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CASE REPORT

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COVID-19 complicated with chronic necrotizing pulmonary aspergillosis and aspergilloma progressing to fibrosing aspergillosis: A case report

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Abstract

Aspergillosis superinfections have been reported as acute complications of COVID-19. We report a rare case of combined chronic necrotizing pulmonary aspergillosis, aspergilloma, and fibrosing aspergillosis in a 31-year-old woman with a history of COVID-19. Chest scan remains an important imaging method assisting in the diagnosis and management of post-COVID-19 patients.

KEYWORDS

aspergillosis, complication, CT scan, infection, Madagascar, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) continues to be a worldwide concern since its discovery in December 2019. Its course is sometimes unpredictable. COVID-19 may result in recovery, acute complications, long-term effects, or death.[1] COVID-19 co-infections such as fungal superinfection can aggravate a patient's prognosis.[2] Cases of fatal acute invasive aspergillosis have been reported as a complication of COVID-19 in patients with a severe form of the disease.[2,3] The overall survival rate after 12 weeks was 47.2%.[4] To our knowledge, rare cases of subacute invasive pulmonary aspergillosis or chronic necrotizing pulmonary aspergillosis have been reported as a complication of pneumonia due to COVID-19.[5] Here, we report an unusual combination of chronic necrotizing pulmonary aspergillosis, aspergilloma, and fibrosing aspergillosis in a young woman with a history of COVID-19.

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2 | CASE PRESENTATION

The patient was a 31-year-old housewife. She had a severe form of COVID-19, diagnosed clinically and biologically (positivity of the SARS-CoV-2 RT-PCR test on a nasopharyngeal swab), evolving favorably under a well-conducted treatment including azithromycin for 5 days, ceftriaxone, dexamethasone, and enoxaparine for 14 days. She had no other specific history, including no smoking, no alcoholism, no diabetes, and no history of pulmonary tuberculosis. Her history dates back to 3 months after her hospitalization by progressively worsening shortness of breath (dyspnea), left chest pain of a heavy feeling, without radiation, evolving in a context of impaired general condition such as asthenia and weight loss. She received various treatments including antibiotics, tonics, and bronchodilators, without any improvement. On the contrary, she developed a productive wet cough with yellowish sputum not weaned. Therefore, she was hospitalized again for respiratory discomfort, chest pain, cough, and impaired general condition. The clinical examination on admission objectified a decrease in oxygen saturation at 90% in ambient air (96% with oxygen 4 liters per minute), a respiratory rate of 20 cycles per minute, a heart rate at 75 beats per minute, a blood pressure of 130/60 mmHg, a temperature at 36.9°C, and a fatigue. Her body mass index was 20 kg/m^2. The physical examination had nothing particular. The electrocardiogram was unremarkable. Biological examinations revealed an inflammatory syndrome with a hyperleukocytosis of 22.9 × 10^9/L, predominantly neutrophils (79%), a red blood cell sedimentation rate of 24 mm and a C-reactive protein of 13.9 mg/L. Other biological tests were normal, with a D-dimer level of 348 ng/mL, a glycemia of 5.37 mmol/L and a negative HIV serology. The SARS-CoV-2 RT-PCR test performed on suspicion of a long COVID was negative. SARS-CoV-2 serology was positive for Ig G. The GeneXpert MTB/RIF sputum tests for pulmonary tuberculosis were negative. Sputum cyto-bacteriological tests were also negative. Direct mycological examination of the sputum showed mycelial filaments (hyphae) referring to *Aspergillus*. The chest CT scan without injection of contrast agent revealed a cavitary lesion in the apical segment of the left upper lobe, within which was an approximately spherical shadow surrounded by an "air crescent"; typical of fungal ball lesion, suggestive of an aspergilloma (Figure 1). It should be noted that *Aspergillus* Ig G testing was not available in the country. On the contrary, the bronchoscopy for bronchoalveolar lavage and histopathological examinations was not affordable. On the basis of the clinical, biological, and scan evidences, the diagnosis of probable post-COVID-19 aspergillosis was made. The patient was put on an antifungal treatment with itraconazole 200 mg per day. The clinical course after 14 days of treatment was favorable with disappearance of dyspnea, reduction of cough, chest pain, and asthenia. She was discharged from hospital at the third week of treatment. However, she complained of persistent moderate chest pain. The chest CT scan after 2 months of treatment showed disappearance of the aspergilloma (Figure 2A) with a residual cavity surrounded by parenchymal destruction, suggestive of chronic necrotizing aspergillosis and onset of homolateral fibrosis (Figure 2B). Thus, the same antifungal treatment was continued, but a surgical treatment was planned if no improvement was noted. Unfortunately, we lost of follow-up the patient.

