Aspergilloma complicating previous COVID-19 pneumonitis – a case report

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Aspergillomas are found in pre-existing cavities in pulmonary parenchyma. To the best of our knowledge, aspergilloma has not previously been reported in COVID-19-associated pulmonary architecture distortion combined with barotrauma from invasive mechanical ventilation therapy. We present a case of a 67-year-old woman, who suffered from severe COVID-19 in the summer of 2020 with no suspicion of infection with *Aspergillus* in the acute phase. Ten months after discharge from her COVID-related admission, she developed bilateral aspergillomas diagnosed by image diagnostics, bronchoscopy, and blood samples, and she now receives antifungal therapy. We would like to raise awareness on aspergilloma in post-COVID-19 patients, since it is an expected long-term complication to COVID-19 patients with pulmonary architectural distortion.

Key words: Aspergilloma; fungus ball; COVID-19; pulmonary architecture distortion.

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ABBREVIATIONS

COVID-19, corona virus-2019 disease
HRCT, high-resolution computed tomography
CT angiography, computed tomography angiography
ICU, intensive care unit
FEV1, forced expired volume during the first second
FVC, forced vital capacity
CAPA, COVID-19-associated invasive pulmonary aspergillosis

In December of 2019, a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first discovered in the Wuhan District in China and spread to cause a worldwide pandemic. SARS-CoV-2 can cause severe viral pneumonia, and a few patients develop long-lasting sequelae including pulmonary architectural distortion. Some patients with severe viral SARS-CoV-2 pneumonia might need invasive mechanical ventilator therapy.

Chronic pulmonary aspergillosis consists of 5 different subtypes [1]. Simple aspergilloma may arise in patients at risk due to chronic diseases and pre-existing lung abnormality. An aspergilloma may develop due to aspergillus hyphae colonize pre-existing pulmonary cavities caused by, for example, emphysema, previous tuberculosis, or sarcoidosis.
| Timeline                  | Sample                          | Result                                                                                                                                                                                                 |
|--------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Day of submission        | Throat swab                     | SARS-CoV-2 PCR positive                                                                                                                                                                            |
| 4 days after submission  | Tracheal secretion              | Culture negative                                                                                                                                                                                   |
|                          |                                 | PCR negative for *Legionella pneumophila* DNA                                                                                                                                                       |
|                          |                                 | PCR negative for *Chlamydophila pneumoniae* DNA                                                                                                                                                      |
|                          |                                 | PCR negative for *Chlamydia psittaci* DNA                                                                                                                                                            |
|                          |                                 | PCR negative for *Mycoplasma pneumoniae* DNA                                                                                                                                                         |
|                          |                                 | PCR negative for *Respiratory Syncytialvirus* RNA                                                                                                                                                     |
|                          |                                 | PCR negative for *Influenza* type A RNA                                                                                                                                                               |
|                          |                                 | PCR negative for *Influenza* type B RNA                                                                                                                                                              |
| 9 days after submission  | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 14 days after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 3 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 4 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 5 weeks after submission | Bronchoalveolar lavage          | No growth of any microbe                                                                                                                                                                             |
|                          |                                 | *Aspergillus galactomannan* antigen = 0.129 (negative)                                                                                                                                               |
|                          |                                 | PCR negative for *Pneumocystis jirovecii* DNA                                                                                                                                                         |
|                          |                                 | PCR negative for *Varicella zoster virus* DNA                                                                                                                                                         |
|                          |                                 | PCR negative for *Cytomegalovirus* DNA                                                                                                                                                               |
|                          |                                 | PCR negative for *Herpes simplex virus type 1* DNA                                                                                                                                                     |
|                          |                                 | PCR negative for *Herpes simplex virus type 2* DNA                                                                                                                                                     |
|                          |                                 | Microscopy, PCR and culture negative for *mycobacteria* spp.                                                                                                                                          |
| 5 weeks after submission | Pleural effusion                | No growth of any microbe                                                                                                                                                                             |
| 5 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 6 weeks after submission | Pleural effusion                | No growth of any microbe                                                                                                                                                                             |
| 6 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 7 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 8 weeks after submission | Tracheal secretion              | No growth of any microbe                                                                                                                                                                             |
| 8 weeks after submission | Pleural effusion                | No growth of any microbe                                                                                                                                                                             |
| 9 weeks after submission | Bronchial secretion             | No growth of any microbe                                                                                                                                                                             |
| 8 months after discharge | Tracheal secretion              | Non-growth of any microbe                                                                                                                                                                             |
| 9 months after discharge | Bronchoalveolar lavage          | *Aspergillus fumigatus* moderate growth                                                                                                                                                              |
|                          |                                 | Posaconazole: Sensitive Voriconazol: Sensitive Itraconazol: Sensitive Amphotericin B: Sensitive Isavuconazole: Sensitive                                                                             |
| 10 months after discharge| Bronchoalveolar lavage          | *Aspergillus galactomannan* antigen = 3.412 (Positive) *Aspergillus galactomannan* antigen = 3.802 (Positive)                                                                                           |
| 10 months after discharge| Blood                           | *Aspergillus fumigatus* total IgG units >1600 *Aspergillus fumigatus* total IgG class = 4                                                                                                           |
Progression to other forms of chronic pulmonary aspergillosis including chronic cavitary pulmonary aspergillosis or hemoptysis is a risk [1]. COVID-19-associated invasive pulmonary aspergillosis (CAPA) has become a recognized condition, driven by damage to the epithelium, immune dysregulation, and impaired ciliary clearance, making it possible for *Aspergillus* spp. to invade the tissue [4], as also seen in influenza [5–7].

