

Pulmonary Aspergillosis in a COVID 19 Patient: A Case Report and Literature Review

Fatima Babokh^{1, 2*}, Btissam Ait boucetta^{1, 2}, Soumia Nachat^{1, 2}, Fatimzahra Rahali^{1, 2}, Awatif El Hakkouni^{1, 2}

¹Parasitology and mycology laboratory, Arrazi hospital, CHU Mohammed VI, Marrakech, Morocco

²Faculty of Medicine and Pharmacy in Marrakech, Cadi Ayyad University, Marrakech, Morocco

DOI: [10.36348/sjbr.2022.v07i04.007](https://doi.org/10.36348/sjbr.2022.v07i04.007)

| Received: 19.03.2022 | Accepted: 22.04.2022 | Published: 30.04.2022

*Corresponding author: Fatima Babokh

Parasitology and mycology laboratory, Arrazi hospital, CHU Mohammed VI, Marrakech, Morocco

Abstract

As the COVID 19 pandemic evolves, concerns about fungal co-infections and superinfections are increasing, mainly towards invasive pulmonary aspergillosis (IPA), which increases significantly the risk of mortality in these patients, thus requiring early detection and diagnosis for better treatment efficiency. We're describing the case of a young, non-immunocompromised patient with SARS COV 2 infection, who developed an IPA due to *Aspergillus flavus*.

Keywords: Invasive pulmonary aspergillosis' Bronchoalveolar lavage' mycological diagnosis' COVID-19' *Aspergillus flavus*'.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause direct damage to the airway epithelium, allowing invasion by molds such as *Aspergillus* genus. This superinfection contributes to the worsening of the COVID-19 patients' condition and increases mortality. (Bartoletti *et al.*, 2021).

We report here a new observation of a young, immunocompetent patient with COVID-19 in whom *Aspergillus flavus* has been identified in a pulmonary specimen.

CASE REPORT

A 17-years-old patient with non-significant medical history, hospitalized for suspected respiratory SARS COV 2 infection (dyspnea, coughing and fever), confirmed by an RT-PCR test (reverse transcriptase polymerase chain reaction) on a nasal swab, was transferred later to an intensive care unit for COVID 19 patients, due to worsening respiratory distress and oxygen desaturation.

The patient received an initial treatment of: antibiotics therapy; amoxicillin-clavulanic acid, corticosteroid therapy (dexamethasone at a dose of 6 mg/ kg/day), preventive anticoagulant and oxygen

therapy; according to the Moroccan treatment guidelines for moderate to severe COVID 19 forms.

His initial blood tests showed a high level of C-reactive protein at 96 mg/l, leukocytosis with a cell count of 12380 cells/mm³, thrombocytosis at 601.10³/mm³, a high D-dimer and LDH values, respectively, of 18.26 µg/mL and 403 U/L, and anemia with a hemoglobin level of 10.3 g/dL. In addition, the liver and kidney function tests were normal. Serologies for viral infections (B and C hepatitis viruses and HIV) were negative. And all bacterial and mycological blood cultures remained sterile. Tuberculosis exploration on respiratory samples by GeneXpert® technique was negative. The control PCR for SARS COV 2 came negative after 15 days of treatment. The patient's respiratory status was stable with a slight decrease in CRP to 86 mg/L, a decrease in leukocyte count to 10.86.10³/mm³, and platelet count to 430.10³/mm³ and LDH to 341 U/L.

The clinical evolution was marked by a worsening of his respiratory condition, and he was hospitalized in the Pneumology Department. A chest CT-scan showed a necrotizing pleuropneumopathy associated to several bilateral excavated nodules.

A multiplex respiratory PCR was performed and was positive to *Pseudomonas aeruginosa* and *Staphylococcus aureus*, the patient was then treated by Ceftriaxone and Gentamycin without any clinical

improvement. A bronchial aspiration was performed for mycological testing. Direct microscopic examination of the specimen, and MGG staining showed hyaline septated hyphae with acute angle branching (Figure 1).

