Post Covid Pulmonary Fungal Infection

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Pulmonary cavitation: an under-recognized late complication of severe COVID-19 lung disease,

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- a retrospective review of all patients admitted to our institution with COVID-19 and reviewed electronic medical records and imaging to identify patients who developed pulmonary cavitation.
- Twelve out of 689 (1.7%) patients admitted to our institution with COVID-19 developed pulmonary cavitation, comprising 3.3% (n = 12/359) of patients who developed COVID-19 pneumonia, and 11% (n = 12/110) of those admitted to the intensive care unit.

- Four of twelve patients who had developed pulmonary cavitation (including two of the survivors) had no microbiological, serological, clinical or distinct radiological characteristics of invasive fungal infection and did not receive treatment for this. However, these four patients did have infection with bacterial organisms known to cause cavitation. Infection with mycobacterium tuberculosis (MTB) is also a common cause of lung cavitation and in a recently published case series. it has been described as a coinfection in COVID-19 patients resulting in cavity formation. However, in all 12 of our patients, MTB infection was ruled out based on negative Acid-Fast Bacilli on smear and culture of multiple respiratory specimens.

- We hypothesize that the causes of cavitation in these patients was multifactorial, with contributing factors including: bacterial and fungal co-infection; the immunosuppressive effects of glucocorticoids and tocilizumab; SARS-CoV-2 specific inflammatory pathways; the COVID-19 related predisposition to venous thromboembolism and potential to cause infarct and micro-infarcts leading to cavitation; and the severe morbidity of this patient population.

Overview

- Symptoms of some fungal diseases can be similar to those of COVID-19, including fever, cough, and shortness of breath. Laboratory testing is necessary to determine if a person has a fungal infection or COVID-19. Some patients can have COVID-19 and a fungal infection at the same time.

- People with severe COVID-19, such as those in an intensive care unit (ICU), are particularly vulnerable to bacterial and fungal infections. The most common fungal infections in patients with COVID-19 include aspergillosis or invasive candidiasis.

COVID-19-associated pulmonary aspergillosis

- Severe acute respiratory syndrome coronavirus 2 causes direct damage to the airway epithelium, enabling aspergillus invasion. Furthermore, viral infection hampers ciliary clearance and leads to immune dysfunction or dysregulation, or both, locally or systemically.

- Decline of lymphocyte counts can be accompanied by defective function. Severe lymphopenia has been established as a factor predicting the risk of invasive mould disease in patients with haematological malignancies.

- The syndromes of pulmonary aspergillosis complicating severe viral infections are distinct from classic IPA. IPA, particularly that associated with hematologic malignancies and transplantation, is most frequently encountered in patients with neutropenia and other immuno compromised individuals. Numerous studies have recognized influenza-associated pulmonary aspergillosis (IAPA) associated with respiratory epithelium damage.

- several studies have shown that steroid and other immune-modulatory therapies are linked to an increased risk of a similar syndrome associated with severe COVID-19, termed COVID-19-associated pulmonary aspergillosis (CAPA).

Incidence and risk factors

- **Incidence and risk factors**
- Owing to differences in diagnostic criteria, methods, definitions, and local practices, the incidence of CAPA varies. Therefore, the estimation of CAPA incidence is challenging due to the lack of a gold standard and limitations in diagnostic tests. For this reason, definitions used for IAPA were applied in most studies; however, this approach generated a wide degree of variability in the incidence of CAPA among ICU patients (range: 3.8–34%).

2020 ECMM/ISHAM consensus criteria for research and clinical guidance, LANCET, June 01, 2021

- **CAPA characteristics and host factors**
- There are evident similarities between IAPA and CAPA, including high prevalence, absence of classic host factors for invasive fungal infection, similar timing in the disease diagnosis after ICU admission, and the presence of lymphopenia.
- In the study by Bartoletti and colleagues, most patients received anti-interleukin (IL)-6 treatment with tocilizumab, as well as corticosteroids.
- Indeed, chronic corticosteroid treatment was substantially more frequent in patients with CAPA.