Subacute infection with *Aspergillus* post-COVID-19 has been described in a single case report. In this case, the chest radiograph at admission showed no lung cavities, but three weeks later, fungal ball-like lesions were detected by Computed Tomography scan (CT) and *Aspergillus flavus* was grown in cultures from respiratory secretions [8].

In two reported cases, aspergillus fungus balls (aspergillomas) developed as acute illness recently after mild not hospital-treated COVID-19. In one case, the fungal ball developed within three weeks after COVID-19 was resistant to medical treatment, and the patient underwent upper left lobektomi [9]. In the other case, the fungus ball developed recently after COVID-19 and could be treated with antifungal medicine [10]. Additionally, one case describes a case of latent aspergilloma, which was most likely

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**Table 1** (continued)

| Timeline               | Sample           | Result                                                                 | Susceptibility pattern |
|------------------------|------------------|------------------------------------------------------------------------|------------------------|
| 10 months after discharge | Blood            | *Aspergillus* galactomannan antigen = 0.116 (negative) *Aspergillus* galactomannan antigen = 0.140 (negative) | –                      |
| 10 months after discharge | Bronchial secretion | *Candida glabrata* Non-specified mold-fungi | –                      |

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![Fig. 1](image.png)

**Fig. 1.** Two weeks after submission with COVID-19. CT thorax in arterial phase: Widespread ground glass bilaterally, with a peripheral distribution. In the left upper lobe, large areas of crazy paving (interlobular septal thickening and ground glass) are seen (C, black arrowhead). Several lung emboli are seen in lobar and segmental arteries (B, white arrow). The overall image is consistent with subacute COVID-19 infection complicated with lung emboli. (A) Axial lung window, (B) axial soft tissue window, (C) coronal lung window and (D) sagittal lung window.
activated to a more aggressive chronic cavitary pulmonary aspergillosis after SARS-CoV-2 infection [11].

Aspergillomas in pulmonary parenchyma irreversible damage as a result of previous COVID-19 have to the best of our knowledge not been reported before, though it is expected to appear. Our case report is written to enhance awareness of aspergillomas in patients with long-term structural pulmonary parenchymal damage from SARS-CoV-2 infection, as we expect to see more cases of this complication in patients with previous severe COVID-19.

CASE PRESENTATION

We report the case of a 67-year-old woman, with a past medical history of spastic tetraplegia due to a previous neuro-infection and a tendency to urinary incontinence. She was tested positive for SARS-CoV-2 by RNA-PCR test in the summer of 2020. Her severe COVID-19 required treatment with invasive mechanical ventilation therapy at an intensive care unit (ICU), ≤20 mg dexamethasone daily, broad-spectrum antibiotics and tinzaparin in prophylactic and therapeutic doses. Due to elevated liver enzymes, treatment with remdesivir was contraindicated. At its worst, her condition was complicated by acute respiratory distress syndrome and bilateral pleural effusion. Two and a half months of admission, she was discharged to a rehabilitation facility.

During her admission, no other pathogens than SARS-CoV-2 and a urinary tract infection with Escherichia coli were detected despite extensive testing for microbiological agents, Table 1. There was no sign of Aspergillus infection at any time during her admission and until 9 months after discharge. Imaging diagnostics were performed, Figs 1–4, revealing no signs of aspergillus balls until 11 months after discharge; however, cavities began to develop five weeks after submission.

At an outpatient clinical follow-up two months after discharge, she still complained of cough and shortness of breath. Her spirometry showed a restrictive pattern, with a forced expired volume during the first second (FEV1) 59% and forced vital capacity (FVC) 60%. At an eight-month
follow-up, she felt better; her pulmonary function had normalized (FEV1 89% and FVC 87%), and HRCT scan still showed no signs of Aspergilloma.

