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CASE REPORT

Concomitant tuberculosis and aspergillosis in patients with COVID-19: a case report

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ABSTRACT

Coexisting pulmonary aspergillosis and tuberculosis in a post-COVID-19 patient is rare. Here, we are going to report a case of combined pulmonary aspergillosis and tuberculosis in a 51-year-old female who was previously diagnosed with COVID-19 pneumonia. The patient was treated with voriconazole and anti-tuberculosis agents.

Keywords: Pulmonary; Aspergillosis; Tuberculosis; COVID-19; Coinfection

INTRODUCTION

Pulmonary tuberculosis (PTB) is one of the important reasons for death in its endemic areas (1). The damage and deterioration of lung tissue resulting from this infection as sequelae are considered significant risk factors for chronic lung diseases, such as chronic obstructive pulmonary disease, bronchiectasis, and pulmonary aspergillosis, notably aspergilloma (2). Pulmonary aspergilloma, also called fungus ball or mycetoma, grows due to colonizing *Aspergillus* spp. in the pre-existing pulmonary cavity, which results from previous tuberculosis, emphysematous bulla, carcinoma, or sarcoidosis (3). In the current severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic, coinfections with common viral, bacterial, and fungal pathogens have been reported among COVID-19 patients (4, 5). Recently, it has been reported that these infections in COVID-19 patients can be associated with increased hospitaliza-

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tion period and mortality (5). Patients with COVID-19 received corticosteroids, broad-spectrum antibiotics, and several non-standardized immunosuppressive therapies, which can represent the most important risk factors associated with the development of coinfections (6). Therefore, given the worse prognosis of coinfections, investigating high-risk COVID-19 patients for secondary infections may hold great clinical significance. Here, we present a post-COVID-19 case highlighting simultaneous pulmonary involvement with tuberculosis (TB) and aspergillosis.

Case presentation. The patient was a 51-year-old female with a history of rheumatoid arthritis (RA), uncontrolled diabetes mellitus (DM), hypothyroidism, and hypertension (HTN). She had been taking prednisolone (5 mg/orally/ daily) and methotrexate (7.5 mg/orally/ per week) for RA treatment for the past 4 years. Two months before admission, the patient experienced severe COVID-19 symptoms, including cough, dyspnea, and tachypnea (RR=35) with an SPO2 of 85% in ambient air and extensive bilateral ground-glass opacities (GGO) on chest CT scan (Fig. 1A). She had been treated with intravenous (IV) Remdesivir (200mg stat and then 100 mg/ daily for 5 days) and methylprednisolone 250mg/IV/ daily/ for two days and then dexamethasone 8 mg/IV/ daily for 12 days. After two weeks of hospitalization, the patient was discharged due to a reduced dependence on oxygen support and was advised to take oral prednisolone 10 mg daily. Two months after discharge, despite some improvement in the patient's respiratory conditions, she experienced intermittent fever, loss of appetite, right chest pain, and a productive cough.

On the day of admission to our hospital (day 0), the main complaint of the patient was fever (oral temperature was 39.5ºC), productive cough, and right-sided pleuritic chest pain exacerbated by laying in a supine position two weeks ago. Chest auscultation revealed basal crackle sound in the lower lung lobes bilaterally. In radiological evaluation, a lung CT scan showed several GGO with the presence of lingual consolidation containing a thick-walled cavity (43.52 mm × 47.39 mm) surrounded by multiple satellite lesions. Additionally, there was a hyperdense segment in the superior posterior segment of the left lobe with mediastinal lymphadenopathy (S.A.D =10 mm) (Fig. 1B, C, D).