Imaging

- Atypical features of COVID-19 can be suggestive of other diseases, particularly other infections, such as lobar or segmental consolidation in the setting of bacterial pneumonia, cavitation from necrotising pneumonia.
- In this context, many atypical signs of COVID-19 pneumonia can mimic IPA, and vice versa, and radiology alone is not sufficient to define patients with CAPA. There is additional complexity in patients with ARDS, such as mixed infections or drug toxicities. Indeed, lesions suggestive of IPA can be hidden or mimicked by lung involvement in patients with severe COVID-19. However, use of imaging as a reliable criterion for a case definition of CAPA is debatable.

- Multiple pulmonary nodules or lung cavitation should prompt thorough investigation for IPA, as they are rarely seen with COVID-19 alone.
- Frequently observed radiological features of IPA, such as the halo sign, are not sufficient to define CAPA without mycological evidence. This feature is insufficient because the halo sign suggests local infarction, and an intrinsic part of severe COVID-19 is in-situ thrombosis due to endotheliopathy.

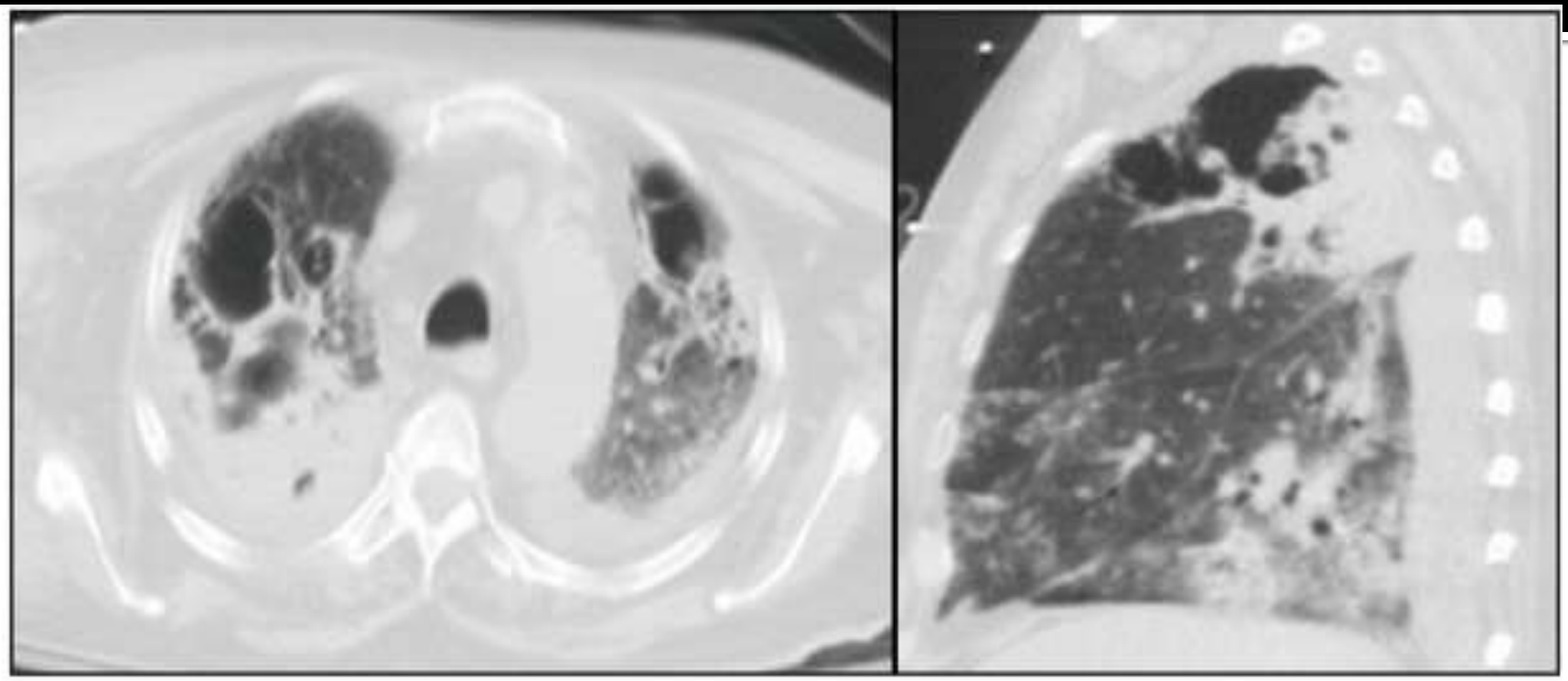

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Fig. 4. Transverse and sagittal images (slices) from CT of chest scan on day + 19 of hospitalization demonstrating bilateral pneumonia and upper lobe cavitations.