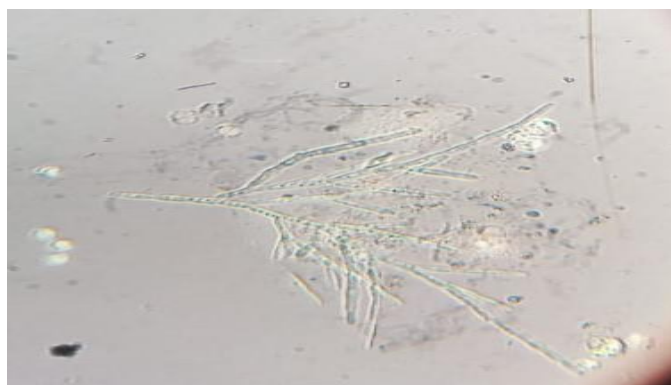


Fig-1: Direct microscopical observation of hyaline septated hyphae with acute angle branching in a bronchial aspirate

The specimen culture on Sabouraud agar incubated at 35°C for 2 days, showed flat colonies with

a woolly to granular texture, a green-yellowish color with a yellowish to brown back (Figure 2).



Fig-2: Culture growth of flat fungal colonies with a woolly to granular texture, and a green-yellowish color

Microscopic examination of the colonies after Lactophenol blue staining showed septate and hyaline Hyphae, with regular, long conidiophores, columnar

and radiate aspergillate head with spherical vesicle and globose conidia in favor of *Aspergillus flavus* (Figure 3).

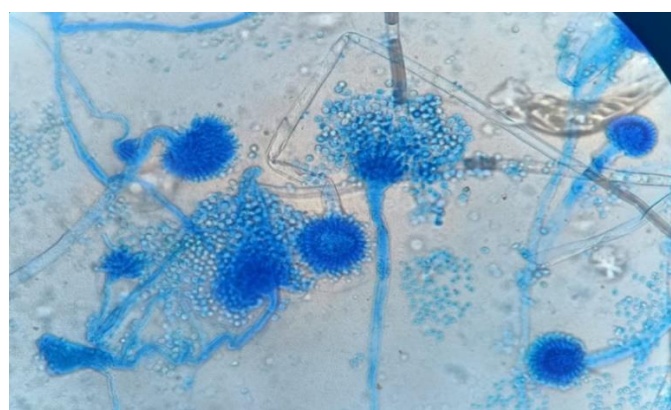


Fig-3: Microscopic examination of the colonies after Lactophenol blue staining

DISCUSSION

SARS COV 2 increases the risk of bacterial and fungal co-infections and superinfections such as invasive pulmonary aspergillosis (IPA), which incidence in (Chong & Neu, 2021) systematic review was of 13.5% (ranging from 2.5% to 35.0%).

As in the case of our patient, patients with SARS COV 2 are prone to develop IPA despite the absence of any underlying risk factor, This may be related to tissue damages in the airway epithelium caused by hyperactivation of inflammatory signaling

pathways, amplification of the inflammatory response, and secretion of proinflammatory cytokines (TNF, IL1, IL6, and IL10), thus establishing a favorable environment for fungal infections (Cunha *et al.*, 2011, 2012; Huang *et al.*, 2020; Sorci *et al.*, 2011). Other factors have also been incriminated in the occurrence of IPA in patients with COVID 19, including concomitant use of corticosteroids, as shown by several studies (Alanio *et al.*, 2020; Koehler *et al.*, 2020; Rutsaert *et al.*, 2020). It has been found that the use of systemic corticosteroids to reduce the inflammatory response in patients with acute respiratory distress syndrome may increase their vulnerability to develop secondary fungal infections (Du *et al.*, 2020; D. Wang *et al.*, 2020). In our patient case, administration of corticosteroids (Dexamethasone 6 mg/day) for two weeks may have increased his susceptibility for an *Aspergillus* infection.

Patients with IPA on SARS COV 2 may not have typical host factors such as neutropenia, hematologic malignancy, or kidney transplantation (Van de Veerdonk *et al.*, 2017). Even the radiological signs vary widely from excavated nodules, as in the case of our patient, multiple pulmonary nodules, ground-glass opacities, or a reverse halo sign. All these radiological signs can also be observed in COVID 19 uncomplicated with IPA (J. Wang *et al.*, 2020).

