormycosis (predominately rhino-orbital involvement) in COVID-19 patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may lead to lymphopenia with impaired cell-mediated immunity (reduction in CD4+ and CD8+ cell population).[8] Pre-existing hyperglycemia (uncontrolled diabetes mellitus) or steroid-induced hyperglycemia with or without ketoacidosis is considered as a sine qua non.[9] Hyperglycemia-induced acidosis or ketosis lowers the serum pH, which leads to glycosylation of ferritin leading to the generation of free iron and facilitating the growth of mucorales.[10] Low serum pH also reduces chemotaxis; the phagocytic effect macrophages and adequate functioning of neutrophils. Fungal ligand spore coating homologue (CotH) protein present on the mucorales binds to the glucose receptor protein-78 (GRP-78) present on host endothelial cells which aid in attachment to the endothelium and angioinvasion.[11] Both hyperglycemia and COVID-19 are known to upregulate GRP-78 and CotH function. Interplay of multiple above-described factors along with upregulation of GRP-78 in COVID-19 disease leads to increased susceptibility as well as angioinvasion of mucorales in these group of patient.[12] Diagnosis of COVID-19-associated pulmonary mucormycosis (CAPM) is based on radiological imaging, culture, and microscopy, and histopathology. Consolidation and cavity are predominate lesions, followed by ground glassing are on CT scan in CAPM, which may mimic CAPA or other cavitary pneumonia.[13] Strict glycemic control is of paramount importance along with anti-fungal drugs. Treatment includes liposomal amphotericin B (infusion at a dose of 5–10 mg/kg per day) initially followed by a switch to posaconazole (gastro-resistant tablets preferred over syrup) after 4 to 6 weeks. Isavuconazole has also been recently recommended with moderate strength for the first-line treatment of mucormycosis based on results from the VITAL study.[14] The optimal duration of anti-fungal therapy is not clear and depends on the clinical and radiological response of the patients. Surgical intervention is frequently needed for complete cure.[15]

Conclusion

These two cases exemplify the relatively rarer fungal diseases in the background of COVID-19. Both of these cases had almost similar clinical presentations which started ~ 1 month after suffering from COVID-19. Diabetes was a common risk factor for both patients. The radiological features were non-specific and bronchoalveolar lavage sampling clinched the diagnosis in both the cases. It is thus important to consider the diagnoses of SAIA and CAM in the background of COVID-19 even in patients who are not overtly immunosuppressed. Early diagnosis and prompt treatment can help in appropriate management of such cases.

Consent
Consent was obtained from the patient directly.

Ethics Approval
Not required (as being a case report).

Authors' Contributions
SS, AR: conceptualization; SS, KS, AR, MJ: involved in patient management. All authors contributed to drafting the initial manuscript. Manuscript was proofread and reviewed by SS and NW.

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Conflicts of Interest
None declared.

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