Mycological evidence

- For diagnosis of IPA, bronchoalveolar lavage fluid and lung biopsy samples are the specimens of choice. Tissue culture and tissue microscopy showing invasive growth of septate fungal hyphae of primarily sterile specimens represent the diagnostic gold standard in proving infection. However, biopsies are high-risk procedures in this patient population and, therefore, are avoided by many clinicians .

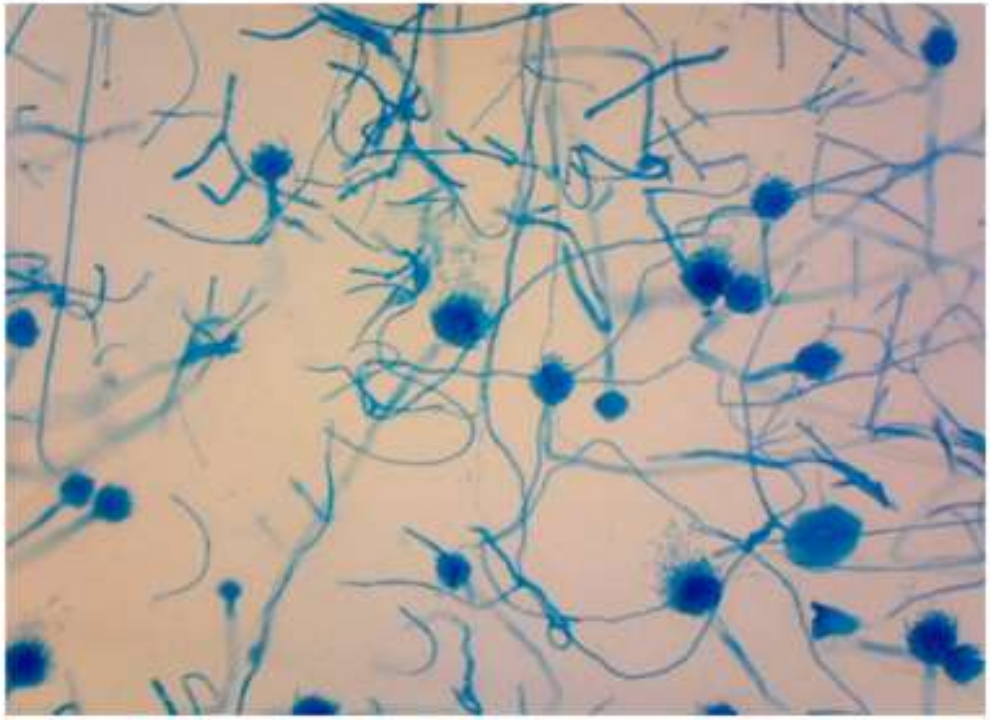

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Fig. 2. Septate hyphae and conidia heads of *Aspergillus fumigatus* from BAL specimen on day +14 (Lactophenol cotton blue, 200X). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

- Detection of galactomannan in BAL fluid is highly indicative of IPA, as the antigen is released during active fungal growth. To date, galactomannan in BAL has been the main diagnostic test to diagnose secondary IPA in patients with severe viral infection.
- Detection of galactomannan in BAL does not prove tissue invasion, and the likelihood of infection is increased if circulating galactomannan is detected. Unfortunately, the diagnostic yield of serum galactomannan is low in CAPA as, at best, 20% of patients showed positive results, and proven CAPA cases have been reported with negative serum galactomannan.
- This low sensitivity is in line with published performance of serum galactomannan detection in non-neutropenic patients in ICUs but lower than the 65% sensitivity of serum galactomannan in patients with IAPA. Overall, serum galactomannan has decreased value for excluding CAPA.