The diagnosis is most often made on non-specific clinical and radiological evidence combined with positive mycological results. A chest CT scans, followed with a swab of the lower respiratory tract for mycological examination in search of aspergillus. Galactomannan can also be measured on serum or BAL. intubated COVID-19 patients, tracheal suctioning and non-bronchoscopic lavage can be obtained regularly, reducing the risk of infection.

Early diagnosis of IPA in COVID 19 patients relies on the detection of the fungus in a respiratory specimen. Bronchoalveolar lavage (BAL) and lung biopsy are the samples of choice (Alanio *et al.*, 2020). However, obtaining mycological evidence remains difficult; lung biopsy is a dangerous procedure in this category of patients, and bronchoscopy has a high risk of exposure and contamination toward operators during this pandemic (Blaize *et al.*, 2020). As for the causal species, *Aspergillus flavus* is the second most common mycological agent of IPA after *A. fumigates* (H. Wang *et al.*, 2003). High levels of Galactomannan (Galactomannan index > 2.5) have been observed in patients with suspected IPA associated to Covid 19 (Koehler *et al.*, 2020; Wahidi *et al.*, 2020). It is therefore a non-specific polysaccharide antigen released by *Aspergillus* but also by other fungi like *Cryptococcus* and *Fusarium*.

The first-line antifungal treatment to be used for IPA in COVID-19 patients is Voriconazole, with a loading dose of 6 mg/kg twice daily, followed by 4

mg/kg twice daily. It should be used cautiously due to potential drug interaction especially for cardiovascular toxicity in patients receiving anti-SARS-CoV-2 therapy (Baniasadi *et al.*, 2015). Isavuconazole can also be used at a loading dose of 200 mg three times daily, followed by 200 mg once daily (12-24 h after the last loading dose). It has the same clinical results as Voriconazole with fewer side effects (Maertens *et al.*, 2016; Mellinghoff *et al.*, 2018). In case of suspected resistance to azoles, liposomal amphotericin B is an alternative treatment at a dose of 3 mg/kg/d. However, the concern for its renal toxicity is particularly relevant for patients who are infected with SARS-CoV-2, because of the renal tropism of this virus (Cornely *et al.*, 2007). Biological monitoring of renal and hepatic function is thus required twice a week during treatment. Echinocandins, which should not be used as monotherapy but rather in combination with azoles, as well as Posaconazole, can be used as a last line treatment option. New classes of antifungals being developed, such as Fosmanogepix and Ibrexafungerp, may become alternative treatment options for IPA (Kupferschmidt, 2019). Optimal duration of treatment for IPA is still not well established, ranging from 6 to 12 weeks, and even longer in immunocompromised patients. Chest CT-scan follow-ups to assess the resolution of infiltrates are necessary before any decision to discontinue treatment (Bartoletti *et al.*, 2021).

An increase in mortality rates associated to IPA in COVID19 patients has also been described. In a prospective cohort of 108 critically ill patients with SARS COV 2, over a 30-day period, the highest mortality rate was observed in patients with IPA: 44% versus 19% in patients without pulmonary aspergillosis (White *et al.*, 2021). Thus, IPA appears to be a serious secondary infection in patients with COVID-19 with poor prognosis. Hence, an investigation for IPA in Covid-19 patients should be performed in the following cases (Schauwvlieghe *et al.*, 2018):

- Refractory fever for more than 3 days.
- Recurrence of fever after a period longer than 48 hours of remission on antibiotic therapy.
- Refractory respiratory failure for more than 5 to 14 days despite adequate treatment.

CONCLUSION

IPA in co-infection or superinfection with SARS COV 2 is a severe condition in terms of prognosis and treatment. *Aspergillus s.p.p.* can become infectious in these patients even without any recognized risk factor and even after remission of COVID 19. This is why health professionals dealing with COVID-19 pandemic must be vigilant to the risk of fungal complications particularly IPA. Diagnosis remains difficult and relies essentially on mycological evidence by isolation and identification of the fungus from pulmonary specimens and on the search for

Galactomannan antigen in the patients' serum or BAL fluid.

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