3 | DISCUSSION

By definition, aspergillosis is a fungal infection caused by *Aspergillus* species. The commonly known manifestations are allergic bronchopulmonary aspergillosis, acute invasive pulmonary aspergillosis, and chronic pulmonary aspergillosis. Chronic pulmonary aspergillosis includes *Aspergillus* nodules, simple aspergilloma, chronic cavitary pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis, and subacute invasive pulmonary

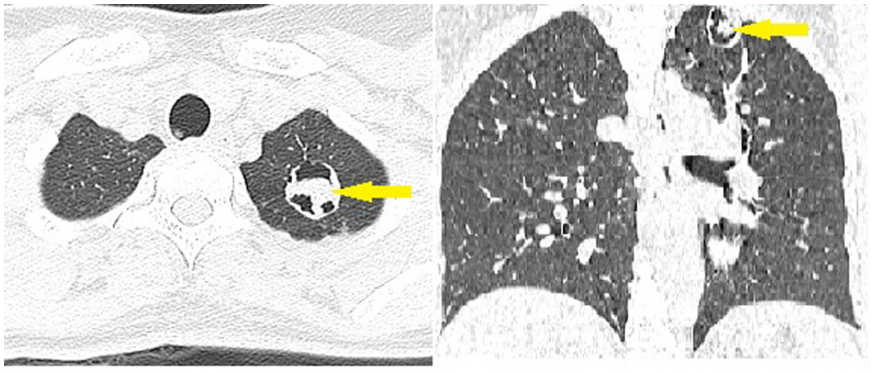

FIGURE 1 CT scan of chest axial and coronal view, showing a thin-walled cavitary lesion containing a homogeneous opacity with "crescent air" sign, suggestive of aspergilloma in the apical segment of the left upper lobe

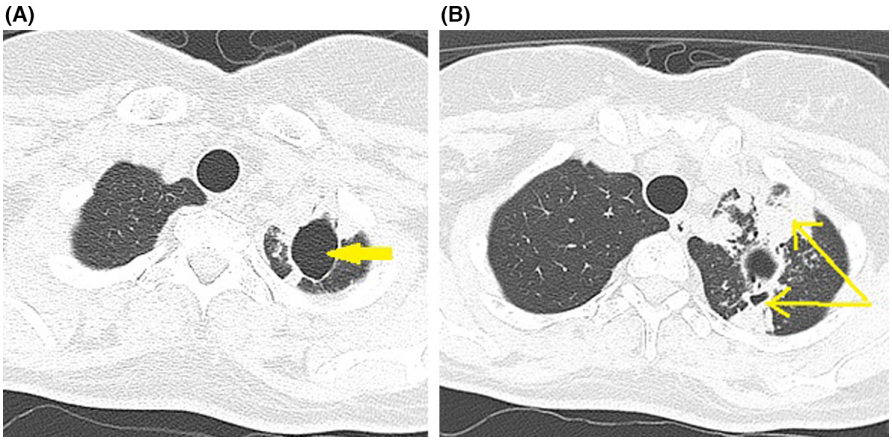

FIGURE 2 (A) CT scan of chest axial view, 2 months after antifungal treatment, showing a thin-walled, regular empty cavity in the left upper lobe. (B) CT scan of chest axial view, 2 months after antifungal treatment, showing the residual cavity surrounded by heterogeneous opacities suggestive of a necrotizing lung lesion and the onset of homolateral fibrosis

aspergillosis formerly known as chronic necrotizing pulmonary aspergillosis.[6,7] The chronic forms generally affect immunocompetent or mildly immunocompromised patients with a pre-existing pulmonary condition. Prior lung tuberculosis and nontuberculous mycobacterial infections remain the most commonly reported primary underlying lung conditions in patients with chronic pulmonary aspergillosis. Other less common predisposing conditions include allergic bronchopulmonary aspergillosis, chronic obstructive pulmonary disease, treated lung cancer, asthma, pneumonia, and fibrocavitary sarcoidosis.[6–8] On the contrary, acute invasive pulmonary aspergillosis are common in patients with severe immunodeficiency and hematological malignancies. In addition, patients with severe pneumonia due to influenza and severe acute respiratory syndrome coronavirus (SARS-CoV-2) are also at a higher risk of developing invasive pulmonary aspergillosis.[8,9] Based on experiences with influenza-associated invasive pulmonary aspergillosis, cases of aspergillosis superinfection have been associated with the severe or critical form of COVID-19.[9,10] In COVID-19 associated with pulmonary aspergillosis (CAPA) patients, the main underlying diseases were diabetes mellitus (33%), and hematological and oncological diseases (31%).[4] The main pathogens were *Aspergillus fumigatus* and *Aspergillus niger*.[4] However, it is not clear whether SARS-CoV-2 infection is in itself the main risk factor for COVID-19-associated pulmonary aspergillosis, or whether other risk factors, such as corticosteroid therapy frequently used in severe forms, increase the risk of the disease progression.[10] Salehi et al. evoked that the COVID-19 patients at high risk of opportunistic fungal infections included those with acute respiratory distress syndrome, in intensive care units, receiving broad-spectrum antibiotics, immunosuppressants or corticosteroid, and supported by invasive or noninvasive ventilation.[11] In Russia, the probability of CAPA developing significantly increased with lymphocytopenia >10 days, decompensated diabetes mellitus, use of glucocorticosteroids in prednisolone-equivalent dose >60 mg/day and monoclonal antibodies to IL-1ß and IL-6.[4] Indeed, proinflammatory cytokines and chemokines, such as tumor necrosis factor a (TNFa), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-1b, and monocyte chemoattractant protein-1 were significantly elevated in patients with severe COVID-19, which would predispose to invasive aspergillosis.[2,11] In our opinion, both the severity of COVID-19 and the corticosteroid therapy induced a moderate immunosuppression that has put our patient at risk of chronic necrotizing pulmonary aspergillosis.