HIV serology testing was negative. Given the history of severe COVID-19 infection, the use of immunosuppressants such as methotrexate and long-term corticosteroid therapy, along with the radiologic findings, were suggestive of necrotizing pneumonia. Also, in the para-nasal sinus, CT scan without contrast showed mucosal thickening in the sphenoid and maxillary sinus without evidence of bone erosion or invasion (Fig. 2). Other diagnostic results revealed that two sets of sputum smears were 3+ positive for acid-fast bacilli (AFB) (14 AFB per field), and the sputum culture in Löwenstein-Jensen medium also showed positive result after two months. Furthermore, subsequent sputum examination using GeneXpert system confirmed the presence of *Mycobacterium tuberculosis* (MTB; with a Ct value of 16 for the *rpoB* gene) with no rifampicin resistance. Based on the direct examination with KOH 10% on the sputum sample, septate acute angle branching hyaline hyphae was consistent. After culturing on Sabouraud dextrose agar (SDA) at 37°C, the colonies exhibited characteristics consistent with *Aspergillus fumigatus (A. fumigatus)* (Fig. 3A). Afterward, DNA was extracted using the phenol-chloroform-isoamyl method, followed by PCR amplification of targeted DNA segments. Specifically, Beta-tubulin (BT1/BT2) primers were employed to amplify the β-tubulin-encoding gene of *A. fumigatus* (GenBank accession number 0Q466614) (7). Simultaneous biopsy sampling under CT-guided radio intervention was done. Histology examination revealed parenchyma with distorted architecture due to extensive necrosis with rather sharp boundary to viable tissue. (Fig. 4 A and B). The necrotic area contained fragmented debris of nuclei without obvious infiltration of neutrophils, eosinophils or other cells. There was only one focal collection of histiocytes and a multinucleated giant cell; granuloma formation was noted in the interstitium (Fig. 4 C and D). The serum galactomannan was measured at 3.79 index with a cut-off value of < 0.5 index. Based on laboratory and microbiological results, voriconazole was started loading 400 mg intravenous (IV) in two doses for the first day, then 200 mg IV twice daily. However, due to the interaction between rifampin and voriconazole, rifampin was discontinued, and anti-TB chemotherapy regime was changed to pyrazinamide 750 mg, ethambutol 1400 mg, and levofloxacin750 mg oral daily. After 10 days of treatment with piperacillin/tazobactam, antibiotic therapy was discontinued. After two weeks post-initiation of treatment with an anti-fungal and TB regimen, the patient’s coughs were noticeably reduced and completely resolved within two months. Given

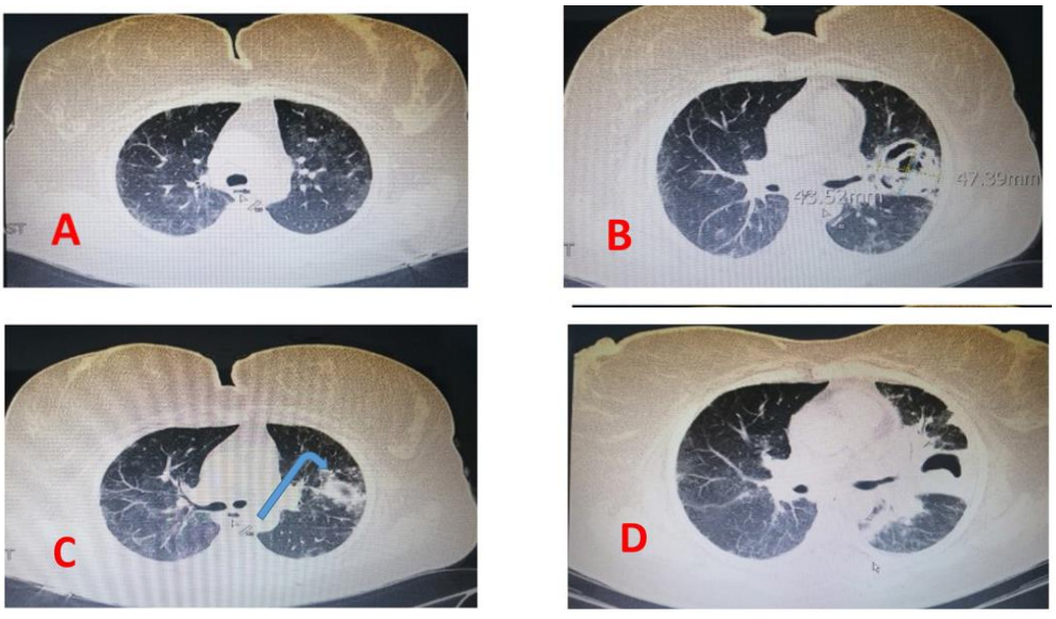

Fig. 1. Chest CT-scan without contrast revealed that several GGO were suggestive of the previous infection with COVID-19 (A) with the presentation of lingual consolidation with a thick-walled cavity (43.52 mm × 47.39 mm) (B) was surrounded by multiple satellite cells (C) with Monod sign leads to aspergilloma (D) what and a hyperdense segment in the superior posterior segment of the left lobe with mediastinal lymphadenopathy with a maximum S.A.D =10 mm is seen.