Ten months after discharge, she was re-admitted due to fever, worsening of her cough and expectoration. Her C-reactive protein was elevated to 119 mg/L. During this admission, her chest radiograph showed a novel cavity, 11 months after discharge, an HRCT scan revealed bilateral aspergilloma. Aspergillus infection was confirmed by Aspergillus fumigatus cultured from bronchoalveolar lavage fluid and a blood sample positive with Aspergillus fumigatus IgG (ELISA) >160,000 units. Antifungal sensitivity testing was performed according to EUCAST methods E.Def.10.0 and E.Def.9.3.2 (azole agar screening supplemented with EUCAST microdilution for isavuconazole and amphotericin B), and the isolate was susceptible to all tested antifungals [12,13]; please see Table 1 for details. No bacteria were found.

The patient started antifungal treatment with voriconazole 200 mg twice daily. Due to increase in liver enzymes, voriconazole was replaced with itraconazol 200 mg twice daily.

DISCUSSION

This is, to our knowledge, the first reported case of aspergillomas complicating COVID-19 lung architectural distortion combined with barotrauma from invasive mechanical ventilation therapy.

Aspergillomas are commonly suspected from radiology findings and thereafter diagnosed by microbiological, immunological, and histological investigations of tissue or bronchoalveolar lavage. Treatment is challenging and can be either with antifungal medicine or surgery. Surgery can be the best treatment option for aspergillomas in cases with a well-shaped aspergilloma, with severe hemoptysis, and acceptable lung function, as it may be curative. But, it is associated with high morbidity and mortality, as severe pleural adhesion and infection of the underlying lung are frequent. Hence, surgery is not suitable for all patients. [1,4]

Aspergillus is an omnipresent fungus, which grows in decaying organic material. Its spores are airborne, and it is likely the patient has been exposed to aspergillus both pre- and post-COVID-19. But, the aspergillus she has been exposed to pre-COVID-19 has

Fig. 3. Eight months after discharge. HRCT: Sequelae after COVID-19 infection with pneumoceles (black arrows), cavitating infiltrates and fibrosis like structural changes (black arrowhead). Significant reduction in consolidated areas and only small remnants of ground glass consolidation is seen. (A) Axial lung window, (B) coronal lung window and (C) sagittal lung window.

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not caused infection with aspergillus during her infection with COVID-19, as seen in other cases.

In our case, the patient had no structural lung damages prior to her COVID-19 and her invasive mechanical ventilation therapy, as shown by the initial CT angiography two weeks after admission. In the pulmonary tissue distorted by COVID-19 and barotrauma, initial HRCT showed no signs of aspergilloma. Similarly, initial bronchial lavage fluid and subsequent respiratory secretions showed no signs of Aspergillus.

Hence, in our case the aspergillomas found bilaterally at the HRCT scan 11 months after discharge developed in the pulmonary cavity-sequelae caused by her severe COVID-19 illness and barotrauma. Her infection likely originates from aspergillus exposure post-COVID-19 infection. This supports existing knowledge on causality in the development of aspergillomas with growth in pre-existing pneumoceles formed by invasive ventilation treatment and secondary barotrauma as well as COVID-19-associated fibrosis.

Cavitary pulmonary lesions after COVID-19 are likely to increase the risk of aspergillomas, and we expect to see more cases due to this complication. Since COVID-19 is a worldwide pandemic, and Aspergillus is a naturally occurring fungus worldwide, we find it important to raise awareness about this complication.

**NOVEL INSIGHTS**

Aspergillus can form fungus balls in pulmonary tissue dominated by architecture distortion after COVID-19.

**ESTABLISHED FACTS**

Aspergillomas can form in pre-existing cavitary spaces in pulmonary parenchyma.

COVID-19 can cause invasive Aspergillus infection in the acute phase and lung architecture distortion as sequelae.

Fig. 4. Eleven months after discharge. HRCT: Thick-walled cavities with central fungus ball and air crescent sign (black arrowhead), at positions of previously described pneumoceles combined with tree-in-bud nodules. Aspergilloma or mycobacterial infection is suspected. (A) Axial lung window, (B) coronal lung window and (C) sagittal lung window.

We acknowledge the willingness of the patient to let us share this intriguing finding.

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CONFLICT OF INTERESTS
The authors have no conflicts of interest to declare.

CONSENT TO PARTICIPATE
In Denmark, for a case report there is only a need to sign a consent form.

CONSENT FOR PUBLICATION
The patient has herself given her written informed consent to publish their case (including publication of images). The consent form is stored in her patient record.

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