- Use of not only galactomannan but also another biomarker, namely (1–3)-β-D-glucan, for serum screening might be beneficial. A study unrelated to COVID-19, comparing patients in the ICU with proven or probable IFD with patients with fungal colonisation and without IFD, showed that two consecutive positive test results for serum (1–3)-β-D-glucan generate a specificity of 90%.
- Two consecutive results for serum (1–3)-β-D-glucan might, therefore, increase suspicion of invasive aspergillosis, although (1–3)-β-D-glucan is not specific for aspergillosis and other causes of elevated serum concentration of (1–3)-β-D-glucan need to be excluded.

- In 2020, aspergillus PCR was included in consensus guidelines for defining IFD, with the requirement of two positive results providing sufficient specificity to confirm a diagnosis.

- BAL testing is preferable, and although the enhanced sensitivity of PCR means it can detect *Aspergillus* spp that are colonising or contaminating the airways, PCR testing of BAL provides specificity that is at least similar to that of galactomannan testing.

- In the presence of clinical or radiological evidence typical of IPA, a single positive bronchoalveolar lavage result from the infected lobe is likely to be indicative of IPA, and galactomannan testing is usually concordant. As with other biomarkers, detection of aspergillus DNA in the bloodstream of non-haematological populations will likely be low, but PCR positivity is indicative of IPA, although multiple blood positives increase specificity (ie, to >95%).

- Evidence for the testing of non-bronchoscopic lavage (considered to be a blind application of 10–20 mL saline recovered by aspiration via a closed suction system in a patient who is intubated) is scarce in patients with and without CAPA.

- **Proven CAPA**
- Proven CAPA is defined as pulmonary or tracheobronchial infection. It is proven by histopathological or direct microscopic detection, or both, of fungal elements that are morphologically consistent with *Aspergillus* spp, showing invasive growth into tissues with associated tissue damage, or (with or without) aspergillus recovered by culture or detected by microscopy, in histology studies or by PCR from material that was obtained by a sterile aspiration or biopsy from a pulmonary site, showing an infectious disease

- In patients with non-proven CAPA, classification relies on aspergillus culture from the respiratory tract or detection of biomarkers.

- **Probable CAPA**
- Invasive aspergillus tracheobronchitis is classified separately from other pulmonary manifestations as it requires a different diagnostic approach. Diagnosis of probable CAPA tracheobronchitis requires observation of tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar, alone or in combination, on bronchoscopic analysis and mycological evidence .T

- The diagnosis of probable pulmonary CAPA require a pulmonary infiltrate or nodules, preferably documented by chest CT, or cavitating infiltrate (not attributed to another cause), or both, combined with mycological evidence. For mycological tests and cutoffs, we aimed to comply with other IPA case definitions, if possible.

- Possible CAPA
- Although definitions of proven and probable disease have been shown to be reliable in research, a possible category has been abandoned in most definitions due to the low probability of IPA being present and an absence of consensus.

- Possible pulmonary CAPA requires pulmonary infiltrate or nodules, preferably documented by chest CT, or cavitating infiltrate (which is not attributed to another cause) in combination with mycological evidence (eg, microscopy, culture, or galactomannan, alone or in combination) obtained via non-bronchoscopic lavage.

- Detection of galactomannan in non-bronchoscopic lavage is considered to be evidence for CAPA, but proposed cutoff values are based on a single study and require further validation.
- Although classification of possible CAPA will most likely be sufficient to initiate antifungal therapy in the clinical setting, in line with other consensus statements, it is not recommended for enrolling patients into clinical trials.

Guidance on clinical management of CAPA

- Any of the following clinical findings: refractory fever for more than 3 days or a new fever after a period of defervescence of longer than 48 h during appropriate antibiotic therapy, in the absence of any other obvious cause; worsening respiratory status (eg, tachypnoea or increasing oxygen requirements); haemoptysis; and pleural friction rub or chest pain, can trigger diagnostic investigations for CAPA in patients with refractory respiratory failure for more than 5–14 days despite receiving all support recommended for patients with COVID-19 who are critically ill.
- However, the onset of clinical features can be variable and patients can present with CAPA on ICU admission or after..