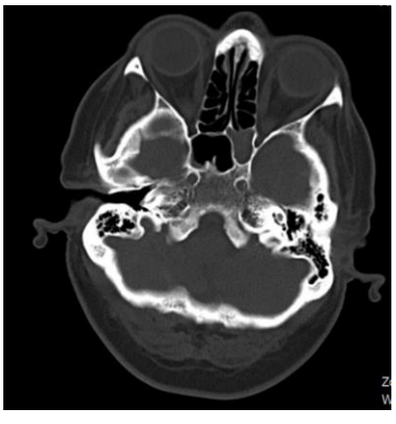

Fig. 2. CT scan without contrast of para nasal sinus showed mucosal thickening in sphenoid and maxillary sinus without bone erosion and invasion.

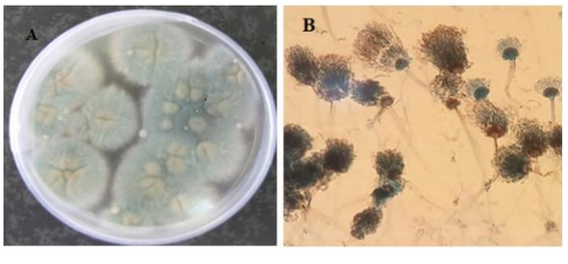

Fig. 3. The sputum sample cultured on Sabouraud dextrose agar (SDA) showed colonies suspected of *Aspergillus fumigatus* (A) *Aspergillus fumigatus* under the microscope (B).

the mentioned drugs, the patient was discharged with induction therapy and scheduled for a follow-up galactomannan test. Her cough gradually subsided, and her appetite improved considerably. The fever abated, and she could perform all daily activities with an overall improvement in glycemic control after 2 weeks. Based on the negative results of sputum Ziehl-Neelsen's smear examination two months after initiating anti-TB chemotherapy, pyrazinamide, ethambutol, and levofloxacin were continued. In addition, to improving pulmonary symptoms, serial serum galactomannan testing was conducted using Enzyme-Linked Immunosorbent Assay (ELISA), and the values obtained at the time of admission, two weeks apart, were as follows: 3.79, 2.1, 1.5, 0.5, 0.3, and 0.13 index value. The results consistently showed negative values. In subsequent radiology findings, there was a significant improvement in cavity lesions, and no signs of new lesions were observed (Fig. 5).

DISCUSSION

Pulmonary involvement caused by fungal coinfections can present challenges in diagnosis and treatment (8). The functional impairment of neutrophils and lymphocytes leads to several micro-

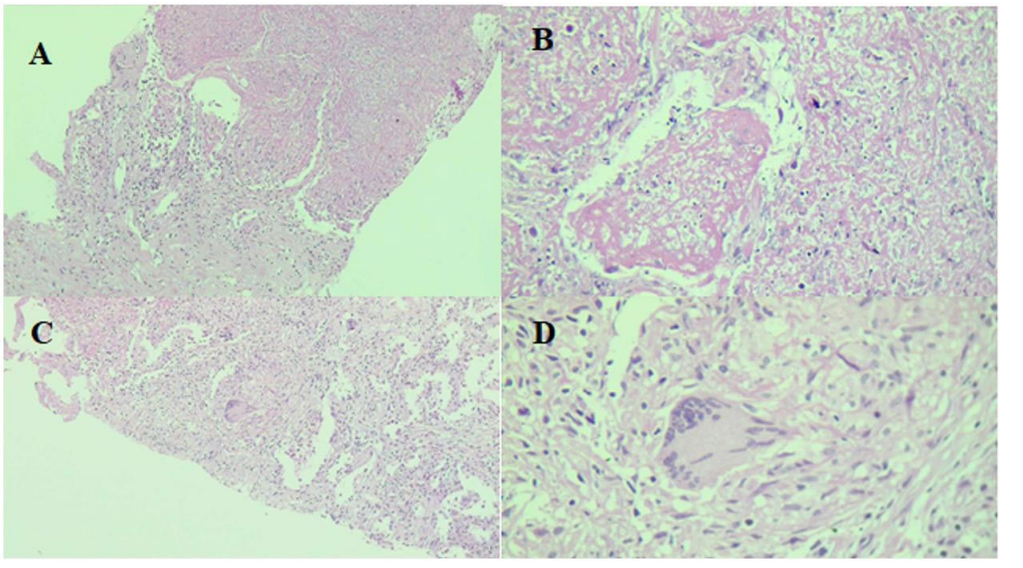

Fig. 4. • Microscopic examination of CT-guided lung biopsy revealed lung parenchyma with distorted architecture due to extensive necrosis with a rather sharp boundary to viable tissue (Figs. A and B). The necrotic area contained fragmented debris of nuclei without prominent infiltration of neutrophils, eosinophils, or other cells.
• Only in one focus collection of histiocytes and a multinucleated giant cell; granuloma formation was noted, located in the interstitium (Figs. C and D).
• In Ziehl-Neelsen and GMS special staining, no acid-fast bacilli or fungal elements were identified.