In the literature, the clinical signs of chronic pulmonary aspergillosis are nonspecific, with or without COVID-19.[7,10] Respiratory and/or general symptoms are often present for 1–6 months: cough, sputum, chest pain, dyspnea, hemoptysis with or without long-term fever, altered general condition with sometimes severe weight loss.[10] So additional examinations are necessary to diagnose aspergillosis. The European Society for Clinical Microbiology and Infectious Diseases, the European Respiratory Society, and the European Confederation of Medical Mycology established diagnostic criteria for chronic pulmonary aspergillosis. Actually, the diagnosis of chronic pulmonary aspergillosis requires a combination of characteristics: one or more cavities with or without a fungal ball present or nodules on thoracic imaging, direct evidence of *Aspergillus* infection (microscopy or culture from biopsy) or an immunological response to *Aspergillus* spp. and exclusion of alternative diagnoses, all present for at least 3 months. *Aspergillus* antibody (precipitins) is elevated in over 90% of patients.[12] In our case, even if there was no *Aspergillus* culture identification nor immunological evidence, an aspergilloma developed in a cavity of chronic necrotizing pulmonary aspergillosis related to SARS-CoV-2 disease was the most probable diagnosis. In other words, clinical and radiological characteristics were met, hyphae were seen on microscopy, but the diagnosis of aspergillosis remained probable. This situation is

common in resource-limited countries like Madagascar as the accurate diagnosis of opportunistic fungal infections remains challenging in resource-poor settings.[4]

About the treatment, there is no evidence that the treatment of aspergillosis is different in patients with or without COVID-19.[10] Indeed, treatment of chronic aspergillosis with or without aspergilloma is based on long-term antifungal agents, including in the first instance itraconazole 200–400 mg/day or voriconazole 150–200 mg twice daily, orally, for 3–6 months or longer. Surgery is reserved for patients who cannot tolerate medical treatment and for patients with active residual disease despite adequate antifungal treatment.[8] However, according to the European Respiratory Society in 2016, chronic necrotizing aspergillosis or subacute invasive aspergillosis should be treated in the same way as acute invasive pulmonary aspergillosis because of its rapidly progressive nature.[12] In this case, treatment is based on intravenous voriconazole at a dose of 6 mg/kg every 12 h on the first day, followed by 3 mg/kg every 12 h and then oral therapy for a total duration of at least 3 months. The evolution of chronic aspergillosis under treatment varies. The disappearance of aspergilloma is correlated with a favorable clinical response to treatment.[7] Unfortunately, voriconazole does not exist in Madagascar. The evolution of post-COVID-19 chronic pulmonary aspergillosis treated by itraconazole is uncertain.

4 | CONCLUSION

Chronic pulmonary aspergillosis post-COVID-19 are less described in the literature. We reported an exceptional association of three forms of pulmonary aspergillosis in an immunocompromised patient probably caused both by the corticosteroid therapy and the proinflammatory cytokines secreted during COVID-19. In practice, in case of persistent respiratory symptoms, physicians should perform a chest CT scan and eventually screening for aspergillosis in order to improve the management of post-COVID-19 patients. In addition, mycological examination and antifungal treatment need to be improved, especially in resource-limited countries. Further studies to identify the underlying conditions and risk factors of aspergillosis in post-COVID-19 patients are necessary for targeted prevention efforts.

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AUTHOR CONTRIBUTIONS

ZAR, KR, and HMT involved in draft of the clinical case report. AMN, FPPA, SMR, and DOA involved in follow-up of the patient. JRR, JLR, and RNR involved in final correction. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT

A written informed consent was obtained from the patient to allow us to publish a report of her case for educational purposes. She has been de-identified in this manuscript and no personally identifiable details have been included.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available due to privacy restrictions. The data are available upon reasonable request from the corresponding author.

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