- Lung imaging findings should be supplemented with sampling from the lower respiratory tract under appropriate precautions for infection control.
- In patients without clinical response or with progressive nodular infiltrates, CT-guided biopsy or bronchoscopy should be considered if the benefits outweigh the risks for the patient or the risk of transmission.

Antifungal treatment

- **Antifungal treatment**
- Either voriconazole or isavuconazole as first-line treatment for possible, probable, and proven CAPA.

- Liposomal amphotericin B is the primary alternative option for treatment of IPA in the ICU, however, the drug is nephrotoxic and might result in a further decline of renal function, especially in patients who already have acute kidney injury.
- Alternative second-line options are posaconazole or echinocandins. Echinocandins should not be used as monotherapy if other options are left, but they can indeed be used for salvage therapy.

- Voriconazole treatment (loading dose 6 mg/kg twice a day for two doses, followed by 4 mg/kg twice a day) has a better outcome than does treatment with amphotericin B deoxycholate, especially with its known serious toxicities.
- However, liposomal amphotericin B can be considered for initial therapy if, epidemiologically, drug-resistant patterns support this treatment, before the results of susceptibility testing for voriconazoles are available. The recommended initial dose of liposomal amphotericin B is 3 mg/kg per day.

- Echinocandins are not recommended for use as monotherapy in primary invasive aspergillosis but, in combination with an azole, might have some therapeutic advantage in critically ill patients·
- •Posaconazole has excellent in-vitro aspergillus activity and has been successfully used as salvage treatment in patients without COVID-19.
- •Itraconazole shows excellent in-vitro aspergillus activity but does not have robust comparative data with established regimens.

- The optimal duration of therapy is unknown and radiological lung imaging might not be a helpful gauge, but the expert panel suggest 6–12 weeks as a treatment course. However, it seems reasonable to include follow-up lung CT imaging to document the resolution of infiltrates before termination of treatment

- In patients who are immunocompromised (eg, with haematological malignancy or receiving immunosuppressive therapy), longer treatment might be necessary than for other patients. Following the galactomannan-index in serum as a measure of therapeutic response might be limited by its poor sensitivity when testing serum in non-neutropenic patients, but attaining follow-up respiratory samples for galactomannan testing could be useful to determine efficacy in patients who are galactomannan positive, which might help to determine treatment duration.

Invasive candidiasis in patients with COVID-19

- Patients hospitalized for COVID-19 are at risk for healthcare-associated infections (HAIs), including candidemia, or bloodstream infections caused by *Candida*. Fungal infections resistant to antifungal treatment have also been described in patients with severe COVID-19. Early diagnosis and monitoring for *Candida* infections and antifungal resistant infections (e.g., *C. auris*, azole-resistant *Aspergillus*) are key to reducing death from COVID-19 in patients with severe COVID-19 fungal co-infections.

COVID-19-associated mucormycosis

- COVID-19–associated mucormycosis is less common than other COVID-19–associated fungal infections, but emerging reports from India highlight the importance of considering this infection. Some medications used to treat severe COVID-19, including high-dose corticosteroids and tocilizumab, might predispose patients with COVID-19 to mucormycosis. Mucormycosis has been reported in patients with severe COVID-19 infection who lacked other classical mucormycosis risk factors, such as diabetes, conditions or medications that weaken the immune system, and cancer.

- Early diagnosis and treatment are key to improving outcomes for patients with COVID-19–associated mucormycosis. Clinicians should consider the possibility of mucormycosis in patients with severe COVID-19 even when patients lack classical risk factors for this disease. Biomarkers for diagnosing invasive aspergillosis, such as beta-d-glucan and galactomannan, are typically negative in patients with mucormycosis. The treatment for mucormycosis frequently involves aggressive surgical intervention and treatment with antifungals, including amphotericin B, posaconazole, or isavuconazole. Voriconazole is not recommended for treating mucormycosis.