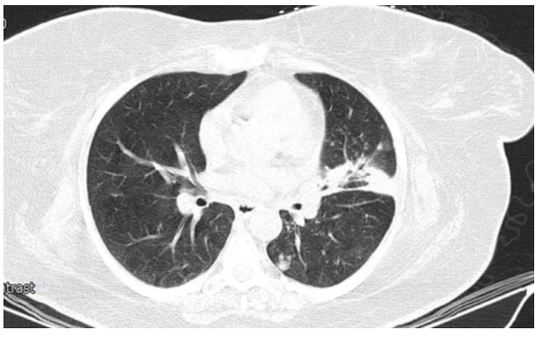

Fig. 5. Chest CT-scan without contrast revealed that significant improvement in cavity lesion and no signs of new lesions

bial infections, including aspergillosis and TB (9). T-cell response dysfunction due to certain diseases, particularly severe COVID-19 and HIV infections, increases the risk of TB (9). Additionally, lung dysfunction, such as granulomas and cavities caused by tuberculosis, raises the risk of pulmonary aspergillosis (10) , which encompasses three forms: allergic aspergillosis, aspergilloma, and invasive aspergillosis (11). These opportunistic pulmonary infections are commonly caused in Immunocompromised patients (12); among them, aging (> 60 years), hypertension, DM, and use of corticosteroids can be related to raised mortality (13). Using steroids to treat COVID-19 can prevent the development of cytokine release storms (CRS) and acute respiratory distress syndrome (ARDS). However, it can lead to secondary infections (14). Although numerous reports on COVID-19 are associated with microbial coinfection, PTB/ pulmonary aspergillosis cases have rarely been reported. Vidanapathirana et al. reported a case in which a young diabetic man with respiratory complaints was diagnosed with invasive aspergillosis and disseminated tuberculosis. Two weeks later, the patient's condition was further complicated by severe COVID-19 pneumonia. He was treated with antituberculous, antifungal, and steroid therapy (15). Also, Gandotra et al. presented a middle-aged male with a history of liver transplant recipients. He had been diagnosed with disseminated TB and invasive pulmonary aspergillosis complicated with hemophagocytic lymphohistiocytosis upon recovery from severe COVID-19 (16). The uniqueness of our patient was due to the presence of aspergilloma, invasive aspergillosis, and PTB in a post-COVID-19 case, which, to our knowledge, have not been reported so far. Aspergilloma, with its most typical sign being hemoptysis, has a predicted mortality rate of 6%. In most cases, the fungal ball remains permanent (17). Although it

may shrink in size in 10% of cases or go away on its own without treatment, the size increase of aspergilloma is rare (18). In our patient, CT scan revealed lingual consolidation accompanied by a cavity and a hyperdense segment in the left lobe. Besides, the direct examination, culture, and molecular test on the sputum sample showed *A. fumigatus* and sputum smear for AFB of MTB were positive. While biopsy sampling under CT guided radio intervention was negative for fungal elements. The probable reason for this result could be associated with inappropriate sampling. These findings confirm aspergilloma and PTB. According to EORCT/MSG definition, the combination of clinical features such as RA, DM, or HTN, corticosteroid use for COVID-19 treatment, elevated serum galactomannan level, and detection of *A. fumigatus* in direct tests, sputum culture, and molecular tests, can propose a probable diagnosis of invasive aspergillosis in the described patient (19). She was treated with voriconazole and antituberculosis. The positive response to treatment in this patient highlights the critical impact of early diagnosis and treatment for those at risk for co-infections such as tuberculosis and aspergillus. Early diagnosis, often referred to as the "golden time," is essential to initiate appropriate treatment and improve patient outcomes (20). Delay in the diagnosis of co-infections in people with underlying conditions can lead to rapid progression of the disease, increased complications, and mortality (21).

In conclusion, comprehensive infection control measures are essential to prevent coinfection with *Aspergillus* and MTB in individuals with underlying conditions and COVID-19. This includes strict isolation, careful use of antibiotics, and targeted antifungal prophylaxis. Management of PTB/ pulmonary aspergillosis remains challenging in the COVID-19 era. This case demonstrates a positive outcome achieved through timely detection and treatment. It is essential to raise awareness of PTB/ pulmonary aspergillosis and differentiate it from other respiratory conditions, such as bacterial pneumonia and chronic obstructive pulmonary disease (COPD).

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